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Feline Cardiology

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WILEY-BLACKWELL
A John Wiley & Sons, Inc., Publication

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This edition first published 2011 © 2011 by John Wiley & Sons, Inc.

Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientific, Technical and Medical business with Blackwell Publishing.

Registered office: John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial offices: 2121 State Avenue, Ames, Iowa 50014-8300, USA
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
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Library of Congress Cataloging-in-Publication Data
Feline cardiology / Etienne Côté ... [et al.].
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-8138-1242-7 (hardcover : alk. paper)
1. Cats–Diseases. 2. Veterinary cardiology. I. Côté, Etienne.
[DNLM: 1. Cat Diseases. 2. Cardiovascular Diseases–veterinary. SF 985]
SF985.F414 2011
636.8'089–dc22
2011007198

A catalogue record for this book is available from the British Library.

This book is published in the following electronic formats: ePDF 9780470960165; ePub 9780470960172; Mobi 9780470960189

Set in 10.5/12.5 pt Minion by Toppan Best-set Premedia Limited

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Cover Image Credits—Top left image: Radiograph of a cat with a permanent epicardial pacemaker. **Second left image:** Echocardiogram of a cat with hypertrophic obstructive cardiomyopathy, showing systolic anterior motion of the mitral valve and associated mitral regurgitation and turbulence in the left ventricular outflow tract. **Third left image:** Electrocardiogram of a cat showing normal sinus rhythm and superimposed motion artifact caused by purring. **Fourth left image:** Spectral Doppler tracing obtained in the left ventricular outflow of a cat with dynamic left ventricular outflow tract obstruction. **Bottom left image:** Cardiac magnetic resonance image of a cat with hypertrophic cardiomyopathy. **Right image:** "Cat Eyes" by Barbara Hartsook, http://WithBrushandPen.com

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For my father, François Côté, and in memory of my mother, Louise Martin, who have been my nature and nurture.

Etienne Côté

For my husband Jim, my mother Nancy, and my daughter Lexi: thank you for bringing so much happiness and support to my life and for encouraging my endeavors.
Thank you to my mentor, Dr. Mark Kittleson, for giving me the opportunity and guidance in my research of feline hypertrophic cardiomyopathy.

Kristin A. MacDonald

For the many, many, many mentors (both human and feline) I have had along the way, thank you.

Kathryn M. Meurs

For Drs. David H. Knight and Jim W. Buchanan—I was privileged to be one of your students.
For Mary Jane, who always believed in me. Thank you, Granny.
For Dave, who loves me anyway.

Meg M. Sleeper

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Preface

Cats are the most popular house pet in the United States, numbering some 88.3 million (contrasting with 74.8 million dogs) (HSUS 2010). Surveys suggest proportionally similar domestic feline populations in many other countries (Murray et al. 2010; Chambre Syndicale 2006; EPFIF 2010). Even so, a textbook dedicated to heart diseases of the cat has not existed until now. By contrast, the first textbook on cardiology of the dog was published over 40 years ago (Ettinger and Suter 1970). Therefore, much of the information on heart diseases of cats in current reference texts is presented in combination with information on heart diseases of dogs. Such an approach provides a framework but is insufficient, especially in practices where cats make up a substantial proportion of the caseload. Cats develop and manifest cardiac disease uniquely, in ways that often do not lend themselves to comparisons or extrapolations from other species.

Our ability to recognize feline heart disease continues to increase, and as a result, some studies suggest that the prevalence of heart disease in cats rivals or surpasses the prevalence of heart disease in humans (Paige et al. 2009). This awareness presents both opportunity and dilemma. What are the appropriate tests to diagnose heart disease in cats, and how can private practitioners best use them in daily practice? "Does every cat with a murmur need an echocardiogram?" Can some confounding factors influence the diagnosis of heart disease (Campbell and Kittleson 2007)? Should a cat be treated if structural changes of the heart are only discovered as an incidental finding? Is the prognosis guarded even if his/her cardiac disorder is stable for years? How should comorbidities be addressed in cats with underlying cardiac disease? Answers exist for some of these questions but not others; what is undeniable is the emergence of these questions in daily feline practice. Despite insufficient published information, dedicated cat owners expect veterinarians to diagnose and treat cats that have heart disease with a high level of proficiency and care.

As veterinarians, we are faced daily with the spectrum of feline heart disease. The severity of our feline patients' problems ranges from the very mild to life-threatening and devastating situations. A multiauthor consensus for providing optimal diagnosis and treatment in an attempt to attain the best overall outcome seemed useful but was lacking in existing texts.

All of these observations pointed to a need for more information, which we chose to address by creating this book. Our primary goal has been to collect and present clinically relevant and applicable approaches to the evaluation and treatment of feline heart disease. Above all, the book is meant to be useful in clinical practice. Within this approach, we have also included advanced or state-of-the-art material as appropriate.

We have aimed to describe and explain the intricacies and nuances of feline heart disease, and the uniqueness of feline heart disease, as we see them. Like so many branches of veterinary medicine, feline cardiology suffers from having few formally accepted guidelines to direct the practice and application of the discipline. This book represents our collective effort at identifying and providing the published information that does exist, interwoven with our own experience, opinions, and practice approaches when peer-reviewed data were lacking.

Several features of this book demonstrate the way in which we have sought to reach these goals, including

- Emphasis on clinically relevant aspects of naturally occurring heart disease in the cat. The cardiomyopathies, aortic thromboembolism, heart murmurs, congestive heart failure, and other cornerstones of feline cardiovascular disease are explored in detail. The largest part of the book describes individual cardiovascular diseases as they occur in the veterinary setting. The length of chapters deliberately reflects the importance of individual diseases, so that reader-practitioners may find the most information on the diseases they encounter most often.
- Organization in a predictable and user-friendly format. Chapters begin with key points to summarize the most important elements of each chapter and then proceed through the natural sequence of information, typically: introduction, pathophysiology, signalment, history, physical exam, and so on.
- Anticipation and recognition of the realities of veterinary practice. For example, Chapter 27 on general anesthesia contains sections on "Anesthetizing the Fractious Cat" and "Planning Anesthesia in the Cardiac Patient without an Echocardiogram"; Chapter 29 summarizes treatment recommendations for the most common feline heart diseases in a streamlined

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way and is titled simply "Which Drug for Which Disease?"; Chapter 24 describes managing heart disease in cats that have concurrent kidney disease, allergic airway disease, and other comorbidities; and Chapter 30 is a drug index that serves as a quick reference to the commonly—and less commonly—used cardiovascular medications for cats.

- Presentation of new and innovative information, ranging from cardiac biomarkers and cardiac magnetic resonance imaging to current approaches for genetic screening programs and prebreeding evaluation of cats for heart disease.
- Full-color illustrations. Photographs present physical abnormalities, diagnostic images, and other visually engaging material as clearly as possible.
- Inclusion of reference citations in print at the end of each chapter to allow for quick referencing without needing to consult a CD or website.
- Comprehensive normal *feline* reference values for cardiovascular parameters and diagnostic tests including electrocardiography, echocardiography, and thoracic radiography are available on the inside covers for immediate access.

We were fortunate to benefit from the advantages of communications technology throughout the creation of this book. We wished to have the best of both worlds: taking advantage of our individual strengths and regional exposure, while creating a textbook that is seamless and uniform in style. This was made possible by numerous conference calls and a 6-month comprehensive review period that involved all four of us in a series of 15 desktop-synchronized teleconferences. As a result, each one of us has reviewed and discussed every chapter. We hope readers find that the result is a textbook that is both insightful and cohesive.

This book is resolutely and unapologetically devoted to the cat. Nevertheless, we strived to present cardiology concepts and medical reasoning with the greatest possible clarity, and our hope is that readers not primarily interested in learning about cats will still find that our explanations help them understand cardiology in general.

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Acknowledgments

We thank the group at Wiley-Blackwell, notably Antonia Seymour, Erica Judisch, Erin Magnani, Nancy Turner, Nancy Albright, Justin Jeffryes, and Ray Kersey, for the spark that started this project and their unfailing support throughout its preparation and completion. Their efforts successfully transformed a series of Word documents and digital images into this attractive book.

We owe a great deal of gratitude to many people who helped us make this book possible. Several colleagues, notably Drs. John Bonagura, Phil Fox, Steve Ettinger, Fiona Campbell, and others provided their feedback, their own materials, or both, for us to include in this book. We are truly thankful for their incredible generosity.

Dr. Bruno Pypendop, DrMedVet, DrVetSci, Dipl. ACVA, Associate Professor, Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California, Davis, lent his expertise to our group to create an outstanding chapter on general anesthesia in cats with cardiovascular disease (Chapter 27). We thank him sincerely for his dedication of time and his generous contribution of a truly clinically relevant, insightful chapter.

The American Association of Feline Practitioners and the International Association of Cat Doctors kindly responded to our requests by offering dozens of ideas and suggestions for what a good feline cardiology book should contain. We are truly grateful to them for this contribution. This feedback "from the trenches" was extremely valuable, both for confirming the importance of what we planned to include and for proposing new ideas.

Many thanks are due to graphic illustrators John Doval and Maggie Lillo, who transformed our rudimentary ideas and basic sketches into several beautiful, clear, engaging illustrations.

Finally, and above all, we thank our coworkers, friends, and family. Their understanding and support allowed us to make this book a reality.

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NORMAL CARDIOVASCULAR AND RESPIRATORY REFERENCE VALUES FOR THE DOMESTIC CAT

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HEART RATE

Environment	Rate (beats/minute)	References
Home (Holter)	157 ± 3.7 beats/min (range: 68–294) 165 (range: 70–303)	Ware, 1999 (n = 20) Hanås, 2009 (n = 23)
Home (auscultation)	118 ± 11	Hamlin, 1989 (n = 25)
Home (telemetry):	132 ± 19	Abbott, 2005 (n = 16)
Hospital: outpatient physical exam	180 (range: 140–260)	Côté, 2004 (n = 103)
Hospital: at rest (telemetry)	150 ± 23	Abbott, 2005 (n = 16)
Hospital: kitten	250	McMichael, 2009
Hospital: restrained for ECG - kitten Hospital: restrained for ECG - adult Hospital: restrained for ECG - adult	238 ± 9 182 ± 20 197 ± 27	Gomes, 2003 (n = 30) Hamlin, 1989 (n = 27) Gompf, 1979 (n = 48)
Hospital: restrained for echocardiography	187 ± 25	Abbott, 2005 (n = 16)
Intrinsic (denervated)	158 ± 4	Diepstra, 1980 (n = 7)

RADIOGRAPHY (Litster 2000a, Litster 2000b, Hayward 2004)

Parameter	Value
Vertebral heart size (lateral) Vertebral heart size (dorsoventral) Vertebral heart size (ventrodorsal) Vertebral heart size - obese cats	7.5 V (±0.3) 8.1 V (±0.45) 8.2 V (±0.43) same as normal cats
Pulmonary artery size	Width ≤ narrowest portion of the 4th rib where they intersect (lateral view) Width ≤ diameter of the 9th rib where they intersect (DV view)
Pulmonary vein size	Width ≤ narrowest portion of the 4th rib where they intersect (lateral view) Width ≤ diameter of the 9th rib where they intersect (DV view)

V, vertebral body lengths; *DV*, dorsoventral

ARTERIAL BLOOD PRESSURE

Method		Systolic (mm Hg)	Mean (mm Hg)	Diastolic (mm Hg)	References
Direct arterial Direct arterial	n = 6 n = 6	125 (±11) 126 (±9)	105 (±10) 106 (±10)	89 (±9) 91 (±11)	Brown, 1997 Belew, 1999
Oscillometry Oscillometry	n = 104 n = 60	139 (±27) 115 (±10)	99 (±27) 96 (±12)	77 (±25) 74 (±11)	Bodey, 1998 Mishina, 1998
Doppler ultrasonography Doppler ultrasonography Doppler ultrasonography	n = 33 n = 50 n = 53	118 (±11) 162 (±19) 134 (±16)			Kobayashi, 1990 Sparkes, 1999 Lin, 2006
Risk for future target end-organ damage	minimal risk mild risk moderate risk severe risk	<150 150–159 160–179 ≥180		<95 95–99 100–119 ≥120	Brown, 2007

ECHOCARDIOGRAPHY

2D

IVSd (mm)	LVDd (mm)	LVFWd (mm)	IVSs (mm)	LVDs (mm)	LVFWs (mm)	FS%	LA (mm)	Ao (mm)	LA:Ao	References
4.5 ± 0.3	13.4 ± 2.3	4.4 ± 0.4		6.6 ± 1.7		50 ± 9	12.1 ± 0.6	8.5 ± 0.6	1.4 ± 0.1	Campbell, 2007 (n = 10)
4.5 ± 0.8	15.4 ± 1.6	4.1 ± 0.7		7.5 ± 1.9		53 ± 11	11.3 ± 1.7	9.5 ± 1.4	1.2 ± 0.19	Adin, 2007 (n = 44)
4.6 ± 0.67	15.9 ± 2.40	4.5 ± 0.73	7.8 ± 1.17	7.3 ± 2.63	7.8 ± 1.05	54.9 ± 10.97			0.9 ± 0.09	Chetboul, 2003 (n = 4)

M-mode: LV, LA, AO

IVSd (mm)	LVDd (mm)	LVFWd (mm)	IVSs (mm)	LVDs (mm)	LVFWs (mm)	FS%	LA (mm)	Ao (mm)	LA:Ao	
4.03 ± 0.3	12.95 ± 1.2	4.02 ± 0.4	–	8.59 ± 1.6	–	34.05 ± 2.5	10.3 ± 0.7	9.0 ± 0.7		Allen, 1982 (n = 10)*
5.0 ± 0.7	15.1 ± 2.1	4.6 ± 0.5	7.6 ± 1.2	6.9 ± 2.2	7.8 ± 1.0	55.0 ± 10.2	12.1 ± 1.8	9.5 ± 1.5	1.29 ± 0.23	Moïse, 1986 (n = 11)
3.1 ± 0.4	15.9 ± 1.9	3.3 ± 0.6	5.8 ± 0.6	8.0 ± 1.4	6.8 ± 0.7	49.8 ± 5.3	12.3 ± 1.4	9.5 ± 1.1	1.3 ± 0.17	Jacobs, 1985 (n = 41)
3.7 ± 0.7	14.6 ± 2	3.6 ± 0.6		8.2 ± 1.5		44.2 ± 8.2	10.9 ± 1.8	9.5 ± 1.1		Fox, 1995 (n = 36)
3.8 ± 0.8	14.9 ± 2.2	3.8 ± 0.9	6.4 ± 1.2	8.3 ± 2.2	6.8 ± 1.1	44 ± 11				Koffas, 2006 (n = 25)
4.6 ± 0.67	15.9 ± 2.4	4.5 ± 0.73	7.8 ± 1.17	7.3 ± 2.63	7.8 ± 1.05	54.9 ± 10.97			0.9 ± 0.09	Chetboul, 2003 (n = 4)
4.2 ± 0.7	15.0 ± 2	4.1 ± 0.7	6.7 ± 1.2	7.2 ± 1.5	6.8 ± 1.1	52.1 ± 7.1	11.7 ± 1.7	9.0 ± 1.4	1.25 ± 0.18	Sisson, 1991 (n = 79)
4.7 ± 0.6	16.0 ± 2.3	4.5 ± 0.7	7.7 ± 1.2	8.2 ± 1.8	7.5 ± 1.1	49 ± 7			0.9 ± 0.1	Carlos Sampedrano, 2006 (n = 56)

M-mode: MV

D-E ampl (mm)	EF slope (mm/s)	EPSS (cm)	
	54.5 ± 13.4	0.04 ± 0.07	Moïse, 1986 (n = 10)
5.27 ± 1.25	87.2 ± 26.0	0.02 ± 0.09	Jacobs, 1985 (n = 41)

Systolic time intervals

VcF (cm/s)	Ej time (sec)	PEP (sec)	
2.045 ± 0.48	0.168 ± 0.02		Allen, 1982 (n = 10)*
3.5 ± 0.8	0.116 ± 0.011	0.044 ± 0.009	Fox, 1986 (n = 30)*

Spectral Doppler

Ao (m/s)	PA (m/s)	Transmitral E (m/s)	Transmitral A (m/s)	E:A	LV IVRT (msec)	Peak systolic velocity PVF(S; m/s)	Peak early diastolic velocity PVF (D; m/s)	Peak atrial reversal velocity PVF (AR; m/s)	E decel time (msec)	
		0.67 ± 0.14	0.33 ± 0.11	2.27 ± 1.0	71 ± 17	0.25 ± 0.07	0.23 ± 0.04	0.18 (0.10–0.39)	66 ± 13	Schober, 2003 (n = 7)*
1.1 ± 0.2	0.9 ± 0.2	0.7 ± 0.1	0.5 ± 0.1	1.5 ± 0.3	43 ± 9					Chetboul, 2006a (n = 100)
		0.7 ± 0.04	0.29 ± 0.04	2.49 ± 0.28	45.7 ± 3.3					Bright, 1999 (n = 12)
		0.67 ± 0.13	0.59 ± 0.14	1.19 ± 0.3	55.4 ± 13.24				59.9 ± 14.07	Santilli, 1999 (n = 20)
1.1 ± 0.2		0.7 ± 0.1	0.5 ± 0.1	1.4 ± 0.4	54 ± 11					Carlos Sampedrano, 2006 (n = 56)

Tissue Doppler imaging

PW TDI

	Septal (left apical view)			Lateral (left apical view)				
Longitudinal	E′ (cm/s)	A′ (cm/s)	S′ (cm/s)	E′ (cm/s)	S′ (cm/s)	S′ (cm/s)		
	6.42 ± 1.25	3.64 ± 1.47	4.19 ± 0.82	8.34 ± 2.04	3.99 ± 0.41	3.99 ± 0.41	Schober, 2003 (n = 7)*	
				9.7 ± 1.36	4.7 ± 0.76	4.7 ± 0.76	Chetboul, 2004 (n = 4)	
	6.8 ± 1.9	6.16 ± 1.61	4.79 ± 1.41	9.28 ± 2.14	3.8 ± 1.02	3.8 ± 1.02	Koffas, 2006 (n = 25)	
	Septal			**Left ventricular free wall**				
Radial	E′ (cm/s)	A′ (cm/s)	S′ (cm/s)	E′ (cm/s)	S′ (cm/s)	S′ (cm/s)		
				9.7 ± 1.7[endo]	4.4 ± 0.82 [endo]	4.4 ± 0.82 [endo]	Chetboul, 2004 (n = 4)	
				2.2±0.74 [epi]	1.9 + 1.9 [epi]	1.9 + 1.9 [epi]	Chetboul, 2004 (n = 4)	
	5.2 ± 1.69	5.34 ± 2.22	5.65 ± 1.26	5.6 ± 1.58	6.16 ± 1.26	6.16 ± 1.26	Koffas, 2006 (n = 25)	

COLOR TDI

Longitudinal	E′ annular	E′ basal	E′ apical	A′ annular	A′ basal	A′ apical	S′ annular	S′ basal	S′ apical	
	5.9 ± 1.8	5.7 ± 1.9	2.3 ± 1.1	3.4 ± 1.4	3.1 ± 1.1	0.9 ± 0.5	4.7 ± 1.4	4.5 ± 1.3	1.7 ± 1.0	Carlos Sampedrano, 2006 (n = 48–56)
	5.5 ± 1.6	5.8 ± 1.6	2.7 ± 1.2	2.9 ± 1.3	2.9 ± 1.0	0.8 ± 0.6	4.4 ± 1.3	4.5 ± 1.2	1.7 ± 0.9	Chetboul, 2006a (n = 100)
		5.9 ± 2.2	2.2 ± 1.0		2.7 ± 1.0	0.7 ± 0.5		4.1 ± 1.1	1.4 ± 0.5	Chetboul, 2006b (n = 22)
Radial	E′ (endo)	E′(epi)	A′ (endo)	A′(epi)	S′ (endo)	S′ (epi)				
	6.1 ± 1.7	2.4 ± 1.0	3.3 ± 1.1	1.3 ± 0.7	5.0 ± 1.1	2.5 ± 0.9		Carlos Sampedrano, 2006 (n = 48–56)		
	5.7 ± 1.5	2.4 ± 1.0	3.0 ± 1.0	1.2 ± 1.0	4.7 ± 1.1	2.5 ± 0.9		Chetboul, 2006a (n = 100)		
	6.3 ± 1.9	2.2 ± 1.0	3.3 ± 1.1	1.2 ± 0.7	4.6 ± 0.8	2.1 ± 0.6		Chetboul, 2006b (n = 22)		

*cats sedated or under general anesthesia. *2D*, two-dimensional echocardiography. 2D and M-mode: *IVS*, interventricular septum; *LVD*, left ventricular diameter; *LVFW*, left ventricular free wall; *d*, diastole; *s*, systole; *FS*%, fractional shortening; *LA*, left atrial diameter; *Ao*, aortic diameter; *D-E ampl*, D-E amplitude; *EPSS*, E-point to septal separation. Systolic time intervals: *VcF*, velocity of circumferential fiber shortening; *PEP*, pre-ejection period. Spectral Doppler: *Ao*, velocity across aortic valve; *PA*, velocity across pulmonic valve; *LV IVRT*, left ventricular isovolumic relaxation time; *PVF*, pulmonary venous flow velocity; *AR*, velocity of PVF atrial reversal wave; *decel*, deceleration. All velocities expressed as peak velocities. Tissue Doppler imaging: *PW*, pulsed-wave; *TDI*, tissue Doppler imaging, *endo*, endocardial; *epi*, epicardial.

NORMAL CARDIOVASCULAR AND RESPIRATORY REFERENCE VALUES FOR THE DOMESTIC CAT

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MACROSCOPIC ANATOMY

Parameter	Value	References
Heart weight - absolute	17.4 g (range: 11–23 g)	Kaneshige, 2006 (n = 10)
Heart weight - relative	4.5 ± 0.2 g/kg	Kaneshige, 2006 (n = 10)
	4.8 ± 1.2 g/kg	Fox, 1995 (n = 36)
Body surface area	$m^2 = 0.087\ kg^{2/3}$	Bartorelli, 1963 (n = 12)

RESPIRATORY PARAMETERS

Parameter	Value	References
Respiratory rate		
Awake adult	37.5 ± 1.5 breaths/min	Orem, 1977
Awake kitten	30 breaths/min	McMichael, 2008
Asleep adult-nonREM sleep	25.5 ± 0.35 breaths/min	Orem
Asleep adult-REM sleep	41.8 ± 1.9 breaths/min	Orem
Anesthetized adult (chloralose)	20.6 ± 6 breaths/min	Nadeau, 1965
Peak inspiratory flow rate		
Awake adult	4.324 L/min	Orem, 1977
Asleep adult-nonREM sleep	3.03 L/min	Orem, 1977
Asleep adult-REM sleep	2.572 L/min	Orem, 1977
Tidal volume		
Awake adult	33.2 ± 0.73 ml	Orem, 1977
Asleep adult-nonREM sleep	35.1 ± 0.43 ml	Orem, 1977
Asleep adult-REM sleep	24.4 ± 0.63 ml	Orem, 1977
Minute volume		
Awake adult	1081 ± 25 ml	Orem, 1977
Asleep adult-nonREM sleep	883 ± 9.9 ml	Orem, 1977
Asleep adult-REM sleep	806 ± 19 ml	Orem, 1977

REM, rapid eye movement

ELECTROCARDIOGRAPHY (Gompf, 1979; Côté, 2010)

Parameter	Value
Rhythm	Normal sinus, sinus tachycardia, or sinus bradycardia, depending on context
P wave amplitude	≤0.2 mV in leads II and aVF
P wave polarity	Positive in II and aVF; may be positive in lead I
P wave duration	≤0.04 seconds (inverse correlation with heart rate)
PR interval	0.04–0.09 seconds (inverse correlation with heart rate)
QRS complex duration	≤0.04 seconds
R wave amplitude	≤0.9 mV in lead II; up to 1 mV in lead V4; no minimum in lead II in the cat
Mean electrical axis	0–160 degrees (frontal plane); highly variable at least in part due to inconsistent limb position and electrode placement
QT interval duration	0.12–0.18 seconds (inverse correlation with heart rate)
T wave amplitude	≤0.3 mV
T wave polarity	Usually positive in lead II, may be negative or biphasic
Precordial leads	R wave ≤1 mV in V2, V4; T wave negative in V10, with R/Q ≤1

MAGNETIC RESONANCE IMAGING (GENERAL ANESTHESIA) (MacDonald, 2006)

Parameter	Median (range)
Left ventricular mass index (g/kg)	1.6 (1.6 – 1.9)
Left ventricular mass (g)	7.7 (6.7–11.1)
End-systolic volume (ml)	1.4 (1.1–2.1)
End-diastolic volume (ml)	4.0 (3.4–4.9)
Stroke volume (ml)	2.6 (2.3–3.3)
Cardiac index (ml/m^2)	75.0 (58–87)
Early filling rate (ml/s)	22.0 (19.6–30)
Maximum filling rate (ml/s)	23.3 (19.6–28.5)
Mean filling rate (ml/s)	7.0 (5.4–8.7)
Early filling %	85.0 (67.7–92.4)

HEMODYNAMICS

Parameter	Value	Technique	References
Central venous pressure	4.2 ± 1.1 mm Hg	Unsedated	Lamont, 2001 (n = 7)
Pulmonary arterial pressure (mean)	16.0 ± 0.9 mm Hg	Unsedated	Lamont, 2001 (n = 7)
Pulmonary capillary wedge pressure	2.9 ± 0.6 mm Hg	Unsedated	Lamont, 2001 (n = 7)
Cardiac output	1.3 ± 0.09 l/min	Thermodilution; unsedated	Lamont, 2001 (n = 7)
Cardiac index	108 ± 38 ml/kg/min	Thermodilution; isoflurane anesthesia	Beaulieu, 2009 (n = 5)
	4.42 l/min/m^2	Thermodilution; unsedated	Lamont, 2001 (n = 7)
Stroke volume*	6.8 ± 0.565 ml	Thermodilution; unsedated	Lamont, 2001 (n = 7)
Stroke index*	23.0 ± 2.1 ml/beat/m^2	Thermodilution; unsedated	Lamont, 2001 (n = 7)
Systemic vascular resistance*	8506 ± 589 dynes X s/cm^5	Thermodilution; unsedated	Lamont, 2001 (n = 7)
Pulmonary vascular resistance*	844 ± 94 dynes X s/cm^5	Thermodilution; unsedated	Lamont, 2001 (n = 7)
Rate-pressure product	34232 ± 1063 beats/min X mm Hg	Unsedated	Lamont, 2001 (n = 7)
RV stroke work index	0.0036 ± 0.00032 g X m/m^2	Thermodilution; unsedated	Lamont, 2001 (n = 7)
LV stroke work index	0.042 ± 0.0041 g X m/m^2	Thermodilution; unsedated	Lamont, 2001 (n = 7)

*calculated value; *RV*, right ventricular; *LV*, left ventricular

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SECTION A

Clinical Entities

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1

Heart Murmurs and Gallop Heart Sounds

Key Points

- Cardiac murmurs can be present due to primary heart disease (for example, hypertrophic obstructive cardiomyopathy with systolic anterior motion of the mitral valve), high-output heart disease (for example, anemia), or they can be innocent. It is usually impossible to differentiate between these possible underlying etiologies on physical examination alone. However, higher-intensity murmurs, such as those that produce a precordial thrill, are more likely to be associated with underlying structural heart disease.
- Although early heart disease can be present in cats without cardiac enlargement on thoracic radiographs, over time the left (most commonly) atrium typically enlarges due to elevated ventricular filling pressures associated with cardiomyopathy. Usually left atrial enlargement is present prior to the development of congestive heart failure. Therefore, thoracic radiographs are a reasonable screening tool when a murmur or gallop sound is detected on physical examination.
- Because early disease can be missed radiographically, echocardiography is the most appropriate screening tool for breeding stock of high-risk breeds (such as Maine coon cats), and in clinical situations where definitive ruling in or ruling out of heart disease is desirable (e.g., preanesthetic evaluation, owner's desire to know, etc.) because cardiomyopathy may be clinically silent.
- Echocardiography is the best diagnostic modality to define underlying cardiac disease and identify the cause of the murmur. It is the only diagnostic tool that allows the clinician to definitively identify the cause of a cardiac murmur that has been noted on physical examination.
- A gallop sound is said to be present when S_3 or S_4 (the diastolic filling sounds) are auscultable. A summation gallop can be ausculted in normal cats when the heart rate is fast enough to allow superimposition of early and late ventricular filling (S_3 and S_4). However, auscultable gallop sounds most often indicate cardiac disease in cats.

INTRODUCTION

A thorough clinical examination is of critical importance for complete investigation of the heart no matter how many advanced diagnostic tests are available. It can provide valuable information about cardiac functional status, circulatory physiology, and the likely etiology of heart disease. History taking and a complete physical examination are always the essential first steps that should guide the choice of diagnostic tests. It is optimal to measure the respiratory rate in the cage or carrier before the patient is stressed by removal for physical examination (Bond 2005). The auscultatory examination of the heart and lungs should include the identification of auscultable normal heart sounds (S_1 and S_2) and the identification of any abnormal heart sounds (Figure 1.1). The most important part of becoming adept with a stethoscope is experience; however, its proper use is essential (Box 1.1).

Approach to Auscultation

Prior to auscultation, the chest should be palpated for the apex beat (the palpable heart beat on the chest surface). The examiner's palpation identifies the location of the strongest apex beat—which is a useful place to begin auscultatation—and, without compressing the chest, characterizes its strength and position. With experience, the astute clinician will come to appreciate the difference between an increased apex beat caused by excitement (which will decrease as the patient calms) and an increased apex beat due to cardiac enlargement (which will be present in a calm patient).

Feline Cardiology, First Edition. Etienne Côté, Kristin A. MacDonald, Kathryn M. Meurs, Meg M. Sleeper.
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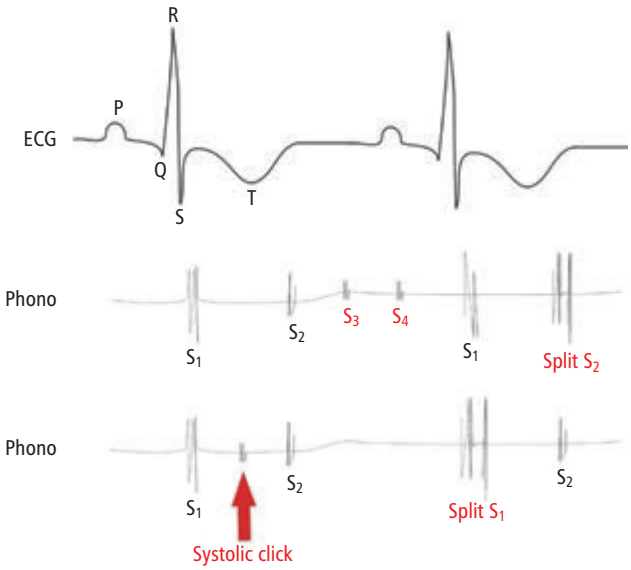


Figure 1.1. Illustration of relationships between the electrocardiogram (ECG) and timing of heart sounds.

Box 1.1. Anatomy of the stethoscope

A good stethoscope should have comfortable earpieces that angle slightly toward the examiner's chin to direct sounds down the ear canals. The chest piece should be capable of detecting high-frequency (normal heart sounds and most murmurs) or low-frequency sounds (S_3 and S_4). When the bell is placed gently against the skin, it accentuates low-frequency sounds, but this capacity is lost if the bell is placed too firmly against the skin because the stretched skin acts as a diaphragm. When the diaphragm side of the chest piece is placed against the chest wall, it tends to minimize the low-frequency sounds and accentuates high-frequency sounds (such as the normal heart sounds, S_1 and S_2). Some chest pieces are capable of acting as both a bell and a diaphragm depending on how firmly they are placed against the chest wall. Such a stethoscope design is actually intended for human cardiology. It may be suboptimal in most cats (exception: Sphynx) because the haircoat interferes with the dual diaphragm-bell function. Stethoscope chest pieces/heads come in a variety of sizes. The pediatric size is advantageous for more specific sound localization in cats; it is often difficult to localize a murmur's point of maximal intensity to the heart base or apex with an adult size chest piece in small animals.

The stethoscope diaphragm is optimal for hearing higher frequency sounds such as the normal first and second heart sounds. Abnormal heart sounds can be defined as either transient (brief in duration) such as split heart sounds or gallop sounds (S_3 or S_4), or of longer duration (e.g., most murmurs). Gallop sounds are low-frequency, diastolic sounds heard best with the bell of the stethoscope (see Box 1.1). Cardiac murmurs are usually associated with turbulent or high-velocity blood flow in the heart or great vessels. A quiet environment is essential for successful auscultation. Extraneous sounds, such as purring, can make auscultation very difficult in some cats. Restraining the animal near a sink with slowly running water or placing a cotton ball soaked with isopropyl alcohol near the cat's face can sometimes be useful to make the cat stop purring. Occasionally, breath sounds or fur rubbing against the stethoscope can be mistaken for sounds originating from the heart. Careful auscultation while watching the cat's breathing pattern can be useful to differentiate heart sounds from breath sounds.

Location and Characterization of Heart Sounds

It is very important that complete auscultation is performed in order to identify all abnormal sounds and rhythms. A simple approach is to auscult the left heart base, medial to the triceps musculature (which is the region of the aortic and pulmonic valve areas) and the left apex (which is the mitral valve area). The right heart base and apex should also be ausculted. The right apex is the area over the tricuspid valve area and tricuspid regurgitation is usually loudest in this region. Murmurs associated with ventricular septal defects are usually loudest at the right heart base but often radiate ventrally to the sternum. In cats, cardiac murmurs of many origins are often loudest over the parasternal region because of the cardiac positioning in this species, particularly as cats age and a greater amount of contact occurs between the sternum and the heart. Therefore auscultation along the left and right parasternum is crucial for a complete assessment. In cats, systolic murmurs loudest at the left apex are most often due to systolic anterior motion of the mitral valve (SAM; most often seen with hypertrophic obstructive cardiomyopathy). Murmurs caused by congenital cardiac malformations are much less common than those caused by myocardial disease because of the distribution of congenital versus myocardial disease in this species. In one echocardiographic survey of 92 cats in shelters, 18–62% had left ventricular concentric hypertrophy but none had a congenital cardiac lesion (Wagner et al. 2010), and in over 400 cats presented to a referral hospital for another study, the ratio of cats with myocardial disease to cats with congenital heart defects was approximately 23:1 (Ettinger 2010). Systolic murmurs that are loudest at the left heart base may be caused by SAM, congenital aortic stenosis, incompletely ausculted patent ductus arteriosus, or physiologic (benign) murmurs. A common cause of physiologic murmurs in cats is mild, dynamic right ventricular outflow tract obstruction, which can produce a systolic

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Box 1.2. Websites with libraries of digital heart and respiratory sounds

Veterinary
http://cal.vet.upenn.edu/projects/newsmcardiac/default.htm
http://www.vetgo.com/cardio/index.php

Human
http://depts.washington.edu/physdx/heart/demo.html
http://www.dundee.ac.uk/medther/Cardiology/hsmur.html
http://www.med.umich.edu/lrc/coursepages/M1/anatomy/html/surface/thorax/hsounds.html
http://www.blaufuss.org/
http://www.bioscience.org/atlases/heart/sound/sound.htm
http://www.med.ucla.edu/wilkes/intro.html
http://www.medstudents.com.br/cardio/heartsounds/heartsou.htm
http://www.csulb.edu/org/college/bme/respiratory_sounds/medic.htm
http://www.cvmbs.colostate.edu/clinsci/callan/breath_sounds.htm
http://www.rale.ca/

murmur along the right or left parasternum (Rishniw and Thomas 2002; Allen 2010). There are several good websites, which include libraries of normal and abnormal heart and respiratory sounds, that are excellent for educational purposes. See Box 1.2 for a list of these sites.

HEART MURMURS

Cardiac murmurs are most often caused by the vibrations associated with high-velocity, disturbed, and turbulent blood flow. Such disturbances may be caused by valvular insufficiency (regurgitation), valvular stenosis, or the presence of a shunt. Disturbed flow that is low velocity, such as pulmonic valve regurgitation/insufficiency, may not be auscultable. Low-velocity abnormal flow often is of no consequence (e.g., pulmonic valve regurgitation) but in some instances may exist with a severe cardiac lesion (e.g., low-velocity flow through a large atrial septal defect). Murmurs can also be created by other physiologic or pathological processes. For example, murmurs are often heard with changes in the viscosity of blood (anemia), and high-output diseases such as hyperthyroidism can be associated with the development of murmurs due to increased velocity of ejected blood. The Reynolds number is used for predicting whether a flow pattern is likely to be laminar or turbulent. Typically it is defined as v_sL/v, where v_s is the mean fluid velocity in ms^{-1}, L is the characteristic length of the blood vessel in meters, and v is the kinematic fluid viscosity in m^2/s. Simplified, the relationship is inertial forces/viscous forces. Therefore, in a large-diameter vessel with rapid flow, or when blood viscosity is decreased (with anemia), there is a tendency toward turbulence. Rapid changes in vessel diameter such as occurs with stenotic lesions may also lead to turbulent flow.

Box 1.3. Grading of murmurs (6 grade scale)

Grade 1: a very soft, localized murmur detected only in a quiet room after intense listening
Grade 2: a soft murmur, heard immediately, localized to a single area
Grade 3: a moderate-intensity murmur that is evident at more than one location
Grade 4: a moderate-intensity to loud murmur that radiates well, but a consistent precordial thrill is not present
Grade 5: a loud murmur accompanied by a palpable precordial thrill
Grade 6: a loud murmur with a precordial thrill, audible when the stethoscope is removed from the thorax

Classification of Heart Murmurs

Murmurs are classified in several ways:

Timing in the cardiac cycle (systolic, diastolic, continuous). While most common cardiovascular diseases in the cat result in systolic murmurs, occasionally feline patients will present with diseases such as mitral stenosis (which results in a diastolic murmur) or patent ductus arteriosus (which results in a continuous cardiac murmur).

Intensity is the loudness of the murmur most often graded using a 6-tier scale. See Box 1.3 for definitions in this classification scheme. The intensity of the murmur does not necessarily correlate with the severity of the underlying heart disease, as some well tolerated abnormalities (such as restrictive/resistive ventricular septal defects) produce very loud murmurs, while some severe lesions may produce soft murmurs (i.e., large unrestrictive/unresistive ventricular septal defect or severe tricuspid regurgitation).

Point of maximal intensity is the area at which the murmur is loudest, and it generally relates closely to the underlying source of turbulent flow. For example, a left-to-right patent ductus arteriosus murmur is usually heard loudest over the left heart base at the pulmonary artery, because high-velocity flow from the aorta is shunting through the duct into the pulmonary artery at this location.

Radiation of a murmur refers to how widely the murmur can be heard from the point of maximal intensity. Generally, the wider the radiation of the murmur, the greater the amount of turbulence being generated.

Pitch and quality are subjective descriptions of the character of a murmur (i.e., coarse, musical, etc.). These descriptors are not precise and do not have the same objectivity as timing and point of maximal intensity.

Associations between Heart Murmurs and Cardiovascular Disease

Certain murmurs are pathognomonic for specific diseases. For example, a continuous murmur at the left heart base is almost always caused by a patent ductus arteriosus (although rarely an aortic-pulmonary window or an arteriovenous fistula can produce a similar murmur). A systolic murmur with a point of maximal intensity at the right heart base is usually associated with a ventricular septal defect. See Box 1.4 for a list of murmur characteristics for the common feline cardiac diseases. However, it is often impossible to differentiate innocent (benign) murmurs from those murmurs secondary to heart disease based on auscultation alone—particularly in the cat, where innocent murmurs are very common. Benign dynamic right ventricular outflow tract stenosis is an important and common cause of innocent murmurs in cats (Rishniw and Thomas 2002; Allen et al. 2010). In the authors' experience, soft (≤ grade 4/6), musical quality murmurs at the heart base that disappear at slower heart rates are more likely to be innocent, particularly if thoracic radiographs reveal a normal heart size; however, enough overlap exists with mild forms of HCM and other disorders to prevent any definitive conclusion from being reached on auscultation alone. While ausculting the feline patient, it is often possible to slow the heart rate by covering the cat's face in the examiner's hand or in the crook of the examiner's arm (Figure 1.2).

Changes in heart murmur characteristics are common when a cat's heart rate changes. The clinical significance of this phenomenon is mixed: in many instances, a murmur that appears only during tachycardia can be benign (e.g., dynamic RVOT outflow obstruction). But in many other cases such a murmur is associated with structural heart disease: a cat with a murmur audible only when the cat is provoked or aroused is 6.1 times more likely to have dynamic ventricular outflow tract obstruction than a cat that does not develop a murmur under the same circumstances (Paige et al. 2009). Therefore, the appearance of a heart murmur, or an increase in murmur intensity, when the heart rate increases is not a finding that definitively confirms either a benign or a pathologic condition. It is also important to remember that it is possible to create murmurs, particularly in lean small animal patients, by applying excessive pressure to the cat's thorax with the stethoscope chest piece/head. When a murmur is ausculted, it is useful to reduce the pressure with which the stetho-

Box 1.4. Murmur characterization based on point of maximal intensity and timing

Left heart base
Systolic
- Aortic stenosis (dynamic or fixed; including hypertrophic obstructive cardiomyopathy)
- Pulmonic stenosis (dynamic or fixed)
- Tetralogy of Fallot
- Physiologic (benign)

Continuous
- Patent ductus arteriosus

Diastolic (rare)
- Aortic regurgitation

Left heart apex
Systolic
- Mitral regurgitation
- Physiologic (benign)

Diastolic (rare)
- Mitral stenosis

Parasternal
Systolic
- Left ventricular outflow tract obstruction (dynamic or fixed; including hypertrophic obstructive cardiomyopathy)
- Dynamic right ventricular outflow tract obstruction
- Ventricular septal defect
- Physiologic

Right heart base
Systolic
- Ventricular septal defect (left to right)
- Dynamic right ventricular outflow tract obstruction

Right heart apex
Systolic
- Tricuspid regurgitation



Figure 1.2. During auscultation, gently covering the feline patient's face with the hand or in the crook of the arm often results in appreciable slowing of the heart rate. This technique is useful to aid in accurately determining the timing of heart sounds, as well as to see whether the murmur character changes.

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scope is applied to the thorax and evaluate whether the intensity of the murmur changes. These "false murmurs" are easiest to produce at the heart base and likely represent compression of the great vessels in an animal with a compliant chest wall.

Prevalence of Heart Murmurs

Heart murmurs are a common finding in the general cat population. Various screening studies have identified a prevalence of heart murmurs in overtly healthy cats of 21% (blood donor candidates; n = 103) (Côté et al. 2004), 16% (privately owned cats; n = 103) (Paige et al. 2009), 27% (same privately owned cats after provocation, wherein the examiner quickly lifted the cat in the air twice) (Paige et al. 2009), and 34% (cats in shelters; n = 199) (Wagner et al. 2010). No association between heart murmurs and overt physical characteristics (coat color, eye color, or breed) has been identified (Côté et al. 2004). Echocardiography in these groups has revealed structural heart disease in a substantial proportion of cases: 16 (16%) of 103 seemingly healthy cats had hypertrophic cardiomyopathy (HCM) in 1 study (5 with a heart murmur, 11 without a heart murmur) (Paige et al. 2009), and 18–62% of 92 cats (depending on criteria used for defining ventricular wall thickness) had left ventricular concentric hypertrophy in another study (Wagner et al. 2010).

The presence of a heart murmur does not confer a diagnosis of a structural cardiac lesion. Between 25% (Bonagura 2000) and 69% (Paige et al. 2009) of cats with murmurs on physical examination have no echocardiographic evidence of heart disease, showing that no conclusions can be drawn about the structure of a cat's heart based on the detection of a heart murmur. Moreover, although they are a common finding, murmurs in cats can be challenging for many practitioners to evaluate for several reasons. The rapid resting heart rate of many cats (routinely > 200 beats/minute), particularly when nervous at a veterinary hospital, can abbreviate the duration of murmurs to such a point that they are not auscultable. Making murmur characterization even more difficult in cats is the close proximity of heart valve areas on the thorax, so clear definition of valve areas is less certain in this species. Additionally the heart position in the thorax changes with age in cats resulting in all valve areas becoming more parasternal in location (Figure 1.3). Despite these difficulties, characterizing murmurs by timing in the heart cycle and the point of maximal intensity is a critical part of the physical examination and should be undertaken using the suggestions presented earlier in this chapter. This accurate characterization of murmurs is crucial for the development of a thorough, specific differential diagnostic list, particularly in young animals. Once the differential diagnosis list is formulated, further diagnostic tests such as thoracic radiography and/or echocardiography can help to establish a definitive diagnosis.

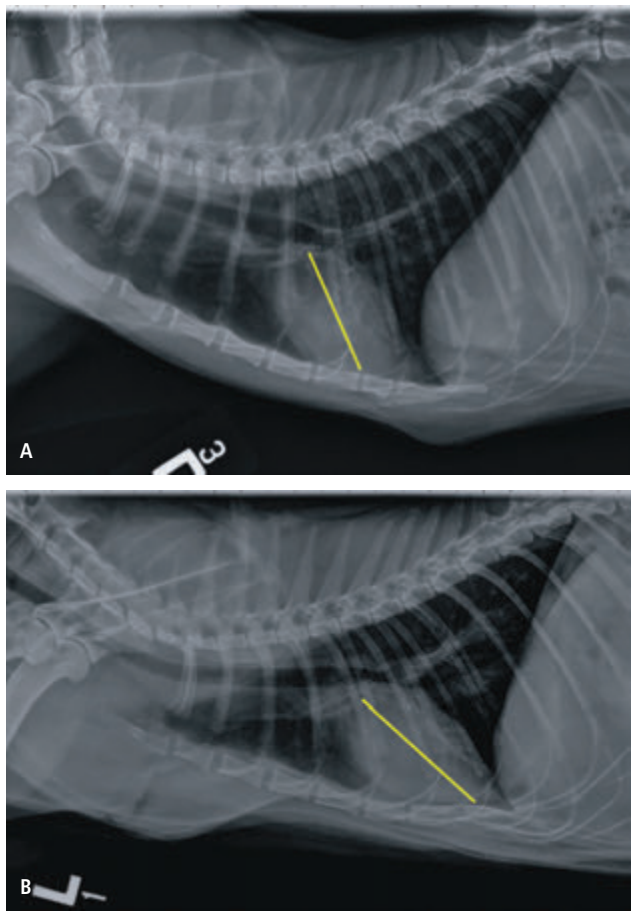


Figure 1.3. Left lateral radiographs from a young cat **(A)** and from a middle-aged cat **(B)** showing the flattened cardiac angle (yellow line), which can occur normally as cats age and which can further concentrate normal and abnormal heart sounds in the parasternal region in adult, older cats.

Although findings on physical examination may suggest the cause of a murmur, echocardiography is the only readily available way to identify the specific cause of a murmur (and the type of heart disease, if heart disease is present). However, echocardiography may not be feasible in all patients with murmurs, due to various constraints. In these individuals, a reasonable approach is serial radiography. If the heart size is normal, hemodynamically significant structural heart disease is unlikely and regular monitoring of heart size with this modality is a reasonable alternative when echocardiography is not available. For example, if the heart size is normal and remains normal over subsequent studies, the patient is unlikely to benefit from cardiac medications. It is important to remember that cardiac medications are not instituted to treat murmurs, but to treat the underlying diseases that produce the murmurs.

Murmur character can change (e.g., become louder) due to physiologic changes in the patient that do not necessarily reflect the presence or progression of cardiac disease.

The mere existence of a heart murmur does not justify beginning cardiac medications. A common conundrum is the cat with an incidentally found heart murmur and grossly apparent cardiac changes on radiographs—but no evidence of congestive heart failure and no overt clinical signs—whose owner is unable or unwilling to pursue echocardiography. At least two approaches are recognized by cardiologists in such cases, and each carries substantial advantages and drawbacks. First, it may be inferred that in a cat with a murmur and heart enlargement noted radiographically, cardiac medications (an angiotensin-converting enzyme inhibitor for concentric or eccentric hypertrophy suggested by generalized cardiomegaly and aspirin for blood stasis associated with atrial enlargement) may be warranted because these abnormalities suggest that cardiac remodeling has occurred. If bursts of tachycardia or an irregularly irregular rhythm at an elevated heart rate is persistent, a drug such as atenolol may be beneficial. On the other hand, echocardiography allows a noninvasive and detailed assessment of cardiac structure and basic cardiac function. The advantages of deciding whether to pursue treatment based on cardiac appearance on radiographs alone are

- Simplicity of diagnostic testing
- Lower expense

The advantages of deciding on whether to pursue treatment based on echocardiographic findings are

- Elimination of misdiagnosis when the heart is in fact structurally normal (but peritoneopericardial diaphragmatic hernia, pericardial effusion, or an artifact such as patient obliquity, expiratory-phase films, or ventrodorsal projection instead of dorsoventral, give the mistaken impression of cardiomegaly on radiographs)
- Quantification of structural lesions (e.g., atrial enlargement, outflow tract velocities associated with obstruction, Doppler assessment of diastolic function) that help in deciding whether to initiate treatment, and may help stratify risk and owner concern/monitoring for the future

It must also be considered that the physical administration of medications to an asymptomatic cat for a period commonly lasting months to years—and attendant discouragement of the patient, the client, or both—may compromise the willingness to pursue later treatment when it becomes indispensable (e.g., CHF, ATE; see Chapter 11).

Therefore, a reasonable approach to the overtly healthy cat with an incidentally discovered heart murmur appears to be to

1. Consider the context of the case, since preanesthetic evaluations or evaluations of breeding stock carry greater implications for the cardiovascular health of patients immediately or for many generations, respectively (and echocardiography would be more immediately important in such patients).
2. Discuss the advantages and drawbacks of echocardiography with the cat's owner, recommending echocardiography if it is feasible.
3. Pursue treatment if indicated based on diagnostic imaging findings following a realistic and comprehensive discussion with the owner of advantages and drawbacks of such treatment, particularly when cardiac morphology has not been determined.

GALLOP HEART SOUNDS

Key Point

The term *gallop rhythm* is a misnomer because the underlying cardiac rhythm is most often sinus. The additional heart sound, which results in a triple cadence in conjunction with the normal first and second heart sounds, is more accurately called a *gallop heart sound*.

The third (S_3) and fourth (S_4) heart sounds are not normally audible during cardiac auscultation in small animals. When present in dogs or cats, the extra sound results in a triple beat cadence reminiscent of a cantering horse. Because of this similarity, some refer to it as a gallop rhythm; however, this term leads to confusion because a true arrhythmia (change in the rhythm of cardiac electrical activity) is not present. In fact, gallop sounds are usually associated with sinus rhythms. An extra heart sound (and this triple-sound, galloping character of each heartbeat) can be noted due to the presence of auscultable S_3 or S_4 sounds, a systolic click, or a split heart sound, but only the diastolic sounds (S_3 and S_4) are correctly termed "gallop" sounds. The various extra sounds occur secondary to differing abnormalities and mechanisms, so accurate identification is important. S_3 and S_4, as diastolic filling sounds, are best ausculted using the bell of the stethoscope (see Box 1.1).

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In small animals, gallop sounds (S_3 and S_4) are generally reflective of abnormal diastolic function. As blood from the atria fills the ventricles during diastole, rapid deceleration of the blood column in a stiff, noncompliant ventricle (such as occurs with hypertrophic or restrictive cardiomyopathy) results in auscultable vibrations. S_3 sounds are generated by rapid ventricular filling during early diastole (see Figure 1.1). When present in a cat, they imply ventricular dilation and/or systolic dysfunction. Other possible causes include hyperthyroidism and anemia. The S_4 sound is associated with active ventricular filling caused by atrial contraction and occurs late in diastole (see Figure 1.1). S_4 sounds are most commonly ausculted in cats with hypertrophic cardiomyopathy. However, it is often difficult to differentiate between S_3 or S_4 when the heart rate is fast, and when they merge, the result can be a single auscultable extra sound, called a *summation gallop*. Summation gallop sounds occasionally can occur in some normal cats when their heart rates are fast enough that S_3 and S_4 become audible and are superimposed. However, in general, gallop sounds suggest underlying structural heart disease and further diagnostic tests are warranted. Because their presence is often associated with elevated left ventricular filling pressure, the presence of a gallop sound (S_3, S_4, or summation) is highly suggestive of imminent or existing congestive heart failure in a cat exhibiting respiratory distress or receiving fluid therapy.

Systolic clicks are a different type of third heart sound with a very different causative mechanism and character. Systolic clicks are short, midsystolic sounds that are higher in frequency than gallops sounds. When systolic clicks are present, the result is a triple cadence, which can be confused with that produced by a gallop sound, especially given the rapid heart rate of many cats in the clinical setting. However, the high-frequency sound of a systolic click is distinctly different from the low frequency of a gallop sound; therefore, the two can be differentiated by their frequency, with clicks mimicking the normal heart sounds (which are high-frequency and thus more easily heard with the diaphragm of the stethoscope) and gallops being more prominent during light application of the bell of the stethoscope to the chest surface (low-frequency sounds). Systolic clicks are most often associated with abnormalities of the atrioventricular valves, such as mitral valve prolapse. In general, systolic clicks, and specifically, mitral valve prolapse, are rare in the feline population, although anecdotally such clicks may be noted in cats with hypertrophic cardiomyopathy.

Split heart sounds can also produce a triple cadence as already described and thus constitute another differential diagnosis for gallop sounds. Asynchronous closure of the atrioventricular valves (S_1) or the semilunar valves (S_2) can result in split heart sounds. Split first heart sounds and split second heart sounds are very rare in cats. In humans and dogs, split second heart sounds can occur with pulmonary hypertension and delay of pulmonic valve closure, but this finding has not been recognized in cats with pulmonary hypertension (see Chapter 25, "Pulmonary Thromboembolism and Pulmonary Hypertension").

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2

Exercise Intolerance and Syncope

Key Points

- Syncope is an uncommon occurrence in cats.
- When it occurs, it most commonly is the result of an arrhythmia—typically a pathologic bradycardia—in a cat with underlying structural heart disease, but systemic illness and tachycardias can cause syncope in cats.
- Detailed diagnostic evaluation is essential in order to confirm syncope and rule out neurologic or other phenomena.

INTRODUCTION

Syncope is a "sudden and brief loss of consciousness associated with a loss of postural tone, from which recovery is spontaneous" (Kapoor 2000). To the layperson, syncope is "fainting" or "passing out." A synonym for syncope caused by a cardiac arrhythmia is a "Stokes Adams attack" or "Stokes Adams syndrome" (Harbison et al. 2002).

ETIOLOGY AND PATHOPHYSIOLOGY

Syncope is caused by a temporary, marked decrease or cessation of cerebral blood flow. It manifests as sudden-onset ataxia and disorientation, immediately followed by loss of all skeletal muscle tone and consciousness. This collapse and unconsciousness may occur quietly or may be preceded by profound disorientation, vocalizing, and signs of extreme distress. In either scenario, clients witnessing syncope often describe initially believing that the cat has died. Indeed, syncope may be terminal in cases where the incriminating mechanism—e.g., arrhythmia—does not resolve quickly. Therefore one of the characteristics of syncope is that it rarely lasts more than a few seconds and virtually never more than 30 seconds; longer-lasting episodes are more likely to be seizures or other disorders (Figure 2.1). The profound hypotension that accompanies syncope (mean arterial pressure typically is <25 mm Hg) (Kittleson 1998), if it persists sufficiently long as to cause >30 seconds of unconsciousness, is likely to be fatal. When the mechanism causing syncope (e.g., arrhythmia) terminates, a spontaneous resumption of adequate cerebral circulation is responsible for the return of consciousness. Brief reactive cerebral hyperemia can occur initially, but complete recovery likely takes longer than clinical signs suggest. For example, a persistently subnormal cerebral blood flow has been noted for 3 hours after a 1-minute burst of ventricular tachycardia at 300 beats/minute in cats (Kobari et al. 1992). Nevertheless, the most dramatic overtly visible aspect of termination of syncope is the speed and completeness of clinical recovery. In contrast to patients with seizures or other forms of episodic disturbances, syncopal patients generally recover a normal or near-normal mentation, posture, gait, and general demeanor within 1 minute of regaining consciousness. The mechanism of recovery separates survivors of syncope from those patients in which syncope becomes sudden cardiac death (Figure 2.2). Recovery is likely due to multiple factors that make up the response to acute cerebral hypoperfusion, including reduced baroreceptor

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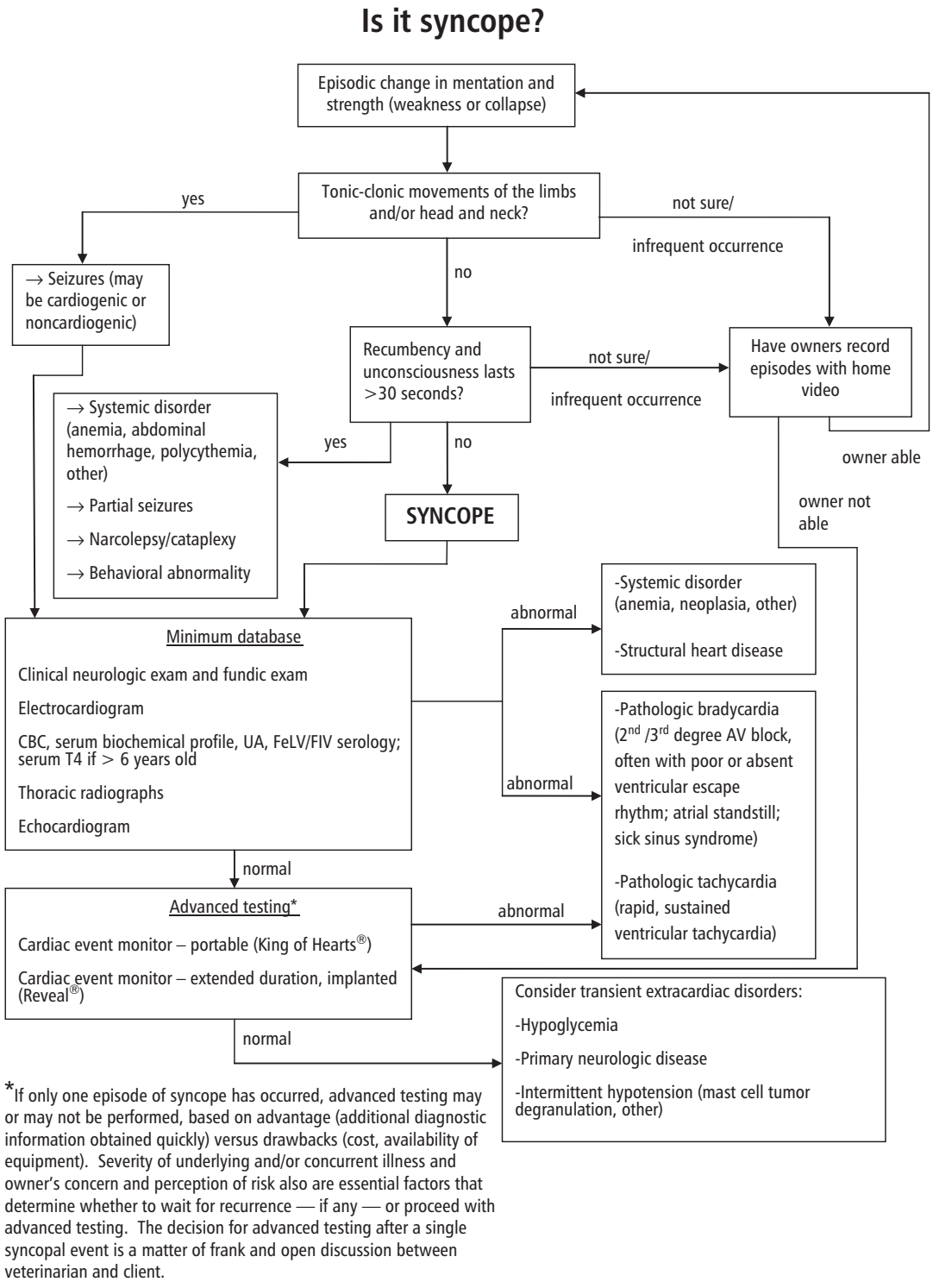


Figure 2.1. Diagnostic algorithm for transient episodes suspected of being syncope.

discharge (peripheral arterial hypotension eliciting a decrease in parasympathetic tone), the central nervous system ischemic response (sympathetically mediated arterial constriction originating from hypercarbia in the vasomotor center of the medulla), and the Cushing reaction (rise in arterial pressure in response to elevated intracranial/cerebrospinal fluid pressure) (Guyton and Hall 2006). The nonchalance with which cats walk away from a syncopal episode and resume their activities is often striking to owners. A substantial exception is the

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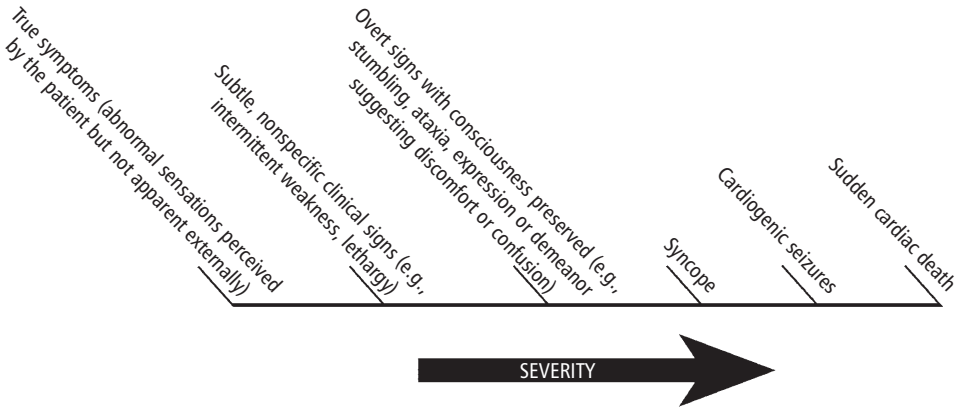


Figure 2.2. Scale of severity of clinical signs caused by poor cerebral perfusion (forward heart failure), from least to most severe.

cat in whom a persistent cause for syncope only partially resolves such that the end of one episode of syncope is not clearly distinguished from the onset of the next (Fox et al. 1991; Penning et al. 2009). Such patients, who may experience dozens of syncopal episodes daily, typically have a grave prognosis if the cause of the syncope is not identified and treated immediately.

While neurologic disease (Darke et al. 1989), and autonomic disturbances (Kapoor 2002) may cause syncope, these etiologies are rare in feline syncope. Rather, syncope in cats is generally associated with structural cardiac lesions and a concurrent arrhythmia: profound tachycardia or profound bradycardia, with the latter appearing to be more common. Bradycardia decreases cardiac output (stroke volume × heart rate), causing cerebral hypoperfusion. This is especially likely to cause overt signs like syncope when bradycardia is very severe (e.g., feline heart rate = 100 beats/minute or less) and peracute in onset, before vasoconstrictive and other adaptive mechanisms have had sufficient time to optimize cerebral perfusion. Severe tachycardias also can produce cerebral hypoperfusion; at very rapid heart rates, diastolic filling time is compromised, and stroke volume can fall dramatically (see Chapter 18). For example, anesthetized cats experimentally induced to have ventricular tachycardia at 300 beats/minute for 1 minute experience a 30% decrease in cerebral blood flow (Kobari et al. 1992). Therefore, a patient suspected of having syncope presents 3 levels of diagnostic challenge: Is it truly syncope? If so, is it due to an arrhythmia? And if it is, is the arrhythmia a tachycardia or a bradycardia?

In feline general practice, syncope is an uncommon clinical sign. When it does occur, an underlying structural heart lesion is generally present: syncope in cats has been associated with hypertrophic cardiomyopathy (HCM; n = 23) (Rush et al. 2002; Kaneshige et al. 2006; Fox et al. 1995; Stamoulis et al. 1992; Harpster 1977; Johnson and Sisson 1993), heartworm disease (HWD; n = 6) (Malik et al. 1998; Atkins et al. 1985), atrial septal defect (ASD) (n = 2) (Chetboul et al. 2006), arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C; n = 2) (Fox et al. 2000; Harvey et al. 2005), cardiac lymphoma (Meurs et al. 1994), hyperthyroidism (Forterre et al. 2001), hyperthyroidism in which syncope and 3rd-degree AV block occurred during methimazole treatment but syncope resolved after radioiodine therapy despite the persistence of 3rd-degree AV block for an additional 32 months (Johnson and Sisson 1993), defecation in a cat with multiple systemic and cardiac problems (Whitley and Stepien 2001), and a current diagnosis (Darke et al. 1989) or distant history (Fox et al. 1991) of dysautonomia. In 5 cats with syncope, echocardiographic results were within normal limits (Fox et al. 1991; Stamoulis et al. 1992; Ferasin et al. 2002; Willis et al. 2003; Côté et al. 1999); in 2 of these, necropsy revealed excessive left ventricular moderator bands and myocardial and conductive tissue fibrosis (Liu 1994) and normal gross and histologic results (Willis et al. 2003). The latter results are mirrored in human medicine, where in one-third of patients with syncope, an inciting cause is never found (Kapoor 2002).

SIGNALMENT

There is no distinguishing feature about the signalment of cats with syncope. It appears to mirror the expected signalment of cats with the associated structural heart disorders described above.

HISTORY AND CHIEF COMPLAINT

Classic syncope is a sudden-onset, sudden-termination loss of consciousness and ambulation. Owners observing

a cat's episode of syncope describe such signs as "appearing dazed," "seeming glassy-eyed," "stumbling," vocalizing, ptyalism, and/or appearing disoriented before collapsing, or the cat may simply collapse without forewarning. The prelude is variable, and cats may have syncopal episodes while physically active, while at rest, or between the two extremes. For example, in the midst of physical exertion, a cat will typically dramatically slow down, such as suddenly slowing mid-run, lie in sternal recumbency, and then roll into lateral recumbency, unconscious. Although the duration of unconsciousness in syncope is very brief (<30 seconds), an owner may not recall time accurately due to his or her own emotional distress. Individual cats may have specific inciting factors (e.g., type of intense physical activity or arousal, such as being startled or stimulated to play) that owners recognize as often leading to syncope. The main value of recognizing such triggers is to recommend their reduction so as to avoid more episodes.

There may or may not be prodromal signs, physical manifestations suggesting that syncope is about to occur as described above. Historically, prodromal signs were felt to indicate seizures rather than syncope, but evidently the onset of syncope may be preceded by several seconds' duration of such signs while consciousness is maintained. These signs may sometimes terminate before collapse/syncope occurs, a situation referred to as *near-syncope*, *presyncope*, or *aborted syncope*.

PHYSICAL EXAMINATION

Physical findings likewise reflect the inciting cause. A heart murmur, gallop sound, arrhythmia (particularly bradycardia), or combination of these signs is a common finding. Many cats with syncope, however, present only mild if any abnormal physical findings, or physical abnormalities that are sufficiently mild (e.g., soft murmur in an otherwise bright, alert, responsive cat; echocardiogram is within normal limits) as to make the clinician question whether they are related to the more dramatic clinical signs of syncope.

DIFFERENTIAL DIAGNOSIS

Differentiation between syncope and other phenomena is described in Figure 2.1. The distinction between collapse and syncope should be clear, because collapse indicates a loss of muscle tone, whereas syncope specifically identifies collapse with concurrent loss of consciousness. In practice, however, collapse and syncope can represent discrete points on a spectrum of clinical signs (see Figure 2.2). The mildest point on this spectrum likely consists of subtle weakness or sluggishness, or even milder true symptoms that only the cat feels but that are not noted by owner or clinician. Increasingly severe manifestations are found across the spectrum, and at the most extreme point of severity lies sudden cardiac death. Often, a patient's episodes may blur the line of demarcation between collapse and syncope (Fox et al. 1991; Penning et al. 2009), and owners, or even attentive clinicians, may be uncertain as to whether consciousness was preserved during a brief, subtle, and/or poorly witnessed episode. Therefore, cats that manifest any clinical signs on this spectrum are candidates for evaluation as described in Figure 2.1.

Seizures are easily distinguished from syncope based on well-recognized characteristics (see Figure 2.1). However, in certain individuals with syncope, seizures can occur during the syncopal event. It is theorized that cerebral hypoxia is responsible for the crossing of the seizure threshold. In such cases, features of both syncope at first, and then seizures, are seen, with the features of seizures often predominating in an owner's or clinician's memory. Any cat thought to have seizures but that also has manifestations of heart disease (e.g., heart murmur or arrhythmia on physical exam; abnormalities on the electrocardiogram (ECG), thoracic radiographs, or echocardiogram) should be investigated thoroughly as indicated in Figure 2.1. Testing is particularly important if the neurologic signs are about to be pursued with cerebrospinal fluid sampling or imaging, which generally require general anesthesia and therefore could pose a substantial risk to an uncontrolled arrhythmia patient. Instances of cats being induced under general anesthesia for magnetic resonance imaging of the brain (to investigate seizures) and developing intractable, fatal 3rd-degree AV block (because the seizures were cardiogenic and a subtle clue such as a relative bradycardia or soft heart murmur had not been detected) have been reported anecdotally. Vigilance and complete diagnostic evaluation of the cardiovascular system is warranted in these cases: in a landmark study, 31/74 (41%) of human epilepsy patients were found to be misdiagnosed and to in fact have a cardiovascular cause for their clinical disorder (Zaidi et al. 2000).

DIAGNOSTIC TESTING

In all cats with suspected or confirmed syncope, a complete medical and cardiovascular evaluation is warranted (see Figure 2.1). Specific parameters for investigating cardiac arrhythmias are described further in Chapter 18. In most cases, a bradyarrhythmia is the underlying arrhythmia. Two cases of syncope in cats with HCM—one with supraventricular tachycardia (Harpster 1977) and one with ventricular tachycardia (Bright and Call 2000)—are important exceptions.

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TREATMENT

Ideally, the underlying cause is addressed. Doing so is often difficult, both because many lesions are irreversible (e.g., fibrosis of the conduction system in HCM [Kaneshige et al. 2006]) and because often the cause of syncope is not recognized (e.g., structurally normal heart and no identifiable systemic extracardiac disorder).

When a cardiac arrhythmia is conclusively identified at the time of a syncopal event, antiarrhythmic treatment may be initiated. Broadly, such treatment generally consists of medications for pathologic tachycardias and cardiac pacemaker implantation for pathologic bradycardias (see Chapter 18 for detailed recommendations based on the specific arrhythmia identified).

OUTCOME AND PROGNOSIS

Ten cats with HCM and syncope lived 28–1505 (median = 654) days after initial diagnosis, which was longer than the median survival times of cats with HCM and congestive heart failure (563 days) or those with HCM and aortic thromboembolism (184 days), but shorter than the median survival time of cats with HCM and no overt clinical signs (1129 days) (Rush et al. 2002). The influence of long-term treatment such as pacemaker implantation is not described in this case series, and thus it is unknown whether these survival times were naturally occurring, treated, or some of each.

EXERCISE INTOLERANCE

Exercise intolerance occurs as a result of poor oxygen delivery to skeletal muscle, to the brain, or both. It is a rare chief complaint in cats. In a nocturnal species such as the cat, whose members are estimated to spend 85% of a given day sleeping, it is understandable that exercise intolerance is rarely noted, and the subject should be brought up by the clinician with this acknowledgment immediately, to reassure the cat's owner that the clinician has a good understanding of feline behavior in general.

When exercise intolerance occurs in the cat, owners typically note that a cat fails to continue an activity that was previously accomplished without difficulty. Such activities are often initiated by the owner and include chasing a toy such as a feather on the end of a metal wire, running after the dot from a laser pointer, or playing fetch. An exercise-intolerant cat may stop during exertion, with or without signs of dyspnea such as open-mouth breathing/panting and exaggerated abdominal respiratory movements (exertional dyspnea), or in severe cases, pallor and/or cyanosis. Identifying the inciting causes here is useful because owners can be instructed to reduce the intensity and duration of these activities to a level that is well below the level of intolerance. Cats subject to exercise intolerance appear to be most commonly affected with hypertrophic cardiomyopathy that is characterized by moderate to marked ventricular thickening, left ventricular outflow tract obstruction, and/or congestive heart failure. A subset of cats with compensated hypertrophic cardiomyopathy that are treated with beta-blockade (e.g., atenolol at a standard dosage) have improved in their exercise capacity, indicating an unnoticed intolerance to exercise previously, likely due to left ventricular outflow tract obstruction or angina pectoris. Because exercise intolerance and syncope share a mechanism of reduced oxygen delivery to tissues, it is expected that the two clinical syndromes may overlap in a given patient (see Figure 2.2).

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3

Pleural Effusion

Key Points

- Pleural effusion can occur with right or left heart disease in cats, but other causes are also common. If an echocardiogram reveals normal left and right atrial size, heart disease is unlikely to be causing the effusion.
- Pleural effusion responds very slowly to diuretic therapy. If the effusion is sufficient to cause dyspnea, therapeutic thoracocentesis should be performed rather than relying on medical diuresis.

Pleural effusion is the abnormal accumulation of fluid in the pleural space. It can result from conditions that increase systemic and pleural capillary hydrostatic pressure (e.g., congestive heart failure), decrease plasma oncotic pressure (i.e., hypoproteinemia), increase capillary permeability (e.g., vasculitis), or cause lymphatic obstruction (e.g., neoplasia). Pleural effusion has traditionally been thought to occur secondary to right heart failure and elevated right atrial pressure because pleural fluid is primarily cleared by the parietal pleural lymphatics, which empty into the systemic veins. However, a retrospective study of human cardiac patients demonstrated that cardiogenic pleural effusion is most often associated with left heart disease and elevated left atrial pressures (Weiner-Kronish et al. 1967). Cats also develop pleural effusion as a consequence of left heart disease. The most often proposed hypothesis for this development is that the visceral pleural veins drain into the left atrium and the parietal pleural veins empty into the cranial vena cava. When left atrial pressure increases, visceral pleural venous drainage is inhibited, allowing transudation through the vein walls and into the pleural space. Therefore, either left or right heart disease can lead to pleural effusion in the cat, although diseases affecting the left heart are more common in the species than are right heart diseases.

The type of fluid that accumulates depends on the underlying etiology. Chylous effusion is common in cats and can be idiopathic or secondary to poor lymphatic drainage. Hemorrhagic effusion can occur secondary to trauma, coagulopathies, or vascular erosion by a neoplastic process. Transudates and modified transudates occur secondary to processes that lead to increased hydrostatic pressure, decreased oncotic pressure, and/or increased vascular permeability. See Box 3.1 for description of various fluid characteristics. In a series of 82 feline cases of pleural effusion, underlying disease was diagnosed in 63 of the cats. In these 63 cats, 17% were found to have cardiac disease and the pleural effusions associated with the represented heart diseases (hypertrophic cardiomyopathy, unclassified cardiomyopathy and pericardial-peritoneal diaphragmatic hernia in this series) were modified transudates, exudates, or chylous effusions (Davies and Forrester 1996). In a large series of cats with hypertrophic cardiomyopathy (n = 260), pulmonary edema was the more common cause of dyspnea when congestive heart failure was present. In this series, only 15% of the cats with congestive heart failure had pleural effusion of sufficient quantity felt to be responsible for dyspnea. However, pleural effusion was present in 34% of the cats that underwent thoracic radiography (Rush et al. 2002). Echocardiography is the

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Box 3.1. Difference between transudate, modified transudate, exudate

	Transudate	Modified Transudate	Exudate	Chylothorax*	Sanguineous
Total protein (g/dl)	<2.5	2.5–3.5	>3.0	Variable and measurement is inaccurate due to high lipid content in fluid	≥25% of peripheral blood
Cell count (cells/μl)	<1000	500–10,000	>5000	<10,000	Nucleated cell count ≥25% of peripheral blood
Cell type	Monocytes, small lymphocytes, mesothelial cells, nondegenerate neutrophils, neoplastic cells	Eosinophils, monocytes, small lymphocytes, mesothelial cells, neutrophils, neoplastic cells	Activated macrophages, degenerate neutrophils, bacteria, eosinophils, mesothelial cells, mixed lymphocytes, neoplastic cells	Small lymphocytes, neutrophils, lipid-laden macrophages	
Typical causes	Congestive heart failure, hypoproteinemia (liver failure or systemic disease), chronic infection or inflammation, etc.	Congestive heart failure, neoplasia, systemic inflammation or infection	Pyothorax, FIP	Congestive heart failure, neoplasia, trauma, idiopathic	Trauma, neoplasia, coagulopathy, diaphragmatic hernia, etc.
Initial treatment	Thoracocentesis if necessary for emergency stabilization and then diagnostics to determine underlying disease	Thoracocentesis if necessary for emergency stabilization and then diagnostics to determine underlying disease	Thoracocentesis if necessary for emergency stabilization and then diagnostics to determine underlying disease	Thoracocentesis if necessary for emergency stabilization and then diagnostics to determine underlying disease	Thoracocentesis if necessary for emergency stabilization and then diagnostics to determine underlying disease

*If the effusion is truly chylous, it will contain a higher concentration of triglycerides than simultaneously collected serum.

best way to determine whether underlying heart disease is the cause of developing pleural effusion. If the heart is normal echocardiographically, other possible etiologies should be evaluated. Occasionally, the diagnosis may be more challenging if incidentally found heart disease is not felt to be of a sufficient magnitude to explain pleural effusion (see Chapter 24).

The most common historical and physical exam findings in cats with pleural effusion include dyspnea and tachypnea. Affected cats usually have short, shallow respiratory patterns that may be especially apparent to owners as prominent abdominal wall movements (see Chapter 4). Typically, dull ventral heart and lung sounds are appreciated unilaterally or bilaterally on pulmonary auscultation. Coughing or cyanosis is rare. The degree of respiratory compromise is correlated with the volume of effusion present; however, a patient with slowly accumulating fluid may be much less compromised than a cat with an equivalent volume of pleural effusion that formed rapidly. Other abnormal physical exam findings depend on the underlying disease present. A noncompliant cranial chest is consistent with a cranial mediastinal mass causing the effusion. Patients with heart disease usually have concurrent signs attributable to heart disease (murmurs, arrhythmias, etc.); however, some will have normal cardiac auscultatory findings, especially if the effusion masks subtle heart sound abnormalities. Thoracocentesis should be performed before radiography if the animal is severely dyspneic, and thoracic ultrasound, if available, is a rapid means of confirming the presence of free fluid in the pleural space and reduces the risk of centesis in a patient with no effusion, as may occur with blind thoracocentesis.

Radiographs reveal the underlying cause of fluid accumulation in a subset of cats; however, in the majority of cats, pleural fluid accumulation is identified without an underlying cause determined by radiographs. Often pleural effusion obliterates the cardiac silhouette making detection of heart enlargement challenging; dorsal displacement of the carina on the lateral view can help identify enlargement of the cardiac silhouette if it

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Figure 3.1. Comparison of DV **(A)** and VD **(B)** radiographic projections from 2 cats with a similar amount of pleural effusion (based on echocardiographic examination). Note the cardiac silhouette is obliterated by the effusion in the DV view.

is severe. Ventrodorsal thoracic radiographs are superior to the dorsoventral views for assessing heart size when pleural effusion is present because the effusion pools dorsally and allows better assessment of possible cardiomegaly (Fig. 3.1). However, in many cases a dorsoventral view to prove effusion is present prior to thoracocentesis is justified because animals with large-volume pleural effusion are often quite dyspneic and ventrodorsal films are unsafe. If life-threatening dyspnea is present, cage rest, supplemental oxygen, ± mild sedation may be necessary before the cat will allow thoracocentesis. Butorphanol (0.2 mg/kg) with or without benzodiazepine (diazepam or midazolam 0.1 mg/kg) is a commonly used protocol. Intravenous administration is preferred for a more rapid and predictable onset, unless restraint for injection is likely to destabilize the patient. In some cases it may be worthwhile to repeat radiographs after the effusion has been removed for better assessment of lung fields and the cardiac silhouette. Thoracic radiographic findings consistent with a diagnosis of pleural effusion vary with the amount of effusion and include widened interlobar fissures, retraction of the pleural surface of the lung from the thoracic wall, blunting of the costophrenic sulci in ventrodorsal radiographs obscuring the diaphragmatic outline, increased radiopacity of the thorax, ± obliteration of the cardiac silhouette (Figure 3.2).

Echocardiography is critical to rule in, or out, heart disease as the underlying cause of effusion and can be



Figure 3.2. Lateral **(A)** and DV **(B)** radiographic projections from a cat with severe pleural effusion. Note the scalloped appearance of the lung lobes and the obliteration of the cardiac silhouette.

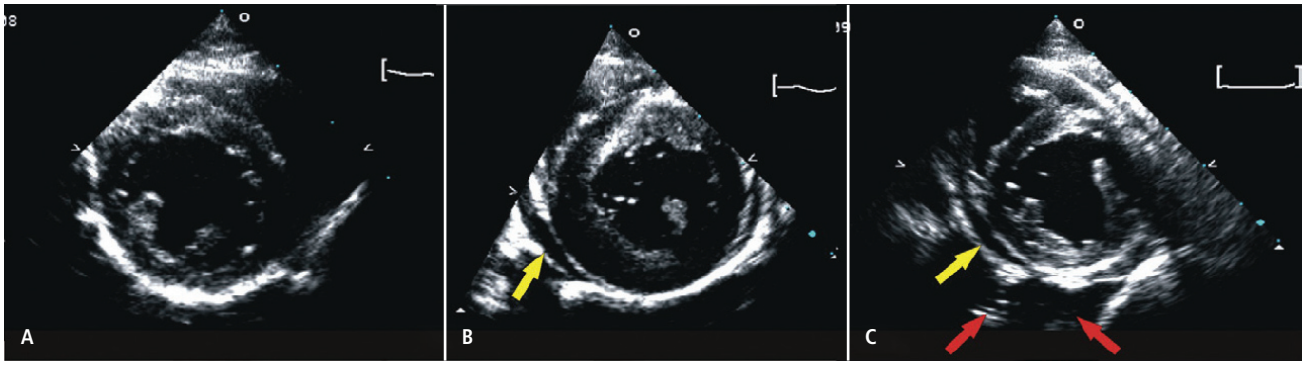


Figure 3.3. Echocardiograms from a normal cat **(A)**, a cat with pericardial effusion **(B)**, and a cat with pericardial effusion and pleural effusion **(C)**. The yellow arrows indicate pericardial effusion; the red arrows indicate pleural effusion.

performed once the cat's respiratory effort and rate have improved following thoracocentesis. If atrial enlargement is not evident, a cardiogenic cause of the pleural effusion is very unlikely. Pleural effusion is visible on thoracic ultrasound as intrathoracic anechoic space surrounding the heart and lungs. If the effusion is cellular or contains a marked amount of fibrin, echogenic debris may be visible floating in the free fluid. Pericardial effusion is also usually anechoic in appearance (Figure 3.3).

Therapeutic thoracocentesis should be performed in any cat that is dyspneic in association with moderate or marked pleural fluid accumulation. Diuretic therapy is useful to slow future pleural effusion development, but it is not adequate therapy alone in a dyspneic animal. See Box 3.2 for a description of the centesis technique. Thoracocentesis is useful for therapeutic and diagnostic purposes. Although there may be considerable overlap between fluid type and underlying disease, cytologic evaluation can be helpful to directly identify the underlying cause of fluid accumulation, particularly in cases of neoplasia. Cardiogenic effusions are usually sterile and therefore bacterial cultures are not routinely performed if the effusion appears to be cardiac in origin.

In cats with congestive heart failure and pleural effusion, respiratory rate and effort should be monitored closely by the owner after discharge from the hospital to determine when repeat ultrasound examinations or radiographs are warranted, when medication changes are necessary, and/or when repeat thoracocentesis is necessary. The authors find it helpful for owners to maintain a log of the daily respiratory rates in animals with congestive heart failure. Owners are directed to contact us if the respiratory rate begins to rise. Typically, a cat that is comfortable and free of large-volume pleural effusion should have a respiratory rate at rest that is less than 30 breaths/minute in the home environment. This method allows worsening heart failure to be addressed

Box 3.2. Thoracocentesis procedure

For most cats, a 19 gauge butterfly catheter is the easiest method for thoracocentesis, and the animal is usually restrained in sternal recumbency. In very obese cats, an 18 gauge over-the-needle catheter may be necessary to penetrate the body wall (kinks easily; body wall stability is important to reduce this occurrence). Most animals tolerate the procedure well, but adequate sedation is important when required. When using sedation, it is best to choose medications that will not depress cardiac or respiratory function. Mild sedation can be achieved with 0.3 mg/kg butorphanol and 0.3 mg/kg midazolam IV or IM, if necessary. Local anesthesia (1 cc of 2% lidocaine) may be helpful and allow the clinician to avoid sedation in some animals. A 3-way stopcock should be placed between the butterfly and a 35–60 cc syringe (Figure 3.4). The stopcock minimizes the risk of pneumothorax as the syringe is used to withdraw effusion with gentle pressure. If available, ultrasound guidance is optimal to ensure the butterfly is directed toward an effusion pocket. If ultrasound is not available to localize the largest pocket of fluid accumulation, the centesis is performed at the 7th or 8th intercostal space at the costochondral junction. The thorax is widely clipped and surgically prepped. Some clinicians wear sterile gloves and others do not; in either case, the sterile field must remain intact during the procedure and reprepped if sterility is broken. The needle is advanced through the skin, subcutis, and intercostal muscles and pleura while one or two technicians gently restrain and distract the patient. Negative pressure is applied continuously until fluid appears within the syringe (Figure 3.5). The effusion is withdrawn until resistance to the suction is felt. The gold standard for preventing thoracocentesis-associated complications, measurement of intrapleural pressures, is not yet used clinically in feline medicine. Limitations to the number of times the procedure can be performed consist of the cat's tolerance, compliance of the lungs, the owner's ability to return for treatments, and rarely protein loss (exudates).

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Figure 3.4.



Figure 3.5.

before progressing to an emergent situation in most cases. Chronic pleural effusion may lead to pleural fibrosis and development of clinical signs with less fluid accumulation (Fife and Côté 2000). Additionally, fluid may become loculated and more difficult to remove by thoracocentesis over time. Medical management of congestive heart failure is discussed in Chapter 19.

Although thoracocentesis is a low-risk procedure when performed by a skilled operator and with a cooperative patient, there are several possible risks including lung puncture and pneumothorax, reexpansion pulmonary edema, hemodynamic collapse secondary to vagally mediated sinus bradycardia, and bronchopleural fistula (Fife and Côté 2000). These sequelae are uncommon; however, the risk increases as greater volumes of effusion are removed. Therefore, some clinicians prefer to minimize this risk by removing large volumes of pleural effusion over separate thoracocentesis procedures (for example, removal of 120 ml at a time and allowing the cat to rest for several hours or overnight before repeating the procedure).

Chronic therapy to address pleural effusion is dependent on the underlying cause. For example, management of heart disease and congestive heart failure is crucial in those patients with underlying heart disease as a cause. Neoplasia may be addressed with chemotherapy, radiation therapy, surgical removal, or debulking, or some combination of these modalities. Similarly, underlying liver disease or protein losing nephropathy should be addressed when present. Occasionally an underlying cause of pleural effusion is not found and empirical therapy with low-dose diuretics (to slow fluid accumulation) and periodic thoracocentesis is necessary. Several palliative surgical treatments are available if refractory pleural effusion persists in spite of these therapies. These procedures attempt to provide additional thoracic fluid drainage or decrease pleural effusion production (Sanders and Sleeper 2004).

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4

Dyspnea and Cough

Key Points

- Episodic, short duration dyspneic events are not typical of congestive heart failure. Dyspneic periods secondary to congestive heart failure tend to be progressive in nature.
- Open mouth breathing/panting in cats can occur secondary to respiratory difficulty or anxiety. Anxious, preoccupied mentation is equally or more closely linked to respiratory difficulty.
- The duration or character of dyspnea does not allow differentiation of the underlying cause (primary respiratory disease vs pleural effusion vs pulmonary edema).
- Coughing is rarely associated with underlying heart disease in the cat. This clinical sign is most often associated with underlying airway disease, such as feline asthma.

Dyspnea, or abnormal breathing (used clinically to describe difficulty breathing), is one of the most common signs recognized by owners with cats experiencing congestive heart failure due to pulmonary edema or pleural effusion. However, although dyspnea in cats commonly occurs secondary to heart disease, it is also frequently associated with lower airway disease or pleural space disease. Some owners will first recognize dyspnea as an increased abdominal effort associated with respiration. One study described 14 cats with tricuspid valve dysplasia, and the most common abnormality recognized by owners was dyspnea visible as discordant/opposite chest and abdominal wall movements (5/14 cats, 36%); this finding was compared to the chief complaints of 36 dogs with the same cardiac disease and none of the 36 dogs' owners described dyspnea this way (Chetboul et al. 2004).

Upper airway disease leads to stridor, a harsh, high-pitched respiratory sound usually heard on inspiration. These cats may also have a history of snoring, intermittent open mouth breathing or nasal discharge. Possible nasolaryngeal and laryngeal disorders include benign polyps and malignant tumors, and other noncardiogenic disorders.

Lower airway disease, in particular feline asthma, is characterized by bronchoconstriction and inflammatory exudate in the airways. These cats often present with a history of coughing and an obstructive respiratory pattern, with an increase expiratory effort (Mandell 2004). Other common clinical signs associated with congestive heart failure in cats include hiding, anorexia, restlessness, or tachypnea (an increased respiratory rate); the cat may even prefer to sit or lie in a sternal position (orthopnea). See Box 4.1 for a differential list of the common diseases causing feline dyspnea. See Figure 4.1 for a therapeutic plan to address the dyspneic feline patient.

Coughing is defined as a sudden expiratory effort, initially against a closed glottis, resulting in expulsion of air from the lungs. The cough reflex results from irritation (mechanical or chemical) at the level of the pharynx, larynx, tracheobronchial tree, and some of the smaller airways. It is a sign of any of a handful of possible underlying disorders. The cough may be

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Box 4.1. Differential list for dyspneic cats

Major Category	Heart Disease and Congestive Heart Failure	Pleural Space Disease	Lower Airway Disease
Underlying etiologies	Hypertrophic cardiomyopathy (±obstruction) Restrictive cardiomyopathy Unclassified cardiomyopathy Congenital heart disease Heartworm disease Dilated cardiomyopathy (rare)	Pleural effusion Neoplasia Vasculitis Hypoproteinemia Pneumothorax Trauma Post endotracheal intubation	Feline asthma Heartworm disease

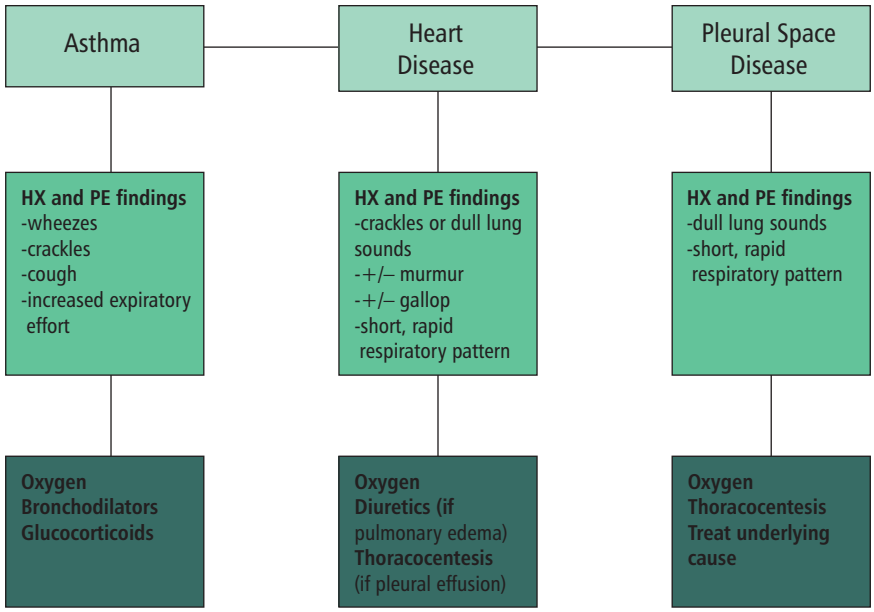


Figure 4.1. An algorithm for diagnosis and therapy of the dyspneic cat. Modified from Mandell DC. Respiratory distress in cats. In King LG: Textbook of Respiratory Disease in Dogs and Cats, St. Louis, 2004, Saunders, page 15.

described as moist, dry, productive or honking. Cats usually have a characteristic posture with an extended head and neck and many owners will confuse coughing for vomiting/"hairballs" or retching. A valuable first step if the owner is uncertain about whether coughing is occurring is to have the owner record an audiovisual clip of the event at home, allowing the clinician to evaluate the episodes objectively before proceeding with diagnostic testing. Unlike dogs, coughing is rarely associated with congestive heart failure in cats (although it may be noted with heartworm disease and/or chylous pleural effusion). Coughing and/or wheezing cats most often have primary respiratory diseases. However, there are many possible etiologic agents including allergic/inflammatory, infectious, neoplastic, parasitic, trauma and physical factors, and rarely cardiac disease, which all must be considered and ruled out as clinically indicated.

Thoracic radiographs are the most important diagnostic tool in a cat that presents with difficulty breathing or coughing. Thoracic radiography provides information about the lung parenchyma, the pleural space and the cardiovascular system. Further diagnostic decisions should be based on the radiographic findings (e.g., an echocardiogram is warranted if heart enlargement is detected). Routine laboratory testing such as complete blood count, chemistry profile, urinalysis, FeLV/FIV and fecal examination are also helpful to exclude some systemic and parasitic causes of cough. Heartworm serology and lungworm (Baermann fecal) testing is recommended for animals living in an endemic area. There is evidence that larval migration of *Dirofilaria*

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immitis results in severe lower airway inflammation in cats and may result in signs similar to feline asthma before the cat becomes heartworm antigen or antibody positive, making definitive diagnosis very challenging (see Chapter 23 for discussion of feline heartworm disease). In some cats, advanced respiratory testing with bronchial wash, cytology, ± culture, bronchoscopy and/or blood gas analysis may be necessary to obtain a final diagnosis.

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5

Cardiopulmonary Arrest and Cardiopulmonary Cerebral Resuscitation

Key Points

- Whenever cardiac arrest is suspected, immediate measures to be taken include 1) confirming unconsciousness via stimulation, and 2) placing intravenous catheter, endotracheal tube, and electrocardiographic (ECG) leads for monitoring.
- The cornerstone of treatment of ventricular fibrillation is immediate electrical defibrillation.

CARDIOPULMONARY ARREST

Popular culture equates cardiac arrest with asystole. This misleading association conveys the impression that cardiac arrest is purely a disorder of cardiac rhythm when in fact it is, more accurately, a disorder of cardiac function: several arrhythmias are consistent with cardiac arrest. Cardiac arrest is the cessation of circulation, depriving the vital organs of oxygen (ECC 2005). The central feature of cardiac arrest is otherwise terminal circulatory dysfunction regardless of cardiac rhythm. This end-stage circulatory collapse may occur with 1) severe bradycardias/asystole (the most common cardiac rhythm in arrested small animal patients: 72%) (Waldrop et al. 2004; 2) severe tachycardias, during which the ventricles cannot fill adequately during diastole and in which case the heartbeat is ineffective because of decreased stroke volume; or 3) relatively normal cardiac rhythms in which the electrical activity of the heart is not translated into mechanical force of contraction (i.e., pulseless electrical activity [PEA], formerly called electromechanical dissociation, EMD). In other words, the ECG in cardiac arrest may demonstrate, respectively, 1) asystole or bradycardias of sinus, atrial/junctional, or ventricular origin; 2) ventricular tachycardia (VT) or ventricular fibrillation (VF); or 3) sinus rhythm or other supraventricular rhythms when PEA is present (ECC 2005; Rush and Wingfield 1992). The ECG alone can provide the rhythm diagnosis during cardiac arrest, but it is the combination of ECG and assessment of circulation, including palpation of the pulse and measurement of the arterial blood pressure, that is necessary to confirm cardiac arrest and initiate treatment.

Cardiopulmonary arrest (CPA) consists of cardiac arrest with cessation of effective respirations. In feline medicine, most cases of cardiac arrest evolve to CPA within seconds or are preceded by respiratory arrest.

DIAGNOSIS

Since it involves cessation of effective circulation and respiration, CPA is recognized by loss of consciousness and recumbency. A palpable pulse is not felt, the mucous membranes are pale or cyanotic, and respirations cease. In CPA, the blood pressure is too low to be measured noninvasively. Electrocardiography may demonstrate a variety of rhythms (above) and should be used for guiding therapeutic intervention during cardiopulmonary cerebral resuscitation (CPCR).

DIFFERENTIAL DIAGNOSIS

An important differential diagnosis for effective respirations during arrest is agonal breathing. Agonal breaths are defined by an opening of the mouth but no appreciable filling and emptying of the chest and, in intubated patients, no appreciable flow of air through the

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endotracheal tube. These silent, gasplike movements of the mouth do not constitute effective breathing, and agonal "breaths" should not delay the administration of CPCR.

Cardiopulmonary arrest requiring treatment must be differentiated from natural death beyond which no measures can revive the patient. This distinction matters both for medical reasons (e.g., termination of intervention at the point of futility) and for emotional, ethical, and moral reasons (e.g., dignified and humane death). CPCR is no longer indicated when all of the following criteria have been met: CPA is confirmed, and CPCR efforts lasting a minimum of 3 minutes, but often longer, have not produced a return of spontaneous circulation or ventilation, and there is no evidence of brainstem function (pupils are fixed and dilated, and/or there is a lack of electrical activity on brainstem auditory evoked response or electroencephalography [EEG]). In human medicine, contraindications to CPCR are any of the following: 1) Do Not Attempt Resuscitation order in place; 2) signs of irreversible death (e.g., rigor mortis, decapitation, decomposition, or dependent lividity [purplish discoloration of tissues due to gravity-induced blood pooling]); or 3) no physiologic benefit can be expected because vital functions have deteriorated despite maximal therapy (e.g., progressive septic or cardiogenic shock) (ECC 2005) and such parameters likely are appropriate in feline medicine also. Termination of life support is considered ethically permissible in comatose patients who, despite optimal treatment, show all the following signs: absent corneal reflex ≥24 hours, absent pupillary light response ≥24 hours, absent withdrawal response to pain ≥24 hours, and absent motor response 24–72 hours (ECC 2005); feline patients in this state likewise should not receive CPCR.

TREATMENT

The treatment approach to CPA has recently been updated (ECC 2005; Plunkett and McMichael 2008). The basic premise still consists of instituting CPCR (Figure 5.1). A stepwise process is appropriate:

A. Airway. Assess airway for obstruction, and if present, remove (foreign body), improve (generally via intubation), or bypass if necessary (tracheostomy).

Note: a solid mouth speculum *must* be solidly in place before manipulating an arresting cat's mouth, because periagonal bites may be profound and unrelenting, and extremely harmful to the rescuer or clinician.

If no obstruction is found, endotracheal intubation is warranted for administering artificial respirations. Placing the endotracheal tube should delay initiation of chest compressions as little as possible and ideally is performed with the cat in lateral recumbency while chest compressions are underway.

B. Breathing. Administer 2 rescue breaths once the patient is intubated, followed by administration of regular artificial breaths; never administer mouth-to-muzzle breaths (risk of agonal bites).

C. Circulation, compressions. There should be no palpable pulse (by definition) in the arrested patient, requiring external chest compressions. In the cat, these are administered with the patient in lateral recumbency and either by using one hand (thumb on one side of the chest, other four fingers on the other) or with the heel of one hand on the visible side of the chest and the fingers or palm of the other on the opposite, dependent side. The position is directly over the heart: ventral half of the thorax approximately over the 5th intercostal space, which can be identified quickly by flexing the forelimb caudally: the point at which the elbow crosses over the costochondral junctions is at or near the 5th intercostal space. Compression strength should cause the ribs to depress to approximately 1/3 of the diameter of the chest; caution is warranted in older cats with bones that are more brittle, and in general with resuscitators who are zealous or excessively forceful and can break ribs, cause pneumothorax or hemothorax, and otherwise inflict injuries during CPCR. It is helpful to remember that a cat's heart is slightly larger than a man's thumb, and chest excursions during CPR generally involve movement of 1–2 cm of chest width (an inch or so). Persons administering compressions should change roles every 2–3 minutes to prevent fatigue.

D. Defibrillation. (Figure 5.2). Electrical defibrillation, which is the administration of an electrical shock that abolishes all cardiac activity so as to allow reemergence of the sinoatrial node's activity as the dominant pacemaker and thus normal sinus rhythm, is the treatment of choice for ventricular fibrillation. Ventricular fibrillation is characterized by a patternless wavy tracing where no semblance of P, QRS, or T deflections can be distinguished (Figure 5.3). The rate is usually >400 waves per minute, reflecting electrical chaos in the ventricles. Defibrillation must be administered early for maximal effect; the success of defibrillation in humans declines from >99% when administered in the first minute of fibrillation to <10% after 10 minutes in the absence of CPCR. The process of defibrillation in cats should take less than 1 minute, and it consists of rapid clip of hair over both sides of the thorax (10 seconds); application of

CARDIOPULMONARY CEREBRAL RESUSCITATION

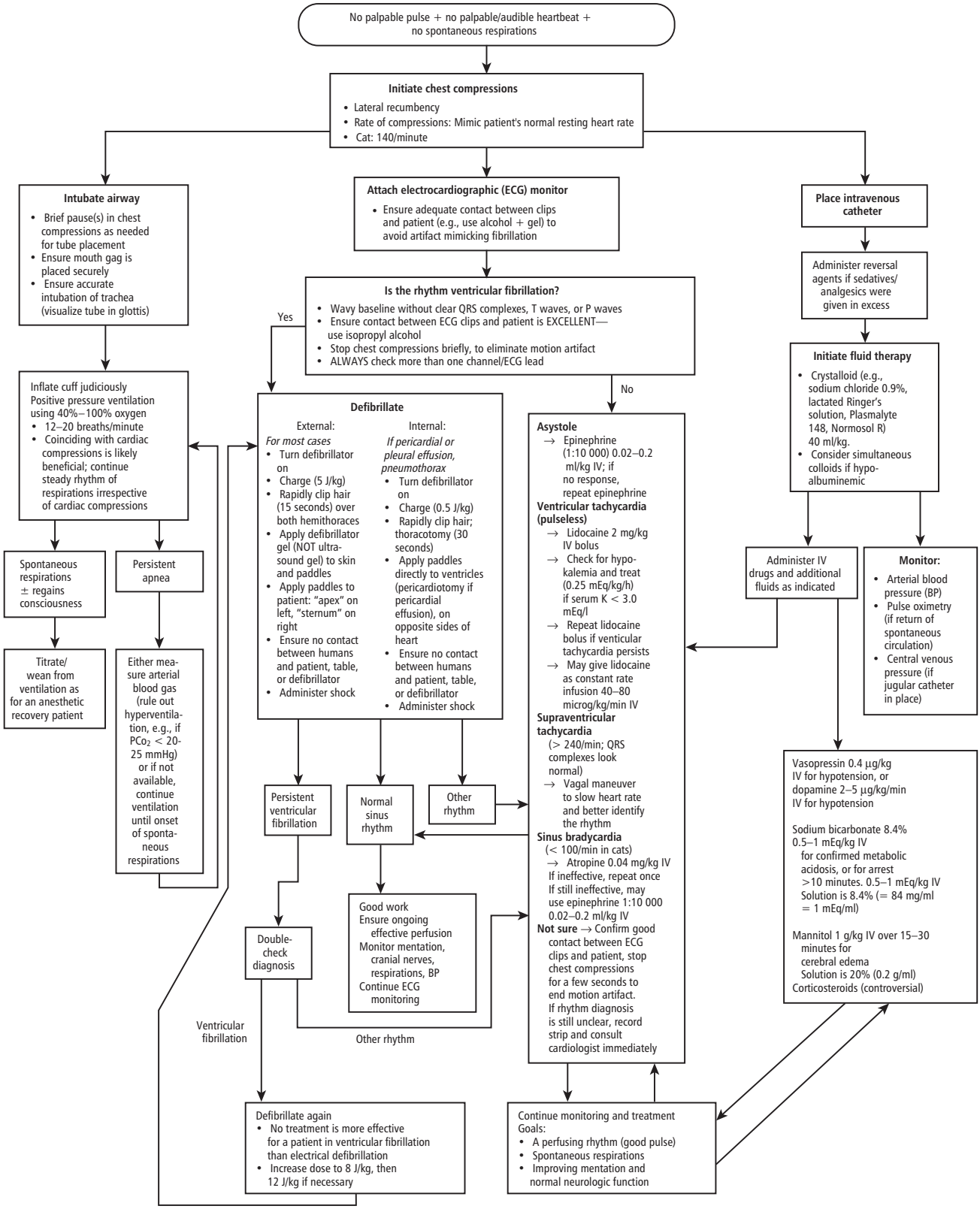


Figure 5.1. Algorithm for treatment, monitoring, and decision-making during cardiopulmonary cerebral resuscitation. Copyright 2004, Etienne Côté; modified with permission.

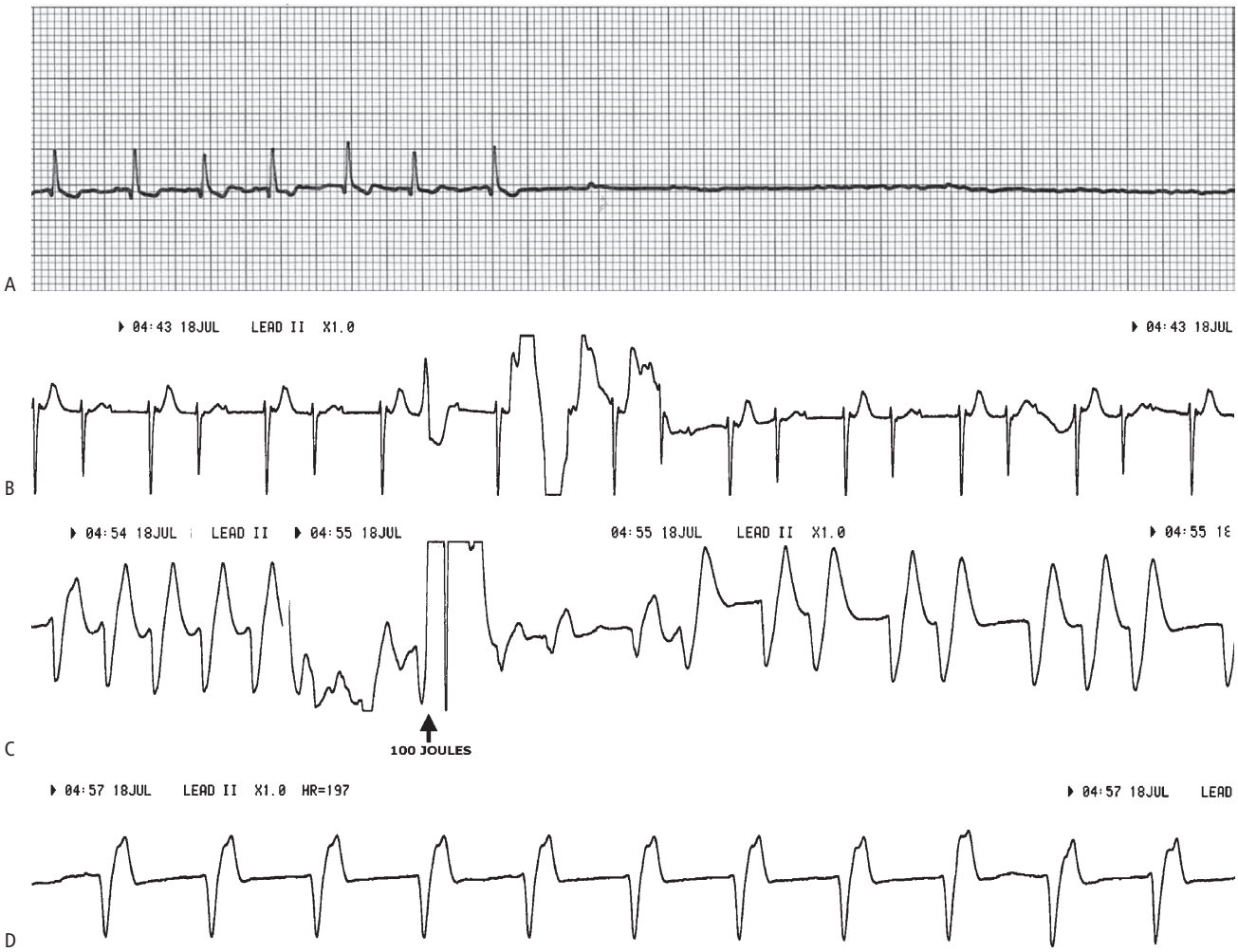


Figure 5.2. Electrocardiograms of rhythms in feline cardiac arrest. All lead II. (A): 5 mm/mV.
(A) Abrupt onset of asystole in a young female domestic shorthaired cat with recurrent syncope. 25 mm/sec, 1 cm = 1 mV. **(B)** Polymorphic ventricular tachycardia not associated with a palpable pulse ("pulseless electrical activity"); note motion artifact in center of tracing caused by administration of chest compressions. **(C)** Pulseless rhythm in (B) was unresponsive to lidocaine and chest compressions, leading to defibrillation (note artifact from electrical shock [100 joules] and associated patient motion), which was unsuccessful. Terminally **(D)**, this cat displayed a slow, idioventricular rhythm not associated with a measurable blood pressure (persistent pulseless electrical activity).

water to the skin, ***not*** alcohol (5 seconds); application of defibrillation gel to the skin, ***not*** ultrasound gel, which is poorly conductive (10 seconds); charging of the defibrillator (25 joules initially; 25–50 joules thereafter if needed) (10 seconds); application of pediatric defibrillator adapters for a smaller footprint on the chest, and placement over the cardiac region of the chest (paddle marked "apex" goes over left hemithorax; paddle marked "sternum" goes over right hemithorax) (10 seconds); brief survey that all individuals, including self, are out of contact with the patient and any connection (table, wires, spilled liquids, etc.), and disconnection of the ECG wires if ECG is not synchronized to the defibrillator (5 seconds); delivery of shock. Cardiac compressions are stopped only for a few seconds for administration of the shock and are resumed immediately thereafter for 2 full minutes before evaluating the ECG and determining whether another shock is needed. There is no known value to a "precordial thump" (blunt blow to the chest in lieu of defibrillation as a mechanical equivalent of electrical defibrillation) and a large prospective study of this technique in humans identified a 79/80 (99%) failure rate, possibly a lower success rate than spontaneous conversion to sinus rhythm without any intervention at all (Amir et al. 2007).

D. Drugs. The algorithm (see Figure 5.1) identifies the indications for, and dosages of, drugs used

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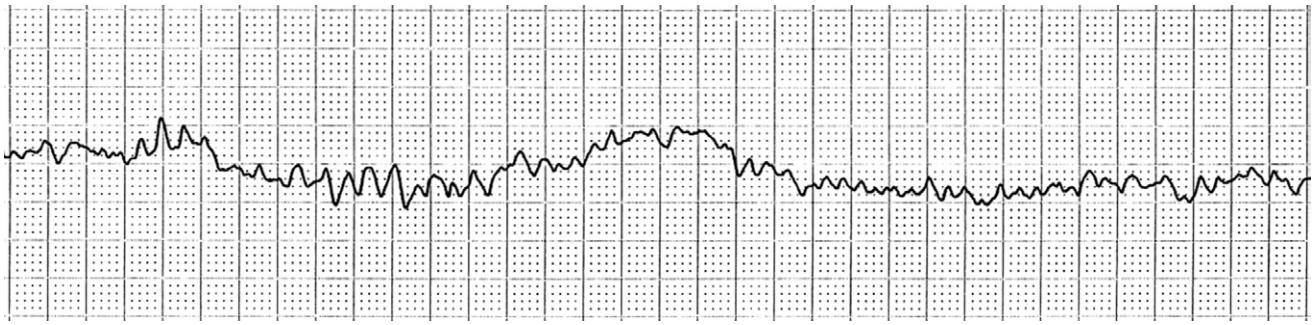


Figure 5.3. Electrocardiogram of ventricular fibrillation. There is a chaotic, patternless cardiac rhythm with no discernible organized ventricular activity. The rate is approximately 600/minute. Lead III. 25 mm/sec; 1 cm = 1 mV.

during CPCR. Additional information is available in Chapter 30.

Synchronizing the Complete Resuscitative Effort

Ideally, resuscitative efforts involve several members of the veterinary team, although effective CPCR may be delivered by a single individual. When others are available to help, the following order of tasks may be optimal:

1. Identification of the arrested patient and indication for CPCR by the first observer. This person calmly but deliberately calls for assistance if such assistance is within earshot and leads the resuscitation effort unless/until handing over the task to another resuscitator.
2. The first observer examines the airway (A) and, barring obvious airway obstruction, begins chest compressions at a rate of 140/minute in the cat.
3. The first observer must also identify any immediately complicating factors that could reduce the efficacy of CPCR, and initiate their correction promptly. Examples include drug overdose, iatrogenic anesthetic complication (e.g., pop-off valve closed, lack of oxygen flow, endotracheal tube problem), and severe acid-base or electrolyte imbalances. Large-volume pericardial or pleural effusions, pneumothorax, rib fractures, and large intrathoracic masses interfering with efficacy of chest compressions are all indications to proceed immediately to open-chest cardiac compressions.
4. A second CPCR team member is tasked with establishing the airway, virtually always via endotracheal intubation but possibly via tracheostomy (mindful of potential tracheostomy-related complications) if the upper airway is completely obstructed by a mass or foreign body. Once this is accomplished, the second team member begins ventilations at a range of 10–14/minute to mimic the normal cat's respiratory rate, and no higher (despite excitement, avoid overventilation). The depth of the respirations should be similar to those observed in a normal cat (the chest rises and falls by 3–4 cm) and if a manometer is in line, positive pressure should not exceed 20 cm H_2O (20 mm Hg).
5. A third team member, if available, places an intravenous catheter or ensures its patency if one is already present. This team member, or a fourth, if available, connects an ECG monitor (with printer, if possible, to document and review the cardiac rhythm) to the patient, usually connected with a combination of isopropyl alcohol and ultrasound or defibrillation gel for lasting contact.
6. Blood pressure should be monitored with a Doppler unit by any team member aware of the location of the palmar metacarpal (forelimb) or plantar metatarsal (hindlimb) artery, and proper technique, in the cat (see Figure 21.10 in Chapter 21).
7. A separate team member, or one involved in the other tasks above, must record time and nature of treatments administered and results of monitoring into the patient's arrest record, because recall and time perception are poor in the arrest setting.
8. The individual leading resuscitative efforts should transfer the task of administering chest compressions to another team member when that team member becomes available. This allows the leader to make decisions regarding management (e.g., drug administration, adjustments in monitoring, troubleshooting) based on physical signs of the patient's response, ECG findings, and other results of monitoring. The leader also should ideally be detached in order to communicate with the patient's owners in a calm, frank manner that helps guide whether to pursue CPCR as well as to convey the patient's status accurately.

There is no fixed duration of CPCR; in one series, the 3 feline CPA survivors that went home had a return of spontaneous circulation within 15 minutes

of the start of CPCR; CPA had been witnessed in all 3 cases (2 perianesthesia, 1 suspected bethanechol toxicosis) (Waldrop et al. 2004).

OUTCOME

The first sign of a positive response to CPCR generally is the return of spontaneous circulation: the ECG indicates a rhythm other than ventricular fibrillation or asystole and a faint but unmistakable pulse is palpable. As the positive response continues, blood pressure approaches or reaches the normal range, and spontaneous respirations return. Since ventilation with supplemental oxygen is beneficial, but may also delay the return of spontaneous respirations, blood gas analysis is useful to better titrate frequency, depth, and oxygen content of manual ventilation. Here, as before, the presence of a mouth speculum is essential, because a cat that regains motor function may otherwise transect an endotracheal tube with one bite, inhaling a tube segment and causing lower airway obstruction that could be fatal. When a perfusing rhythm has returned, spontaneous respirations may be preceded or followed by skeletal motor activity including abrupt head movements, movement of the limbs, or chewing motions. The patient's signs during subsequent recovery from cardiopulmonary arrest at this stage evolve in a way that resembles recovery from general anesthesia. Rearrest is common in the minutes to hours following recovery, though much less so in small animal patients that survive CPA to hospital discharge (Waldrop et al. 2004). Ongoing monitoring, and then measures to correct triggers (such as acid-base imbalances, drug toxicoses, hypoxemia, anemia, or other disorders) that are identified, are the two cornerstones of postarrest management.

Three large retrospective clinical studies in cats confirm that cardiac arrest carries a poor prognosis even with intervention (Hofmeister et al. 2009; Kass and Haskins 1992; Wingfield and Van Pelt 1992). Of 138 cats experiencing cardiopulmonary arrest and receiving CPCR, 9 survived to hospital discharge (6.5% overall survival). However, the survival rate for nonanesthetic-related cardiac arrest is likely even lower; some survivors in these reports experienced cardiopulmonary arrest during general anesthesia, which implies that endotracheal intubation and immediate intravenous access were likely available. Probability of survival was even lower in cats with shock as the underlying cause of arrest, but was higher when more individuals were involved in the resuscitation effort (Hofmeister et al. 2009).

Perhaps the most important aspect of CPCR remains the importance of anticipating it in the first place. The likelihood of survival is inevitably worse when a severe illness or disturbance culminates in CPA compared to the likelihood of survival minutes or hours earlier. Therefore, ideal management of CPA consists of denying it the opportunity to occur.

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SECTION B

Diagnostic Testing

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6

Radiography

Key Points

- In the early stages of feline heart diseases that cause concentric left ventricular (LV) hypertrophy, LV chamber diameter may decrease but radiographic heart size remains normal. With progression of such diseases, the left atrium enlarges and cardiomegaly is therefore usually recognizable on radiographs of cats with moderate or severe concentric left ventricular hypertrophy.
- Thoracic radiographs provide useful, but limited, information regarding cardiac structure in asymptomatic cats but greatly assist in narrowing the differential diagnosis in cats with overt respiratory clinical signs. In this clinical scenario they are the diagnostic test of choice.
- The vertebral heart size as measured on the lateral radiographic projection is a useful technique to objectively assess heart enlargement in cats (normal <8 V).
- Left-sided heart disease is much more common in cats than biventricular or right-sided heart disease.

Thoracic radiography is an essential part of the cardiovascular examination. This modality, which is more widely available than echocardiography, provides direct information about the heart and lungs and may confirm or exclude a particular clinical diagnosis suspected from the history and physical examination. It is also useful for assessing severity of known heart disease and evaluation of therapeutic effect. Also essential in the interpretation is prior development of differential diagnoses derived from a thorough history and physical examination. Although many cardiorespiratory diseases manifest with similar clinical signs (i.e., cough, dyspnea, etc.), heart failure can usually be differentiated from primary respiratory disease using thoracic radiographs. In fact, radiography is superior to echocardiography for initial evaluation of most coughing or dyspneic feline patients because radiography can provide information regarding pulmonary congestion and the respiratory system, unlike the echocardiogram. Patient positioning and adequate radiographic exposure are important for accurate radiographic interpretation, however. A normal heart can appear abnormal when positioning is incorrect, and the reverse is also true. Two orthogonal radiographic projections are required for a correct cardiac assessment, but it is critical to astutely monitor the patient. Some animals may be too dyspneic to allow two radiographic views (or even one) before therapy is initiated.

Radiographic artifacts include any alteration in the image that leads to hindered visualization of the region of interest. Malpositioning, patient motion, incorrect patient identification, double exposure, and many other artifacts are possible. Digital radiography is increasingly available in veterinary radiography, and with its development, in addition to these traditional issues, a new set of artifacts has been introduced. Excellent reviews describe the possible artifacts and how to avoid them (Drost et al. 2008; Jimenez et al. 2008).

Adequate radiographic exposure is achieved when it is possible to define the dorsal spinous processes of the cranial thoracic vertebrae superimposed on the scapula. The forelimbs should be drawn forward so they are not superimposed on the cranial thorax (Figure 6.1); failure to do so is one of the most common errors in feline thoracic radiographic technique, the repercussions of which can be serious (missed lesion, incorrect diagnosis, overdiagnosis). Timing of the exposure should

Feline Cardiology, First Edition. Etienne Côté, Kristin A. MacDonald, Kathryn M. Meurs, Meg M. Sleeper.
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Figure 6.1. A cat correctly restrained for lateral and VD radiographs. The use of sandbags over the hips **(A)** and neck **(B)** and a trough **(C)** are helpful to minimize the need for restrainers and radiation exposure. Similarly, using roll gauze to draw the forelimbs cranially (panels A–C) allows the radiographic exposure to be made without manual restraint.

correspond with peak inspiration whenever possible, to provide maximal separation between the caudal cardiac border and the diaphragm. In the lateral view, the dorsal heads of the ribs should be superimposed. If they are not (barring a vertebral abnormality), the projection is oblique and the cardiac silhouette will be distorted. In the cat, the lungs are normally better inflated in the ventrodorsal (VD) view because the thorax is more completely expanded; it may also be easier to pull the forelimbs cranially in this view. However, results from one study suggest there is more variability in the cardiac silhouette in a VD position compared to the dorsoventral (DV) projection (Carlisle and Thrall 1982). Moreover, mild pleural effusion may be missed in the VD view because the fluid gravitates to the paravertebral fossae (termed by some the "gutters") formed by the rib curvature, where it may not be apparent radiographically. On the other hand, cardiac size and shape may be better characterized because the fluid is less likely to obscure the cardiac silhouette. Although all these variables should be considered, the most important goal is a straight symmetric projection and, above all, patient comfort and respiratory and hemodynamic stability. Straight DV or VD projections will have the dorsal spinous processes of the thoracic vertebrae centered over the vertebral bodies along the entire length of the thoracic spine, and the sternebrae should also be superimposed. As stated above, the radiograph should be taken during full inspiration, as evidenced radiographically by the presence of aerated lung between the caudal cardiac margin and the cupula of the diaphragm. Whenever possible, radiographic positioning should be standardized in a veterinary hospital (either the right or left lateral and the DV or VD views should be used routinely) so that slight differences between views are not misinterpreted as abnormalities.

In a dyspneic or otherwise unstable cat, a DV projection may be much more readily obtained than a lateral view, because the dyspneic patient is in sternal recumbency, the natural posture cats choose when in respiratory distress. Therefore, the "lateral-only" approach for obtaining thoracic radiographs in dyspneic cats is not appropriate, and either a DV view should be considered, or radiography should be postponed altogether until the

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patient has responded to urgent care. Another option for obtaining thoracic radiographs in severely dyspneic cats is a horizontal beam projection. Many models of radiograph units can be rotated to direct the radiographic beam horizontally. Doing so allows a cat to remain in sternal recumbency while the radiographic plate is placed perpendicular to the tabletop, against the cat's lateral thorax. Thus, a lateral projection can be obtained without placing the cat in lateral recumbency.

Thoracic radiographs are the diagnostic test of choice for evaluating the chest in most severely dyspneic cats, but an important exception can be the patient suspected of having large-volume pleural effusion. In these cats, a brief thoracic ultrasound exam with the cat in sternal recumbency may effectively rule in or rule out pleural effusion and the need for immediate centesis.

Radiographic interpretation involves adherence to several steps. Any identified abnormalities supportive of disease should be confirmed on multiple radiographic views:

1. Evaluate films for technical quality and respiratory phase; if they are substandard, they should be repeated.
2. Review the entire thoracic cavity, notably the pleural space, for abnormal presence of air or fluid.
3. Review the portion of the cranial abdomen included in the projection.
4. Evaluate the position, course, and diameter of the trachea and mainstem bronchi.
5. Evaluate the position of the cardiac apex and caudal mediastium.
6. Evaluate the cardiac margin (including all parts as described in the clock face analogy, below [see Figure 6.5]) for enlargement.
7. Evaluate the size, shape, and course of the main pulmonary artery and peripheral pulmonary vessels.
8. Evaluate the caudal vena cava for elevation and/or enlargement.
9. Evaluate the lung fields for hyper- or hypoinflation and for distribution and pattern of increased or decreased opacity including bronchiolar prominence/thickness.

The lateral projection allows assessment of the right side of the heart (the cranial margin of the silhouette) and the left side of the heart (the caudal margin). In the normal cat, the cardiac silhouette is ovoid or egg-shaped, with the apex pointed in shape compared to the wider cardiac base. The heart axis is defined by drawing an imaginary line from the tracheal bifurcation (carina) to the apex, with a resulting angle that usually is approximately 45 degrees to the sternebrae (see Figure 1.3). Cats have far less breed-related cardiac variation than is seen in dogs, but there tends to be more interindividual variation among cats. In particular, the angle of the cardiac long axis orientation is more variable. In older cats the angle decreases (a more "horizontal" alignment) with increased sternal contact (Moon et al. 1993; Nelson et al. 2002). This finding has been termed by some a "lazy" heart conformation. A tortuous, redundant aorta is another common variation in older cats (Figure 6.2). However, this change has also been associated with systemic hypertension in humans and an association is suspected in cats (Nelson et al. 2002). See Chapter 21 for more information regarding systemic hypertension.

The cardiac chambers can be defined by drawing a second line (short axis) perpendicular to the heart long axis at the level of the ventral aspect of the caudal vena cava. The dorsal cardiac segment includes both atria, the pulmonary arteries and veins, the cranial and caudal cavae and the aortic arch. The cranioventral segment is formed by both the right ventricle and right auricle. The ascending aorta is superimposed over the right atrium; the aortic arch extends caudodorsally to form the ascending aorta. The main pulmonary artery cannot be visualized on the lateral projection, but the left pulmonary artery can sometimes be seen extending dorsally and caudally to the tracheal bifurcation while the right pulmonary artery may be seen on "end" as it leaves the main pulmonary artery immediately ventral to the carina.

A method developed by Dr. Jim Buchanan, the vertebral scale system, allows objective measurement of the heart size scaled against the length of specific thoracic vertebrae (Figure 6.3) (Litster and Buchanan 2000a). This form of internal control reduces error associated with subjective interpretations and interpatient variability. On the lateral radiograph, the long axis of the heart (L) is measured with a caliper extending from the ventral aspect of the left mainstem bronchus to the left ventricular apex. The caliper is repositioned along the vertebral column beginning at the cranial edge of the fourth thoracic vertebra, and the number of vertebrae (V) within the distance L is recorded to the nearest 0.1V. The maximal perpendicular short axis (S) is measured in the same manner and likewise is quantified beginning at the fourth thoracic vertebra. Normal cats measure less than 8V; in a series of 100 normal cats, the mean vertebral heart size (VHS) was 7.5V (±0.3) (Litster and Buchanan 2000a). Another study obtained very similar results in 50 clinically normal, adult stray cats, with a greater degree of interindividual variation: the VHS was 7.3 ± 0.49V in the right lateral, 7.3 ± 0.55 in the left lateral, 7.5 + 0.68 in the DV and 7.5 + 0.53 in the VD views (Ghadiri et al. 2008). Thoracic radiographs and VHS have also been compared to echocardiographic findings in a group of cats presenting to an emergency service for dyspnea. None of the cats with a VHS ≤8V

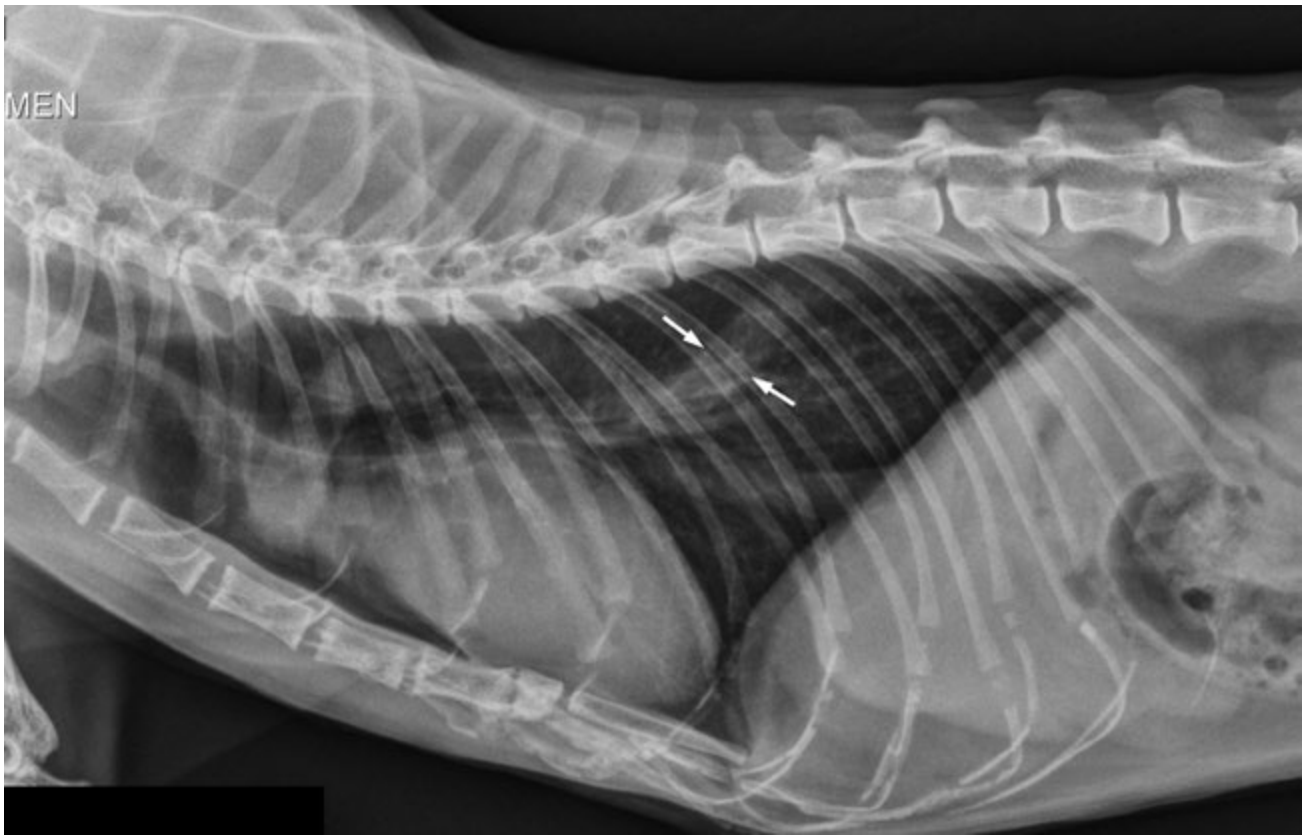


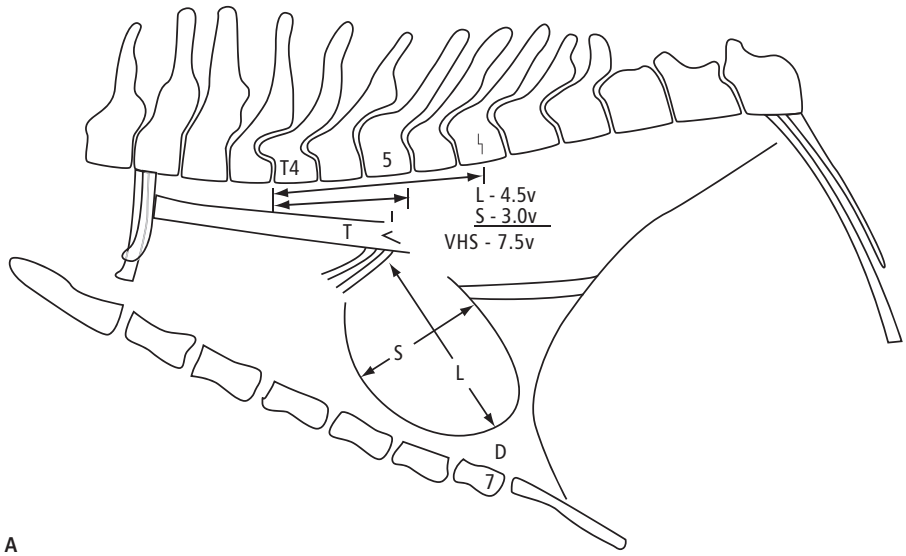
Figure 6.2. Lateral **(A)** radiograph from a cat with a "lazy" (cranioventrally rotated) heart position. Also note the tortuous course of the aorta (arrows).

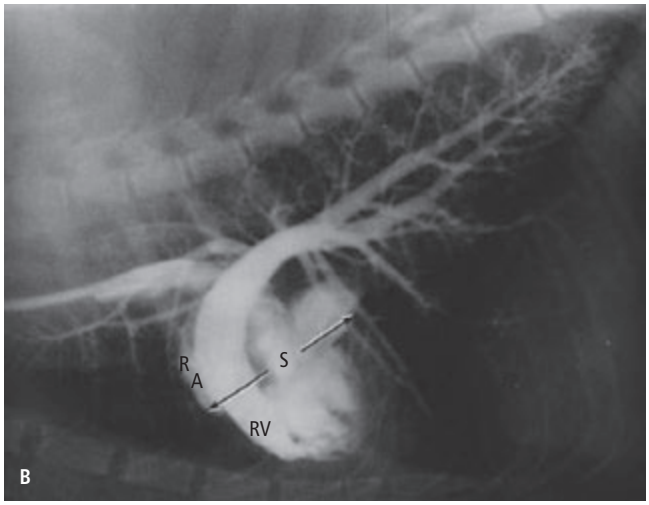
had primary heart disease, while all cats with a VHS >9.3 had heart disease (Sleeper, in press). Therefore, the echocardiogram yielded the most useful information in cats where heart enlargement was questionable (8 V < VHS < 9.3). Excluding pericardial disease cases, cats with a VHS >9.5 were likely to have heart disease, and definitive diagnosis of the underlying heart disease could be pursued once the patient was stabilized. In cats with VHS = 8–9.3 V, an echocardiogram was valuable to determine whether heart disease was, or was not, present.

In obese cats, excessive pericardial fat can make the cardiac silhouette appear enlarged, obscure the cranial margin of the heart, and/or cause tracheal elevation. It is sometimes difficult to identify the true cardiac silhouette, which can cause overestimation of heart size. Although the separation of two soft tissue structures from each other can be accentuated by the presence of fat, pericardial fat represents an intermediate opacity between myocardium and air-filled lung, which complicates identification of the cardiac margins. Additionally, concurrent subcutaneous fat may be substantial, and together these factors may make it difficult to identify the true cardiac silhouette in many obese cats, leading to inaccurate estimation of heart size. Recognizing this possibility usually allows the astute clinician to avoid the pitfall. Examination of the degree of abdominal fat in the falciform ligament and subcutaneous fat can assist in subjectively determining the contribution of pericardial fat to heart size. Also, the margin of the cardiac silhouette appears less well-defined than normal if a substantial amount of pericardial fat is present, and the border near the right atrium often has an angular appearance (squared border as opposed to the normal egg-shaped feline heart) (Figure 6.4). Finally, in some obese cats, altering the exposure by increasing mAs and decreasing kVp enhances radiographic differentiation of fat and heart (Litster and Buchanan 2000b).

In the lateral projection, the cranial pulmonary arteries are dorsal to the bronchus and the cranial pulmonary veins are ventral to the bronchus. The cranial lobar vessels are usually seen as pairs of vessels, each pair with a bronchus (artery-bronchus-vein from dorsal to ventral). The more cranial pair of vessels generally corresponds to the side on which the cat was recumbent when the lateral projection was made. The normal pulmonary arteries and veins should be equal in size, and their width where they cross the 4th rib should not exceed the width of the narrowest portion of that rib (Hayward et al. 2004).

In the DV or VD projection, the cardiac axis is most commonly on or close to midline, and the width of the cardiac silhouette does not usually exceed 50% of the





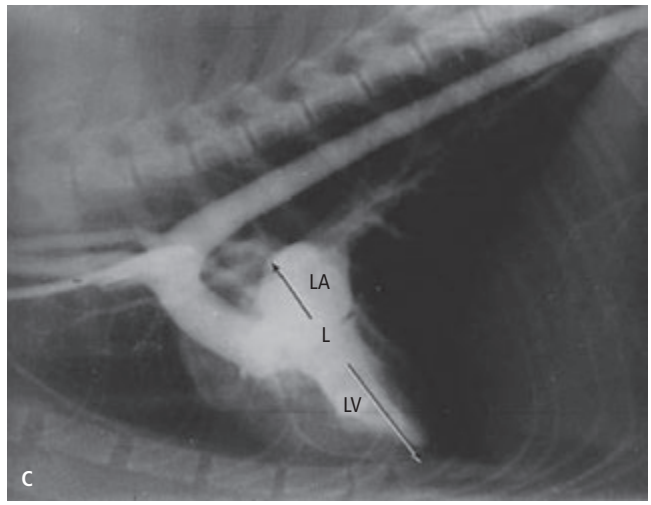


Figure 6.3. **(A)** Diagram of the lateral view of the thorax of a cat demonstrating the vertebral heart size method. The long axis (L) and short axis (S) dimensions of the heart are transposed onto the vertebral column and recorded as the corresponding number of vertebrae (V), as measured caudally from the cranial edge of T4. The values are then summed to obtain the vertebral heart size (VHS). T; trachea **(B)** Lateral angiocardiographic view of a normal feline heart showing the cardiac structures included in the S dimension of the VHS (left and right heart chambers at the level of the coronary groove); RA = right atrium, RV = right ventricle. **(C)** Lateral angiocardiographic view of a normal feline heart showing the cardiac structures included in the L dimension of the VHS (combined length of the left atrium (LA) and left ventricle (LV).
This figure originally appeared in: Litster AL, Buchanan JW. Vertebral scale system to measure heart size in radiographs of cats. J Am Vet Med Assoc 2000; 216:210–214 and is reprinted with permission from the American Veterinary Medical Association.

width of the thoracic cavity during full inspiration. A clock face analogy (Figure 6.5) can be used for estimating the location of normal cardiac structures on the DV or VD projection. The aortic arch extends from 11 o'clock to 1 o'clock while the main pulmonary artery is located in the 1–2 o'clock position. The body of the left atrium forms the 2–3 o'clock position of the cardiac silhouette, the left ventricle forms the left heart margin from 3–5 o'clock, and the right ventricle is located between 7 and 9 o'clock. The right atrium is located at 9–11 o'clock. The left caudal pulmonary artery extends beyond the left heart border at approximately the 4 o'clock position, while the right caudal pulmonary artery extends beyond the right heart border at approximately the 8 o'clock position. The pulmonary veins are usually evident nearest to the cardiac silhouette, where they enter the left atrium, but may be difficult to visualize peripherally. The aortic arch is not usually visible, but the descending aorta is seen as an opacity superimposed over the heart and extending caudally. Malposition of the heart to the right is a normal variant in the cat and occurs more commonly in VD projections, where the cardiac apex can sway to one side or the other of the chest when the cat is in dorsal recumbency.

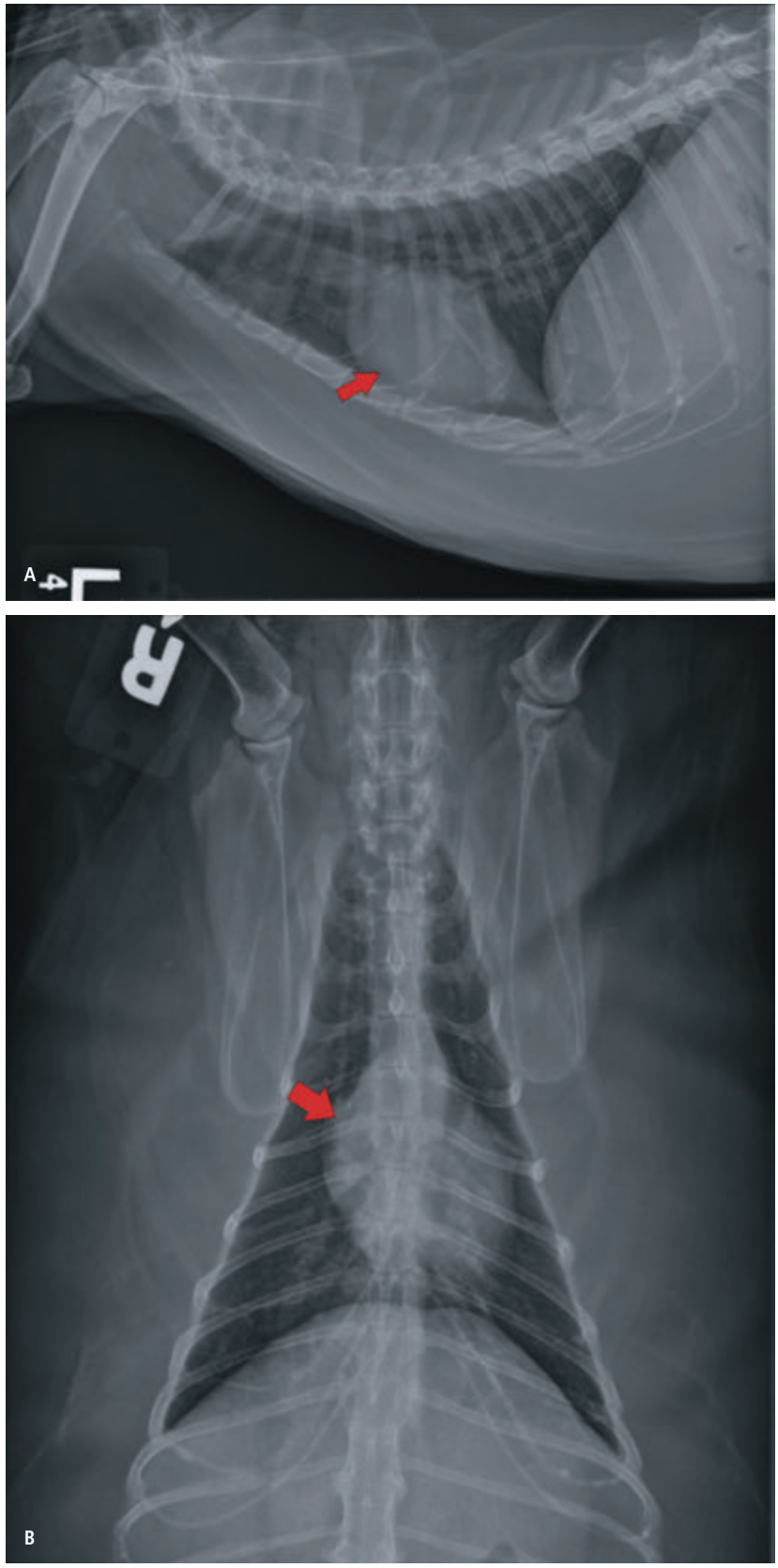


Figure 6.4. Lateral **(A)** and ventrodorsal **(B)** views of an obese cat without heart disease. Note the large amount of fat in the falciform ligament and subcutis, and the double cardiac silhouette (arrows) characteristic of excessive pericardial fat in the cat.

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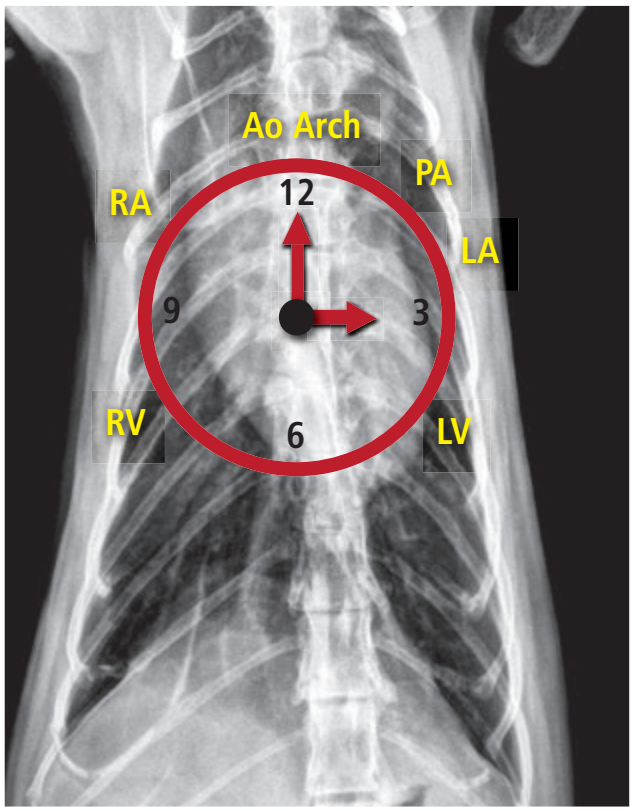


Figure 6.5. Superimposing a clock face on the cardiac silhouette is useful for localizing important structures. The aortic arch (Ao arch) extends from 11 o'clock to 1 o'clock while the main pulmonary artery (PA) is located in the 1 to 2 o'clock position. The body of the left atrium (LA) forms the 2–3 o'clock position of the cardiac silhouette, the left ventricle (LV) forms the left heart margin from 3 to 5 o'clock and the right ventricle (RV) is located between 7 and 9 o'clock. The right atrium (RA) is located at 9 to 11 o'clock.

Assessment of the pulmonary vessels is critical in both projection(s). The branch (lobar) pulmonary arteries originate from the main pulmonary artery and the right branch courses transversely, superimposed over the cranial portion of the cardiac silhouette in the DV/VD projection. The left pulmonary artery courses caudally, superimposed over the caudal left ventricular portion of the cardiac silhouette. As in the lateral projections, the DV/VD projections allow the pulmonary veins to be visualized best as they enter the left atrium along the caudal margin of the cardiac silhouette. They are more axially oriented in the VD/DV projection than the arteries. Feline pulmonary vessels are generally more difficult to identify and trace than are canine pulmonary vessels. However, the sizes of the caudal lobar arteries and veins should be similar to each other and should not exceed the diameter of the ninth rib where they intersect (Bahr 2007). The aortic arch is often not visible, but the descending aorta is superimposed over the heart and extends caudally, dorsally, and medially. The caudal vena cava (CVC) is visible as it courses cranially from the diaphragm to the right of midline and into the right caudal margin of the heart. Its diameter is normally variable depending on the stage of the cardiac cycle. If it is persistently large, right-sided heart disease should be considered (Bahr 2007). In cats, an exact reference interval is lacking, but the canine equivalent may be extrapolated: in dogs, the CVC measurement correlates moderately with the height of the vertebral body of T5 or T6. The mean CVC:V ratio was 0.75 + 0.13 in 100 clinically normal dogs (Buchanan and Bucheler 1995).

When congestive heart failure (CHF) occurs in the cat, heart enlargement is usually present because most disorders that lead to CHF cause cardiac hypertrophy. Rarely, in the early stages of hypertrophic cardiomyopathy, left atrial enlargement may not yet have occurred at the time of CHF, especially if a trigger for decompensation (parenteral fluids, repositol corticosteroids, other) has recently occurred. However, pulmonary venous congestion with engorgement and distension of the pulmonary veins occurs in the earliest stages of congestive heart failure and can be recognized radiographically when the pulmonary vein diameters are greater than those of their corresponding arteries (Figure 6.6). Unfortunately, in cats, this finding can be inconsistent and it is possible for the pulmonary veins to appear unremarkable in a subset of cats with congestive heart failure, particularly if diuretic treatment has been recently initiated. As congestion worsens, interstitial pulmonary edema develops and is recognized as a diffuse increase in lung field radiopacity (Figure 6.7). Because of the perivascular nature of cardiogenic edema, pulmonary vein and artery borders are indistinct. As congestion continues to worsen and fluid floods the pulmonary alveoli, a coalescing, fluffy alveolar infiltrate develops (Figure 6.8). Air bronchograms (black bronchi in a white radiopaque background) and air alveolograms (lung parenchyma with the radiopacity of liver and absent vascular markings) are present. Because bronchi are not flooded with edema, they appear as radiolucent structures in fluid-filled lungs radiographically (air bronchograms). With acute pulmonary edema, groups of fluid-filled (radiopaque) acini mix with air-filled (radiolucent) acini resulting in a finely stippled or nodular pulmonary pattern (air alveolograms). This sequential progression is rarely so distinct, and in reality, the pulmonary infiltrate secondary to heart failure is most frequently a mixed interstitial and alveolar pattern. In cats, cardiogenic alveolar consolidations often appear patchy and asymmetrically distributed. The air alveologram pattern predominates, and, in contrast to the dog, a perihilar distribution is uncommon; the margins of the pulmonary vessels are often completely obscured.



Figure 6.6. Lateral **(A)** and ventrodorsal **(B)** views of a cat with evidence of pulmonary venous congestion. Note the dilated pulmonary vein (larger diameter compared to its corresponding artery) on the lateral view (arrow).

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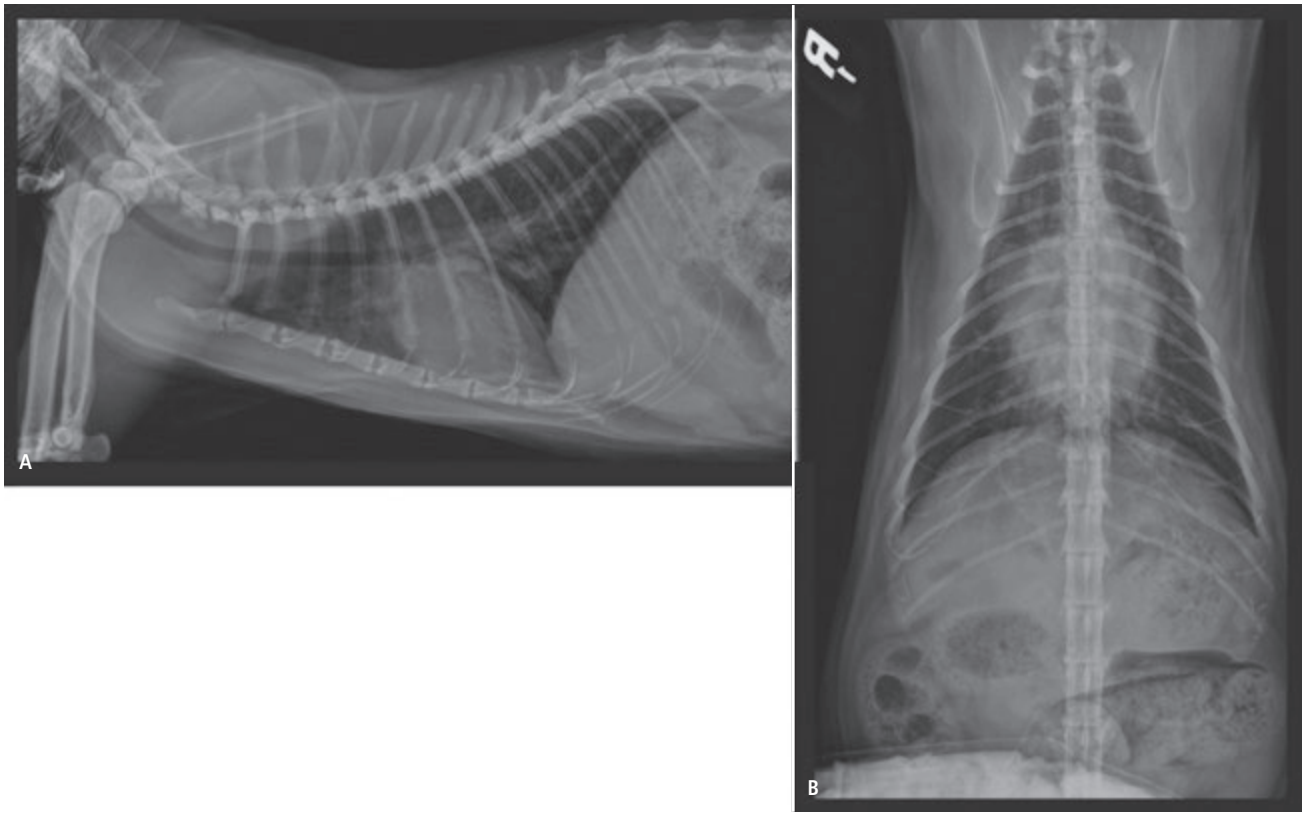


Figure 6.7. Lateral **(A)** and ventrodorsal **(B)** views of a cat with hypertrophic cardiomyopathy and a pulmonary interstitial pattern consistent with congestive heart failure. Note the prominent pulmonary vascular pattern.

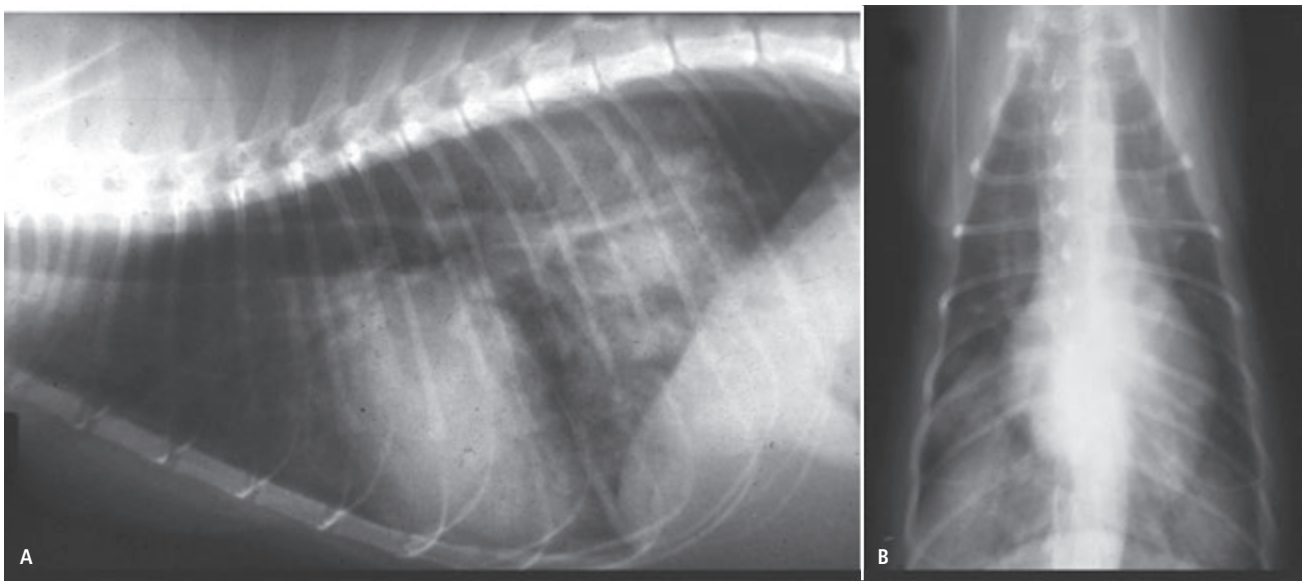


Figure 6.8. Lateral **(A)** and ventrodorsal **(B)** views of a cat with hypertrophic cardiomyopathy and an alveolar pulmonary pattern consistent with severe congestive heart failure. Note the predominantly left-sided cardiomegaly, the"valentine" shaped heart on the VD projection consistent with left atrial or biatrial enlargement and the fluffy radiopacity in the caudodorsal lung fields consistent with severe pulmonary edema.

Differential diagnoses for an alveolar pulmonary pattern include diseases that lead to filling of the alveoli with fluid or loss of air from the alveoli (atelectasis). Diseases that can lead to a generalized or diffuse increase in lung radiopacity include pulmonary edema (cardiogenic or noncardiogenic), pneumonia (aspiration or hematogenous), pulmonary hemorrhage (trauma or coagulopathy), disseminated granulomatous disease, and neoplasia. Parasitic pneumonias (e.g., *Toxoplasma gondii*) may occur in an acute infection or as a relapsing disease resulting in multiple, patchy, coalescing alveolar lesions. Possible causes of noncardiogenic edema include diseases that alter capillary permeability (infection, toxic inhalants, systemic toxins, allergy or anaphylaxis, trauma, uremia), increased capillary pressure or obstruction (fluid overload, lymphatic obstruction, venous obstruction), decreased oncotic pressure (hypoalbuminemia), or neurogenic causes (head trauma, seizures, electric shock, brain disease). In cats with heartworm disease (compared to dogs), lesions of pulmonary arteritis are often less extensive; therefore the main caudal pulmonary arteries must be carefully inspected. Pulmonary arterial hypertension results in enlarged pulmonary arteries; however, the pulmonary veins remain a normal size. Additional possible radiographic changes range from dilation of pulmonary arteries and right ventricular enlargement with "pruning" of pulmonary arteries to a diffuse pulmonary interstitial pattern consistent with pneumonitis. See Chapter 23 for further discussion on feline heartworm disease. In contrast, left to right shunting lesions (e.g., most ventricular septal defects) cause an increased volume of blood in the pulmonary vascular system in proportion to the size of the defect and quantity of blood shunting through it. This increased volume results in enlarged pulmonary veins and arteries, whereas pulmonary arterial hypertension does not cause an increase in the size of the pulmonary veins.

Pleural effusion is a common sequela of heart failure in the cat, even when heart disease is primarily left-sided. However, pleural effusion can also be noncardiogenic. At least 50 cc of effusion must be present for it to be radiographically apparent in a cat (Owens 1982). Potential differential diagnoses of pleural effusion in the cat include hydrothorax (heart failure, uremia, hypoproteinemia, fluid overload), pyothorax, hemothorax, chylothorax, neoplasia, and pleuritis. A complete database including CBC, serum biochemistry profile, urinalysis, retroviral testing, fluid analysis, and thoracic ultrasonography with echocardiography is often required to differentiate cardiogenic from noncardiogenic pleural effusion. Pleural effusion is radiographically evident as focal areas of increased soft tissue opacity located within the thoracic cavity, which separate lung lobes from each other (pleural fissure lines) as well as from the thoracic wall. It may be unilateral or bilateral (most are bilateral since fluid may cross the mediastinum in most cats [Fox et al. 1999]). When pleural effusion is present, the radiographic findings will depend on the quantity of effusate. On the lateral projection, an increased radiopacity in the ventral portion of the thorax will be evident with a scalloped appearance of the lungs when a large volume of effusion is present. On the DV or VD projection, there will be retraction of the lung borders from the thoracic wall and blunting of the costophrenic angles, and the cardiac border may be partially or totally obliterated. The cranioventral and caudoventral segments of the mediastium usually appear widened because of the free fluid. In cases of pleural effusion, the VD projection is preferred over the DV projection for better assessment of cardiac size and shape, as long as the patient is clinically stable enough to tolerate the restraint. Thoracocentesis for therapeutic fluid drainage may be necessary prior to radiography (see Chapter 3 for more information on pleural effusion). If a large volume of effusion is suspected (by clinical signs), radiographic exposure levels should be increased (often abdominal technique chart levels will result in good exposure).

Left atrial enlargement is a common finding in cats with heart disease. A comparison of electrocardiography (ECG), radiography (lateral projection) and echocardiography for diagnostic accuracy at detecting left atrial enlargement in cats revealed good agreement ($r = 0.70$; $p = 0.001$) between radiography and echocardiography (and radiography was superior to ECG) (Schober et al. 2007). Radiographic indices of left atrial enlargement have low sensitivity and high specificity for enlargement, with the vertebral heart size method having the best specificity (0.95) and positive predictive value (0.88–0.9) of all the variables tested (including subjective radiographic interpretation). The lower sensitivity of radiography for detecting left atrial enlargement likely reflected cases of moderate or mild enlargement. Selected ECG variables such as P wave amplitude and duration had a high specificity and positive predictive value but a low sensitivity and negative predictive value for left atrial enlargement in cats; thus, P wave changes may suggest left atrial enlargement but their absence does not rule it out (Schober et al. 2007). When left atrial enlargement is present, the clinician may notice slight elevation of the distal trachea and carina in the lateral projection. If there is left atrial enlargement, but the ventricle is not also markedly enlarged, the cardiac silhouette has been described to have the appearance of a tilted ice cream cone on the lateral projection (Rishniw 2000) (Figure 6.9). On the VD or DV projection, an enlarged left auricular appendage, which extends beyond the heart border,

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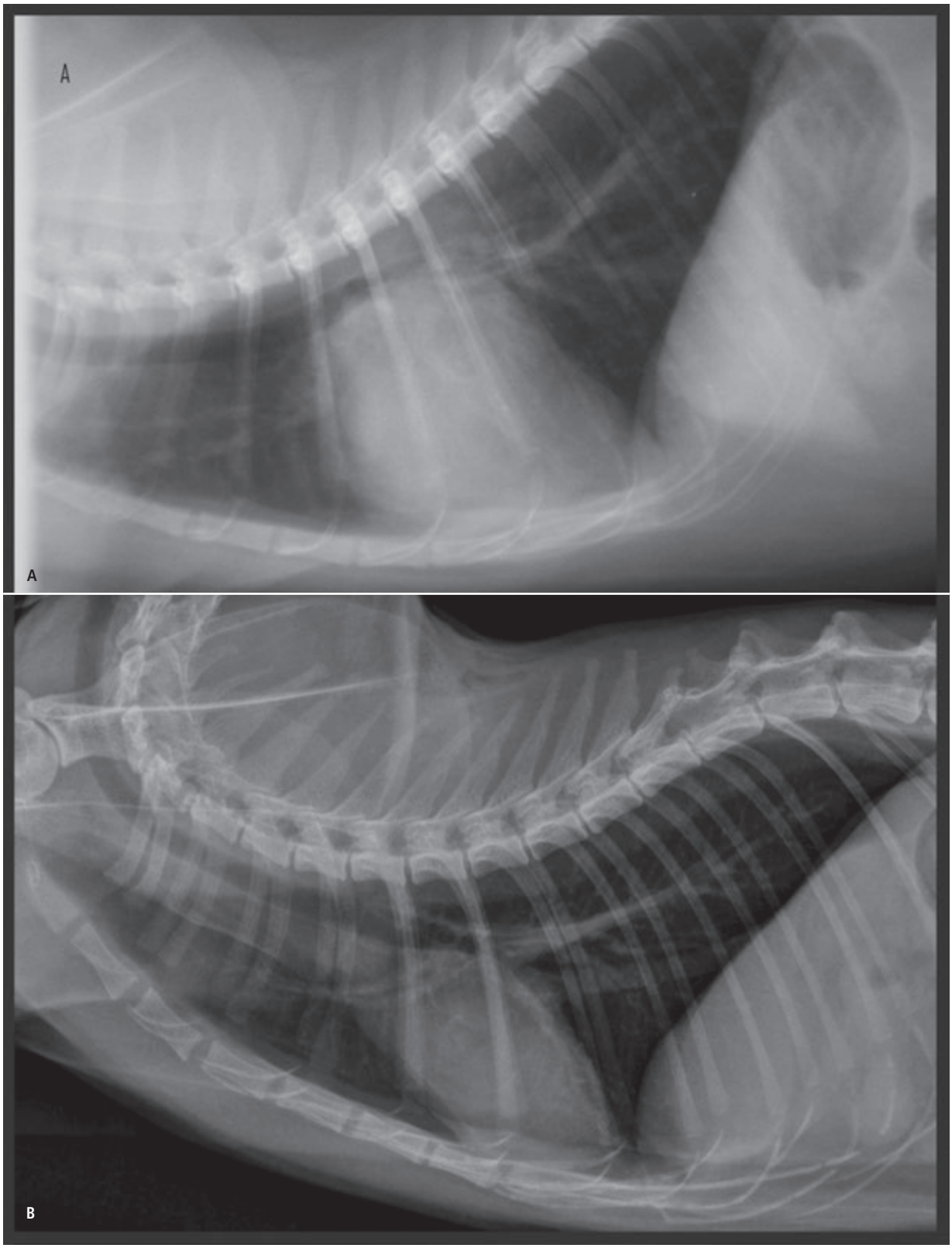


Figure 6.9. Lateral thoracic view from a cat with severe left atrial enlargement **(A)** vs a normal cat **(B)**. Note the ice cream cone appearance of the enlarged heart and that the left atrium is positioned caudoventrally to the carina rather than caudodorsally as in the dog.

may be evident in the 2–3 o'clock position. A double opacity of the atrial body over the heart base may also be evident. The "valentine-shaped heart" can occur due to left atrial enlargement or biatrial enlargement and is not specific to an underlying form of cardiomyopathy. Rather, similar to the tilted ice cream cone appearance on a lateral projection, it is suggestive of left or biatrial enlargement. The VD or DV projection is the most sensitive for detecting left atrial enlargement in cats (Fox 1999).

Left ventricular enlargement can be noted on the lateral projection as a straightened, more vertical than normal, caudal heart border. On the VD/DV projection there may be rounding of the left ventricular border. However, the specific pattern of cardiac enlargement (i.e., tilted ice cream cone) yields no information regarding the underlying heart disease which has led to the remodeling. An echocardiogram would be required to define the underlying disease process. Right atrial and ventricular enlargement are much less commonly observed in cats because the diseases that could lead to these changes are less common than left-sided heart diseases in this species. However, when it occurs, marked right ventricular hypertrophy tends to cause an increased convexity to the cranial cardiac border and dorsal displacement of the apex from the sternum. Right heart disease, particularly if the right atrium is enlarged, will tend to cause vena caval enlargement as well. Despite the potential increase in right ventricular afterload, necropsy-confirmed pulmonary thromboembolism (PTE) has been associated with normal thoracic radiographic findings in cats. Therefore, PTE should be a top differential in a feline patient with severe respiratory distress, no upper airway obstruction, and normal thoracic radiographs (Schermerhorn et al. 2004). See Chapter 25 for further discussion on feline PTE.

Thoracic radiographs should also include the cranial abdomen and a thorough assessment includes interpretation of the visible abdomen. Hepatomegaly and ascites are rare in the cat, but can occur secondary to right heart disease such as tricuspid valve dysplasia. Also, the diagnosis of peritoneopericardial diaphragmatic hernia is supported by an enlarged, rounded cardiac silhouette and missing or cranially displaced abdominal organs (see Chapter 22 for a discussion of common feline pericardial diseases). Important abdominal lesions may be recognized, unrelated to heart disease but associated with clinical or thoracic radiographic abnormalities.

Correct interpretation of feline radiographs requires a complete, systematic approach to the entire radiographic study as well as a good awareness of likely differentials based on a thorough history and physical examination. Echocardiography is more sensitive at evaluating mild changes in heart structure; however, use of the VHS is an objective way to evaluate heart size and an excellent screening technique in clinically ill cats. Radiography may be an effective way to screen asymptomatic cats if echocardiography is unavailable locally or is prohibitively expensive for a client. However, cats with early disease (and normal heart size) can be mistakenly identified as unaffected with this approach, and the cost:benefit ratio of choosing radiographic evaluation for screening must be carefully weighed and discussed with the owner.

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7

Echocardiography

Key Points

- Echocardiography has largely supplanted invasive cardiology techniques such as cardiac catheterization; however, its accuracy is dependent on a complete study and the interpreter's having a good understanding of basic cardiovascular anatomy and physiology.
- Thoracic radiographs are complementary to echocardiography; echocardiography does not give direct information regarding the respiratory system such as the presence of congestive heart failure.
- An echocardiogram should never be performed prior to a thorough history and physical examination. The echocardiogram should be used to rule in or out differential diagnoses that were based on the initial history and physical examination findings.

INTRODUCTION

Echocardiography has become the most important diagnostic tool for feline heart disease, allowing the clinician to assess cardiac size, structure, function, and blood flow within the heart. Echocardiography has largely replaced invasive diagnostic techniques such as cardiac catheterization for most patients; however, it does not replace survey thoracic radiographs for assessment of the lungs and pleura and for widespread availability. Moreover, accurate interpretation of echocardiographic information requires the background provided by signalment and a good physical examination. For example, altered hydration status in normal cats can produce changes in the echocardiographic measurements of the left ventricle (LV) and left atrium (LA) (Campbell et al. 2007). Pseudohypertrophy has been noted with hypovolemia, whereas intravenous fluid administration can result in increased LV and LA diastolic dimensions (Campbell et al. 2007). Some cats with cardiomyopathy are clinically normal and, conversely, a large percentage (25–69%) of cats with heart murmurs on physical examination have echocardiographic studies that are within normal limits (Bonagura 2000; Paige 2009; Wagner et al. 2010). Thus, interpretation of feline physical examination results, even with the benefit of an echocardiogram, can be complicated. Echocardiographic results are one piece in the puzzle.

ECHOCARDIOGRAPHY BASICS

An echocardiogram is simply an ultrasound examination of the heart. Ultrasound waves emitted from the echocardiograph (echo machine) are reflected by the interfaces of tissue and blood within the patient's thorax, and the echocardiograph computer processes the data to produce a two-dimensional (2D) cross-sectional image.

M-mode echocardiography is obtained according to the same principles, but with only a narrow beam of ultrasound that displays the reflected signals on a distance-time graph. Because the frame rate in M-mode is higher than the frame rate achieved using 2D echocardiography, resolution is better and M-mode echocardiography is therefore used for most time-dependent cardiac measurements.

Doppler echocardiography uses the Doppler principle to determine the direction and velocity of blood flow. The Doppler principle states that the frequency of a

Feline Cardiology, First Edition. Etienne Côté, Kristin A. MacDonald, Kathryn M. Meurs, Meg M. Sleeper.
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reflected sound wave depends on the direction and velocity of the reflector and the transmitted frequency. Since the ultrasound frequency emitted from the machine and the velocity of sound in soft tissue and blood are known, the velocity of red blood cells can be calculated and the information used by the echocardiograph to plot curves, called *envelopes*, that represent the movement of blood in a chosen location. Color-flow Doppler superimposes color labeling (of red blood cells) on the black-and-white 2D image, typically with blood moving toward the transducer labeled as red and blood moving away from the transducer labeled as blue. Spectral Doppler (either pulsed-wave, continuous-wave, or high-pulse repetition) calculates the blood flow velocity in a region of interest, selected by the operator by moving a cursor on the 2D image, and displays the results graphically.

Pulsed-wave and continuous-wave Doppler modalities are complementary. Pulsed-wave Doppler allows one to examine the velocity and direction of blood flow in a specific region of interest because the sample volume is chosen by the operator. However, pulsed-wave Doppler cannot record the maximal velocity or direction of flow when blood flow velocity is high, as occurs in various pathologic states. With high-velocity blood flow, pulsed-wave Doppler signals often are aliased, meaning that they are of too high a velocity to be accurately interpreted with the ultrasound probe and Doppler modality being used. Thus, once the site of abnormal flow is located with pulsed-wave Doppler (spectral or color-flow), the direction and velocity of flow can be measured using continuous-wave Doppler. Continuous-wave Doppler samples along the entire cursor line, so although it is not encumbered by velocity limits, the precise anatomic localization of the measured flow is not possible. Therefore, both modalities are necessary to fully define the characteristics of abnormal, high velocity flow (as occurs with mitral regurgitation, ventricular septal defects, etc.).

Pulsed-wave and color-flow Doppler signals alias when flow velocities are above the Nyquist limit (half the pulse repetition frequency; the maximum velocity of flow that can be measured accurately). Therefore, measurements of blood velocity by frequency shifts—the Doppler principle that underlies all of echocardiography—are only accurate when the pulse repetition frequency is at least twice the detected maximal velocity. The limited maximum pulse repetition frequency of ultrasound probes explains the frequent occurrence of aliasing with pulsed-wave Doppler, and the limited range of velocities that can be measured by this technique. Aliasing is depicted on the spectral display as a band signal (envelope) that "wraps around" the baseline (Figure 7.1) and on color-flow Doppler, aliasing is represented by color reversal (Figure 7.2); in both situations, aliasing means that an accurate measurement of blood velocity is not possible. The Nyquist limit is controlled by ultrasound beam depth and transducer frequency. Therefore, the deeper the structure of interest, the lower the transducer frequency that will be necessary. In small animals such as cats, a 7.5 mHz probe is usually adequate for a complete cardiac examination, but in a particularly large or obese cat a lower frequency probe (e.g., 5 mHz) may be necessary.

With tissue Doppler imaging (TDI), the velocity of myocardial wall motion (rather than blood) in a region of interest is measured. Spectral Doppler and TDI results are displayed in graph form (velocity against time with a simultaneous ECG). Blood flow and tissue velocities in the direction of the transducer are displayed as positive signals and those away from the transducer are displayed as negative signals. Tissue Doppler techniques are used for identifying otherwise undetectable myocardial wall motion abnormalities, and hold great promise for early detection of subtle lesions such as the earliest stages of hypertrophic cardiomyopathy (Nagueh et al. 2003).

ECHOCARDIOGRAPHIC EQUIPMENT

Optimal 2D images are obtained when structures are perpendicular to the ultrasound beam, whereas results are most accurate with Doppler echocardiography when the Doppler sound waves are directed parallel to the target. As the angle between the ultrasound beam and moving red blood cells increases, the velocity measured with Doppler will become less accurate. Angles greater than 25° yield unacceptable estimates of velocity. Many ultrasound machines have a feature that corrects for poor alignment (typically called *angle correction*). Unfortunately, this feature is prone to error and should not be used, because correction for poor angulation in one plane does not account for poor angulation in either of the other two dimensions. Incorrect velocity calculations are common with angle correction software.

Echocardiographic machines with these basic capabilities are becoming more and more affordable. Image quality remains the most critical capability, which is also largely affected by the probe (transducer). For cardiac applications, sector probes are superior to linear probes because of a smaller surface area that allows improved imaging through small feline intercostal spaces (smaller "footprint"), and they come in several types. Mechanical probes are most common with basic machines and contain an oscillating piezoelectric crystal. These probes

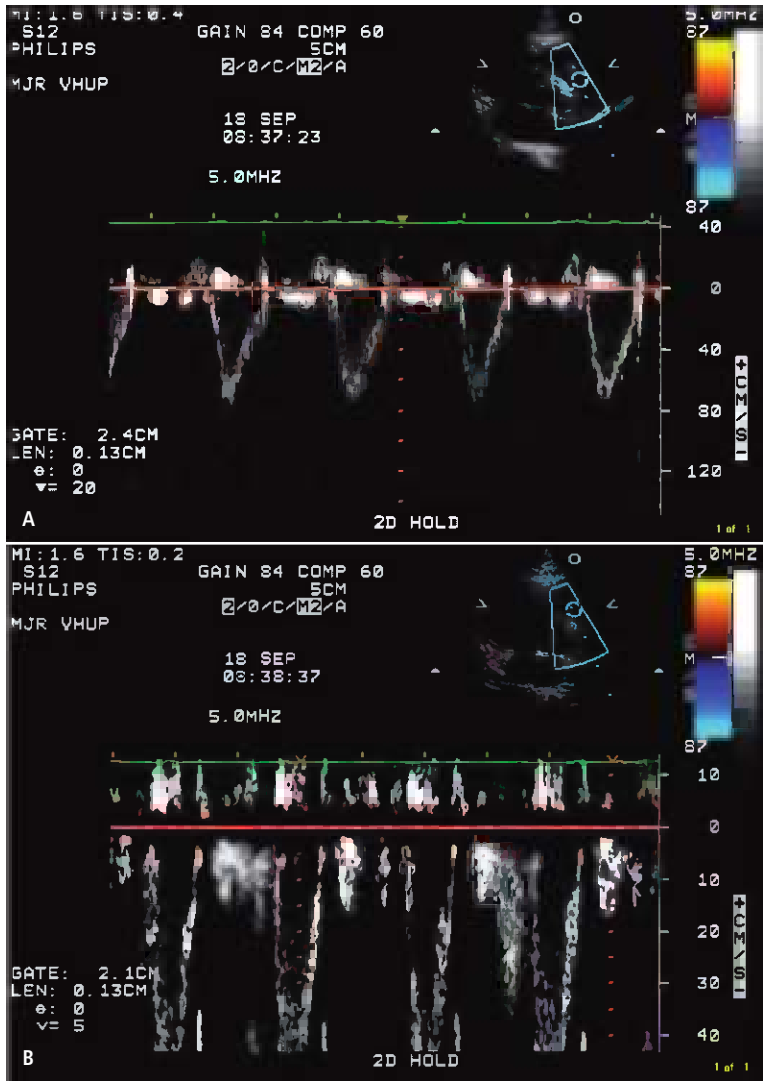


Figure 7.1. Pulsed-wave Doppler echocardiograms obtained at the pulmonary artery from a normal cat. The flow velocity is approximately 70 cm/sec in **(A)** with a laminar flow pattern. Note that when the scale is reduced excessively in **(B)**, the velocity is beyond the measurable range (40 cm/s) and the signal "wraps around the baseline" or aliases, preventing accurate interpretation.

can be felt to vibrate during imaging. Phased array probes are more expensive because they contain an array of crystals, which are electronically fired, resulting in improved focusing. Some commercial probes have a frequency bandwidth, which allows a single probe to operate at more than one frequency; this is an advantage because the optimal frequency can be chosen without changing probes during the echocardiogram. Low-frequency probes have deeper penetration and produce superior Doppler signals; however, the resulting image has poorer resolution. High-frequency probes (7.5–10 mHz) have low penetrating power but high resolution and structural definition; high-frequency probes are superior in cats. Because cats have high resting heart rates, a system capable of high frame rates will produce superior image quality.

Most echocardiographers position the animal in lateral recumbency and approach the thoracic wall from underneath (the dependent chest wall; Figure 7.3) because gravity draws the heart toward the transducer against the thoracic wall, enlarging the acoustic window (Thomas et al. 1993). This approach is particularly helpful in animals with a normal heart size, or when primary respiratory disease is present because hyperinflation of the lungs due to chronic respiratory disease can decrease the size of the cardiac window. Echocardiographic tables can be purchased or manufactured; a cutout allows imaging from below and facilitates the examination. One experienced restrainer is often adequate, but for an uncooperative cat, 2 restrainers are optimal. Some cardiologists recommend using an Elizabethan collar when restraining cats for echocardiography to protect the restrainer (Côté 2005). It is important to be certain fractiousness is not related to a medical problem if the patient becomes uncooperative (pulmonary edema, orthopedic disease, etc.). It is rare that the echocardiographic results

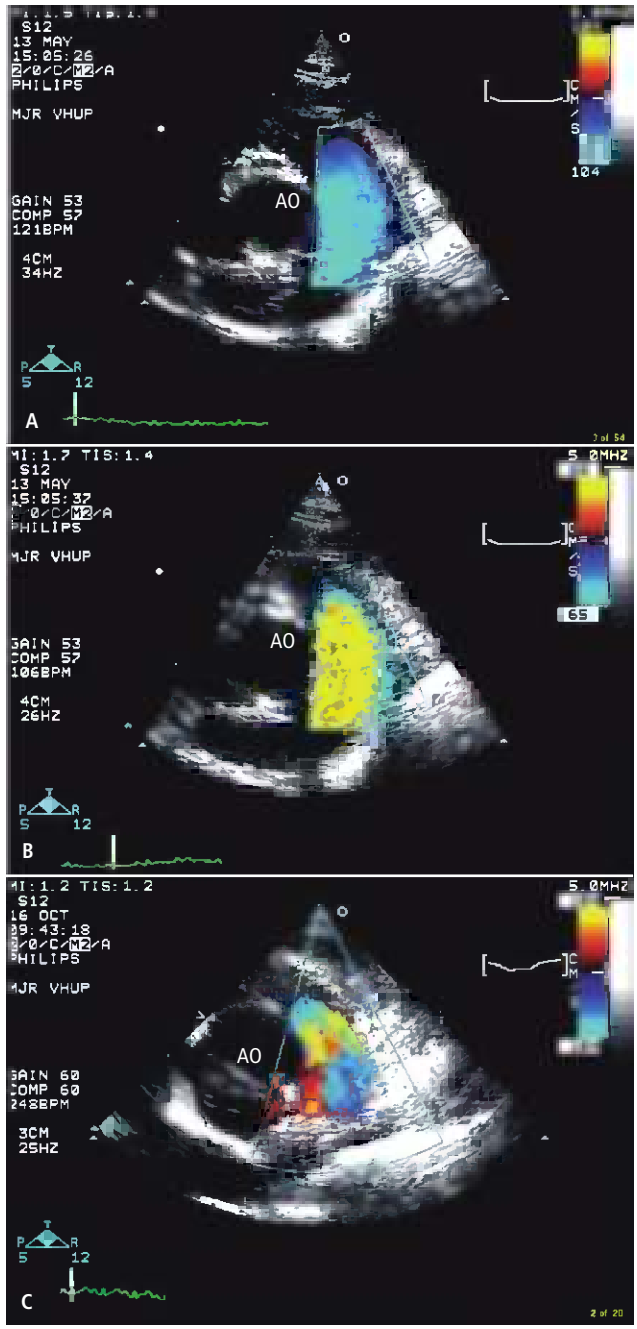


Figure 7.2. The color-flow Doppler echocardiograms obtained at the right parasternal window. The pulmonary artery is being interrogated with color-flow Doppler. **(A)** Right ventricular outflow is labeled in blue because the blood is exiting the heart away from the transducer. Note: the color-flow Doppler scale (upper corner of each frame) is set so that flow velocities of up to 104 cm/sec can be measured before aliasing will occur. **(B)** In this frame, note that the color-flow Doppler scale has been reduced to 65 cm/s and the pulmonary flow pattern shows "color reversal" (both yellow and blue labeling are displayed because the flow velocity is above the range of the current scale, so aliasing occurs). **(C)** "Color reversal" is also noted in this patient's pulmonary artery; however, the color-flow Doppler scale is set at 104 cm/s. When the region is evaluated using continuous-flow Doppler (which can measure high velocity flows), this cat was found to have accelerated pulmonary artery outflow consistent with mild pulmonic stenosis (300 cm/s). Ao = aorta.

will change the immediate treatment plan for a cat in heart failure, and therefore reserving the complete echocardiogram until after therapy and stabilization of the patient in distress is critical. Some echocardiographers prefer imaging animals in a standing position, but restraint is often more difficult. Usually plentiful use of isopropyl rubbing alcohol and acoustic gel on the patient's skin will result in good acoustic contact and optimizes image quality. However, occasionally the hair of obese or long-haired cats will need to be clipped for optimal image acquisition.

Ideally, the patient will be tractable for the examination without sedation. However, if the patient is uncooperative, mild sedation may be necessary. The following combinations are less likely to affect echocardiographic results than general anesthesia (see Chapter 27 for more information):

- *Light sedation*
  - Low-dose acepromazine (0.11–0.22 mg/kg IM or SQ) and an opiate (e.g., buprenorphine (0.005–0.01 mg/kg IV or IM), or

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Figure 7.3. A young cat restrained in lateral recumbency for an echocardiogram with the transducer located on the right parasternum.

- Butorphanol and midazolam (0.3 mg/kg of each, IM or IV)

- *Deep sedation*
  - Dexmedetomidine 0.01 mg/kg IM or IV alone, or with either diazepam (0.2 mg/kg IV) or midazolam (0.05–0.3 mg/kg IV or IM) if hypertrophic cardiomyopathy has been confirmed previously and the patient is not hypertensive (for deep sedation), or
  - Low-dose ketamine (1–2 mg/kg IV or PO) with or without diazepam (0.02 mg/kg IV) or acepromazine (0.11–0.22 mg/kg IM or SQ) for severely fractious cats

It is very important to obtain a simultaneous electrocardiogram (ECG) during the echocardiographic examination to allow accurate timing of measurements. Without a simultaneous ECG, timing of cardiac measurements can easily be incorrect and erroneous diagnoses are possible. The teeth on metal alligator clips can be sanded away to make the clips more comfortable for the patient. Alternatively, atraumatic clips may be used or human ECG electrode patches can be applied with the gelled surface directly against the patient's metacarpal or metatarsal pad and a soft wrap to secure the electrode for the duration of the examination.

PERFORMING THE ECHOCARDIOGRAM

Accurate interpretation of echocardiographic findings requires a complete and thorough examination. The best way to ensure one always obtains a complete study is to adopt a consistent technique. Echocardiography is ideally suited to identification of structural lesions, but quantitative assessment of cardiac dimensions and function is also important. Most sonographers begin the examination at the right parasternal window (most often the right 4th or 5th intercostal space). By convention, the marker on the probe is directed toward the patient's elbow to obtain the short axis views and toward the shoulder to produce the long axis views. Both short and long axis views are required to thoroughly image a 3D structure like the heart using a 2D modality like echocardiography. A simple analogy is to think of the heart as a carrot and the ultrasound beam as a knife. The knife both slices the carrot longitudinally (long axis) for a global overview of the carrot and, with a 90° rotation of the direction of the blade, chops the carrot from tip to top (series of short axis views) to provide a comprehensive evaluation of the structure.

Once the heart is visualized, the depth setting is optimized and the time gain compensation controls, reject, and compression settings are adjusted to ensure structures of interest are ideally visualized. Panning along the entire heart in this plane is important for a complete assessment. Specifically, the short axis view is evaluated at the ventricular level (Figure 7.4A) and at the heart base where the aorta and left atrium are visualized (Figure 7.4B). In addition, M-mode studies at three standard short axis planes should be obtained: the ventricular, atrioventricular (AV) valve, and aortic valve levels (Figure 7.5). The left ventricular measurements are obtained from the M-mode obtained at the level of the chordae tendinae and include the interventricular septum and left ventricular free wall and the left ventricular end-diastolic

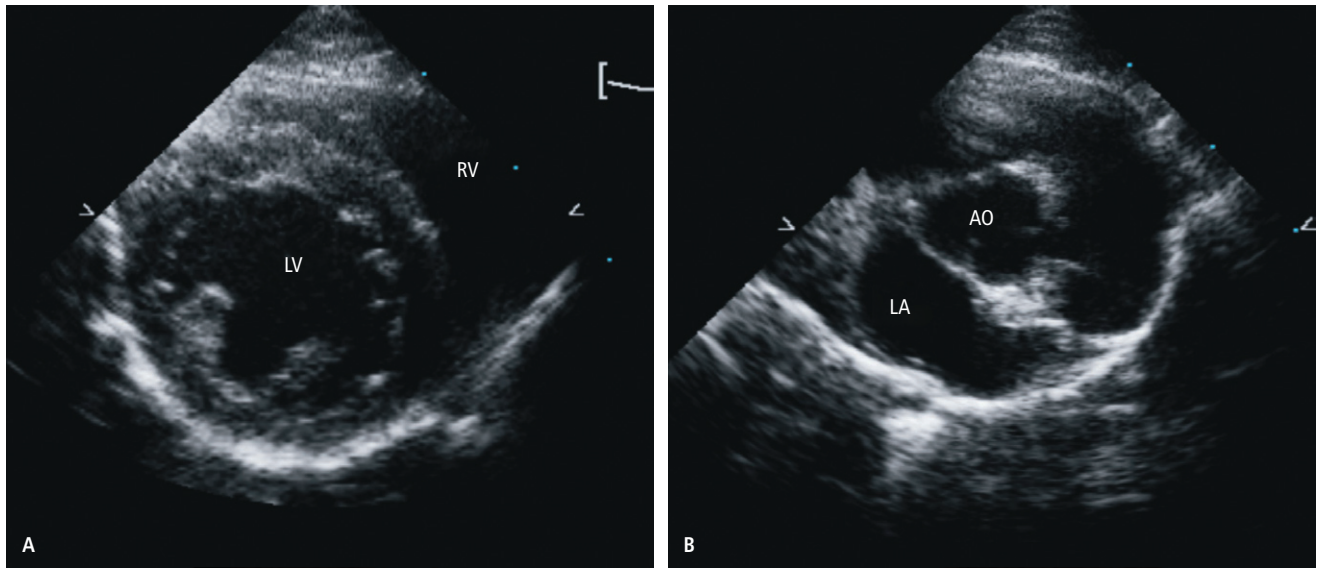


Figure 7.4. Short-axis views of the heart from the right parasternum at the ventricular level **(A)** and the heart base **(B)**. LV = left ventricle, RV = right ventricle, LA = left atrium; Ao = aorta.

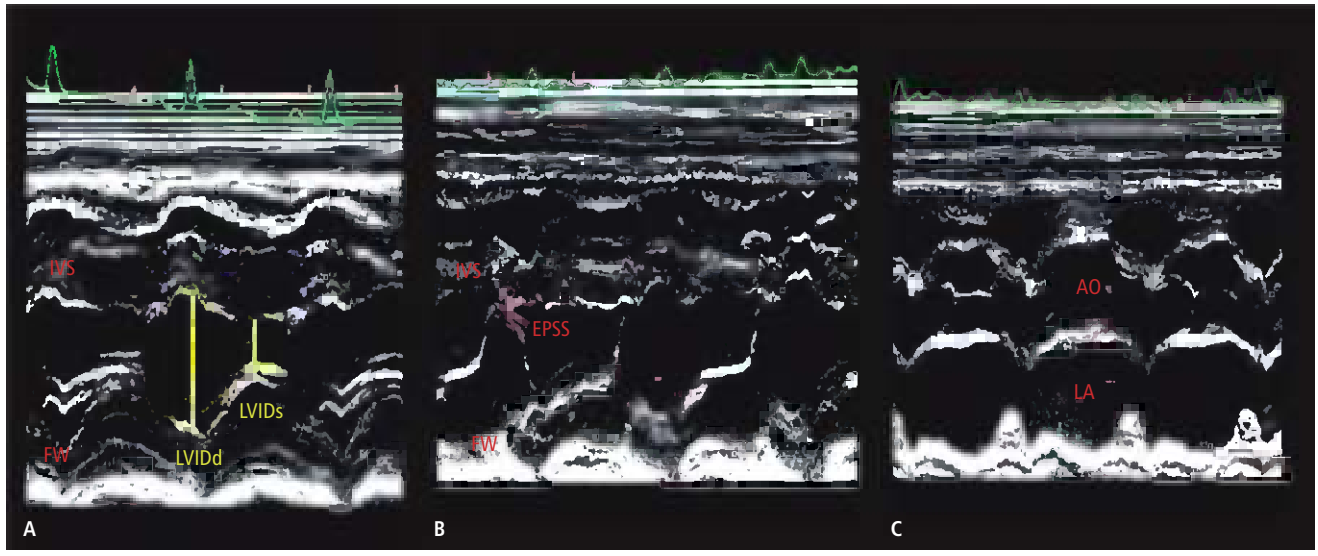


Figure 7.5. M-mode images obtained from the right parasternum at the left ventricular level **(A)**, the atrioventricular level **(B)**, and the heart base **(C)**.

(A) Left ventricular M-mode image with yellow lines marking the correct position for the left ventricular dimension measurements. LVIDd = left ventricular internal dimension during diastole; LVIDs = left ventricular internal dimension during systole; IVS = interventricular septum; FW = left ventricular free wall.

(B) M-mode image obtained at the level of the mitral valve. The E-point to septal separation (EPSS) is the measurement between the interventricular septum (IVS) and the anterior mitral valve leaflet at the valve's widest excursion during diastole. IVS = interventricular septum; FW = left ventricular free wall.

(C) M-mode image obtained at the heart base. Ao = aorta; LA = left atrium.

and end-systolic measurements. Measurements are made from leading edge to leading edge with diastolic measurements made at the onset of the QRS complex on the ECG (left ventricular chamber and wall diastolic measurements) and systolic measurements made at peak excursion of the cardiac walls on the M-mode image. The "leading edge" represents the structure's edge closest to the transducer; the trailing edge is the part farthest from the transducer. Without an ECG for timing, measurements can easily be performed at the incorrect time of the heart cycle and misdiagnosis is possible. Therefore it is critical to have an ECG performed simultaneously with

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the echocardiogram. If the rhythm is irregular, measurements from several beats should be averaged, typically 5 beats occurring at a rate that would be expected to mimic the rate of a healthy cat in the same context (e.g., 160–240 beats/minute). The E point to septal separation (EPSS) is a measurement that is obtained from the M-mode image derived at the level of the mitral valve annulus. The EPSS is the distance from the E point of the anterior mitral valve leaflet to the interventricular septum measured at the valve's largest excursion in early diastole (Figure 7.4B).

M-mode studies are traditionally obtained for measurements at the midventricular (see Figure 7.5A), AV valve annulus (see Figure 7.5B), and heart base levels (see Figure 7.5C). Although an M-mode study is routinely obtained at the heart base, the aortic and left atrial measurements are optimally obtained using the 2D image at this level because M-mode alignment may include the left atrial appendage rather than the left atrial body or may cross the chamber tangentially, resulting in an inaccurate measurement (Oyama 2004; Abbott and MacLean 2006). In the short axis, the left atrium:aorta ratio should be <1.5 during diastole. Left atrial size is commonly expressed as a ratio of the atrial and aortic dimensions, a value that is then independent of body size. Atrial size reflects long-standing ventricular filling pressures and is therefore a good measure of hemodynamic stress and a critical echocardiographic variable to measure. If the left atrial size is normal, diastolic function is likely to be fairly normal suggesting that any concurrently measured LV wall thickening is artifactual or disease such as hypertrophic cardiomyopathy is early/mild. Moreover, increased left atrial size has been associated with poor prognosis in cats affected with hypertrophic cardiomyopathy (Abbott and MacLean 2006). In this study comparing aortic ratio to left atrial size using 2D- or M-mode–based measurements, there was relatively poor agreement between left atrial dimensions obtained from M-mode and 2D studies; however, results were similar and a ratio greater than 1.5 using either technique suggested left atrial enlargement (Abbott and MacLean 2006), suggesting the most important factor is probably consistency of measurement technique, rather than the technique chosen.

Although the standard view to measure the left ventricular (LV) chamber and walls is by M-mode at the level of the chordae tendineae, left ventricular measurements should optimally also be obtained on 2D. 2D imaging is superior for assessing regional, asymmetric hypertrophy, which may not be obvious on the M-mode (Wagner et al. 2010). One group has developed a method using 3 interventricular septal measurements (2 in the short axis [left: from 9 to 12 o'clock; right: from 12 to 3 o'clock] and 1 in the long axis [midseptum]) in addition to M-mode measurements in order to better identify cats with asymmetric disease (Paige et al. 2009). The substantial improvement conferred by this technique is the inclusion of regional abnormalities like focal LV thickening that are otherwise missed on M-mode studies. Measurements should be made on an image that is of excellent quality. Using a poor quality image predisposes to diagnostic error whether the sonographer uses an M-mode or a 2D image. Recall that the leading edge is the part of the line produce by an acoustic interface (i.e., the interface between blood and tissue), which is closest to the transducer, whereas the trailing edge is the part of the line farthest from the transducer. Historically, the American Society of Echocardiography recommended measuring structures from leading edge to leading edge in M-mode and 2D images because this border represented the location of the specific interface. Therefore, the leading edge to leading edge measurement technique resulted in the most accurate measurement of a given structure. However, improvements in image processing have led to echocardiographic machines capable of substantially improved structure resolution so that it is now possible to visualize the actual tissue-blood interface (Lang et al. 2005).

Additionally, in some cats it is difficult to center the M-mode line between the papillary muscles, resulting in erroneous wall thickness measurements. LV papillary muscles are larger in cats with hypertrophic cardiomyopathy than normal cats and a normal range for papillary muscle measurements exists (Adin and Diley-Poston 2007). Papillary muscle hypertrophy would be missed with standard M-mode measurements alone. Although there is overlap between normal and diseased groups, left ventricular papillary muscle measurement may provide additional information for interpretation of the feline echocardiogram, particularly since papillary muscle hypertrophy may be the first indicator of disease.

Left ventricular wall measurements are critical in cats, where myocardial diseases, particularly hypertrophic cardiomyopathy, are a common cause of heart disease. Hypertrophic cardiomyopathy may result in segmental or diffuse concentric ventricular hypertrophy. Less commonly, regional thinning of the ventricular wall may occur secondary to chronic infarction or aneurysm. Diastolic wall measurements must be made at end-diastole, when the walls are at their thinnest, to avoid overdiagnosis of hypertrophic cardiomyopathy. Diastolic measurements are made at the beginning of the QRS. The measurement may also be overestimated using machines with slow frame rates. Normal echocardiographic values have been reported for the cat by multiple investigators (Table 7.1). A left ventricular wall thickness of greater than or equal to 0.6 cm is abnormal in a

Table 7.1. Normal feline M-mode echocardiographic measurements

Parameter	Moïse et al.	Jacobs and Knight(a)	Fox et al.	Koffas et al.	Chetboul et al.	Adin and Diley-Poston	Drourr et al. (Maine coon)
LVIDd (cm)	1.51 ± 0.21	1.59 ± 0.19	1.40 ± 0.13	1.49 ± 0.22	1.89 ± 0.23	1.54 ± 0.16	1.85 ± 0.21
LVIDs (cm)	0.69 ± 0.22	0.80 ± 0.14	±0.81 ± 0.16	0.83 ± 0.22	0.81 ± 0.18	0.75 ± 0.19	0.89 ± 0.2
Ao (cm)	0.95 ± 0.15	0.95 ± 0.11	0.94 ± 0.11	–		0.95 ± 0.14	1.12 ± 0.13
LA (cm)	1.21 ± 0.18	1.23 ± 0.14	1.03 ± 0.14	–		1.13 ± 0.17	1.37 ± 0.17
LA/Ao	1.29 ± 0.23	1.30 ± 0.17	1.10 ± 0.18	–	0.9 ± 0.1	1.20 ± 0.19	1.23 ± 0.16
IVSd (cm)	0.50 ± 0.07	0.31 ± 0.04	0.36 ± 0.05	0.38 ± 0.08	0.46 ± 0.06	0.45 ± 0.08	0.4 ± 0.07
LVFWd (cm)	0.46 ± 0.05	0.33 ± 0.06	0.35 ± 0.08	0.38 ± 0.09	0.43 ± 0.07	0.41 ± 0.07	0.43 ± 0.06
IVSs (cm)	0.76 ± 0.12	0.58 ± 0.06	–	0.64 ± 0.12	0.74 ± 0.13	–	0.75 ± 0.13
LVFWs (cm)	0.78 ± 0.10	0.68 ± 0.07	–	0.68 ± 0.11	0.75 ± 0.11	–	0.8 ± 0.11
EPSS (cm)	0.04 ± 0.07	0.02 ± 0.09	–	–	–	–	–
RVDd (cm)	0.54 ± 0.10	0.60 ± 0.15	0.50 ± 0.21	–	0.3 ± 0.14	–	–
HR (bpm)	182 ± 22	194 ± 23	245 ± 36	150 ± 26	184 ± 33	–	–
Body weight (kg)	4.3 ± 0.05	–	3.88 ± 1.17	4.56 ± 0.8	4.6 ± 1.2	–	5.5 ± 1.33
Age (yr)	–	4.11 ± 1.05	3.36 ± 3.15	6.9 ± 3.5	3.1 ± 2.4	4.7 ± 3.7	–

LVIDd = left ventricular internal dimension during diastole; LVIDs = left ventricular internal dimension during systole; Ao = aortic diameter; LA = left atrial diameter; IVSd = interventricular septum diameter during diastole; LVFWd = left ventricular free wall diameter during diastole; IVSs = interventricular septum diameter during systole; LVFWs = left ventricular free wall diameter during systole; EPSS = E point to septal separation; RVDd = right ventricular internal diameter during diastole; HR = heart rate.

normovolemic cat and suggests the presence of HCM or secondary left ventricular hypertrophy (i.e., systemic hypertension). Some clinicians use a more stringent classification and define left ventricular hypertrophy as being when the walls measure greater than 0.55 cm in thickness (Wagner et al. 2010). Breed-specific differences do not appear to be significant in cats compared to dogs because there is much less body size variation between breeds; however, one group has reported several M-mode echocardiographic parameters for Maine coon cats (Drourr et al. 2005). Not surprisingly, the normal cardiac dimensions are increased in this breed of physically large cats compared to the smaller feline breeds (Table 7.1). After measurements are completed, the heart should be assessed subjectively in real time for abnormalities in chamber size, wall thickness and motion, valve morphology and valve.

Systolic dysfunction, the hallmark of dilated cardiomyopathy, is now observed relatively uncommonly in cats, a species that most frequently develops diastolic abnormalities. However, it is also important to evaluate systolic function by echocardiography. Systolic performance can be assessed by several different echocardiographic measurements, all of which are affected by loading conditions. This means that echocardiographic measurements must be interpreted with consideration given to factors that may increase or decrease heart rate (excitement, hyperthyroidism, medications, sedatives/anesthetics, etc.), intravascular volume (hydration status), blood viscosity (anemia, polycythemia), and blood pressure. The left ventricular shortening fraction (SF% or FS%) is the most commonly used echocardiographic index of systolic function in veterinary medicine. It is calculated using the equation: SF% = [(LVIDd-LVIDs)/LVIDd] × 100. In this formula, LVIDd is the left ventricular internal dimension during diastole and the LVIDs is the left ventricular internal dimension during systole. The SF% increases with improved contractility, increased preload, or decreased afterload. The normal range in cats is 35–55%. Hypertrophic cardiomyopathy patients are said to have an elevated SF% due to a smaller ventricular luminal diameter, but many cases with mild hypertrophy and/or regional, nondiffuse hypertrophy may have a normal SF%. Therefore, SF% cannot be used for ruling in or ruling out hypertrophic cardiomyopathy. The end-systolic dimension is also a marker of systolic function, which correlates in an inverse pattern with systolic function; intuitively, as LV systolic function decreases, LV end-systolic diameter increases. Additionally, the EPSS dimension increases with reduced systolic function. Normally there is no or very little separation; however, as the left ventricular ejection fraction—which is the 3-dimensional equivalent of SF%—decreases, the EPSS increases.

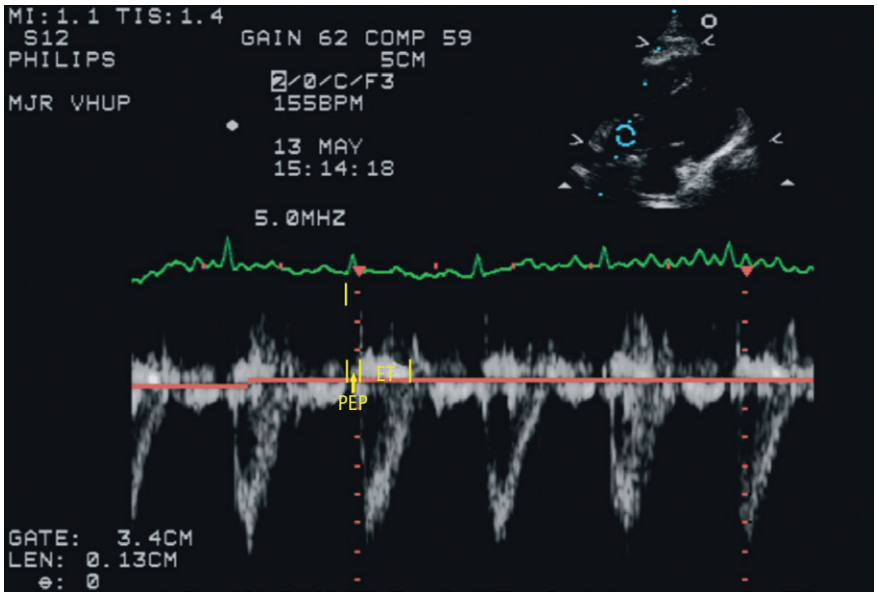


Figure 7.6. Pulsed-wave Doppler echocardiogram obtained at the aorta with correctly positioned calipers for measuring the preejection period (PEP) and the ejection time (ET). Note that the laminar blood flow appears as a single systolic envelope.

Systolic time intervals assess LV systolic performance but are also affected by heart rate, preload, and afterload. The preejection period (PEP) represents the time between initial ventricular electrical activity (the onset of the QRS) and the onset of LV ejection (opening of the aortic valve); the LV ejection time (LVET) is measured from aortic valve opening to closure. Total electromechanical systole is represented by the interval from QRS initiation to aortic valve closure (PEP + LVET). The PEP/LVET index compensates for cardiac loading conditions and is superior to either index alone. These measurements can be obtained using M-mode or Doppler tracings (Figure 7.6), but they are infrequently used in feline cardiology, because they have not convincingly been shown to provide clinically important information. See Table 7.2 for normal echocardiographic feline systolic performance parameters.

After the short axis views are obtained, the probe should be rotated 90° at the right parasternal position to obtain the long axis images. The two standard images include the left ventricular outflow tract view (Figure 7.7A) and the 4-chamber view (Figure 7.7B). The transducer is shifted between these two planes by slight cranial to caudal angulation. Before turning the cat to the other side for evaluation from the left cardiac windows, Doppler imaging from the right should be performed. Color-flow Doppler should be performed at every valve to screen for abnormal transvalvular flow. Screening for valvular insufficiency can be performed using color-flow Doppler at the right parasternal window; however, it is important to recognize that trace amounts of valve regurgitation (a subjective assessment that varies depending on ultrasound software and settings, but generally is too small to produce an audible murmur on physical exam) are common in normal cats, particularly of the pulmonic and tricuspid valves (Adin and Diley-Poston 2005). The color-flow sample volume should also be placed over the interventricular and interatrial septae to evaluate for turbulent flow through septal defects that are not visible two-dimensionally. Color-flow Doppler investigation of the left ventricular outflow tract in the right parasternal long axis view is particularly important in cats to identify systolic anterior motion of the mitral valve (SAM). If SAM is present, aliasing, turbulent flow typically will be noted in the left ventricular outflow tract in conjunction with eccentric mitral regurgitation (i.e., mitral regurgitation directed to the left atrial free wall rather than left atrial roof) during systole. See Chapter 11 for further discussion of hypertrophic obstructive cardiomyopathy. Pulmonary artery flow is recorded from the right parasternal short-axis view (or less commonly from the left cranial parasternal position). Normal outflow will have a single systolic envelope away from the transducer in a pulsed-wave Doppler tracing (with a velocity less than 1 m/s).

For left-sided imaging the cat is turned so that the left parasternum (ventralmost aspect of the left side of the thorax) is located over the cutout in the table. The left apical views (the 4- and 5-chamber views) are used so that the transducer beam will be parallel to blood flow for accurate Doppler assessment of flow across the aortic, mitral, and tricuspid valves. The location for this

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Table 7.2. Normal feline echocardiographically derived systolic performance indexes

Parameter	Sisson et al.	Moïse et al.	Jacobs and Knight(b)	Fox et al.	Koffas et al.	Chetboul et al.	Adin and Diley-Poston	Drourr et al. (Maine coon)	Atkins and Snyder
SF (%)	52.1 ± 7.1	55.0 ± 10.2	49.8 ± 5.3	42.7 ± 8.1	44 ± 11	49 ± 7	53 ± 11	51.85 ± 7.74	
PEP (ms)				44 ± 9					46 ± 5
LVET (ms)			140 ± 20	116 ± 11					116 ± 19
PEP/LVET				0.38 ± 0.08					0.40 ± 0.05
HR (bpm)	–	182 ± 22	194 ± 23	245 ± 36	150 ± 26	184 ± 33			226 ± 25
Body weight (kg)	4.7 ± 1.16	4.3 ± 0.05	–	3.88 ± 1.17	4.56 ± 0.8	4.6 ± 1.2		5.5 ± 1.33	
Age (yr)	5.1;range (0.5–15)	–	4.11 ± 1.05	3.36 ± 3.15	6.9 ± 3.5	3.1 ± 2.4	4.7 ± 3.7	–	

SF = shortening fraction; PEP = preejection period; LVET = left ventricular ejection period; HR = heart rate.

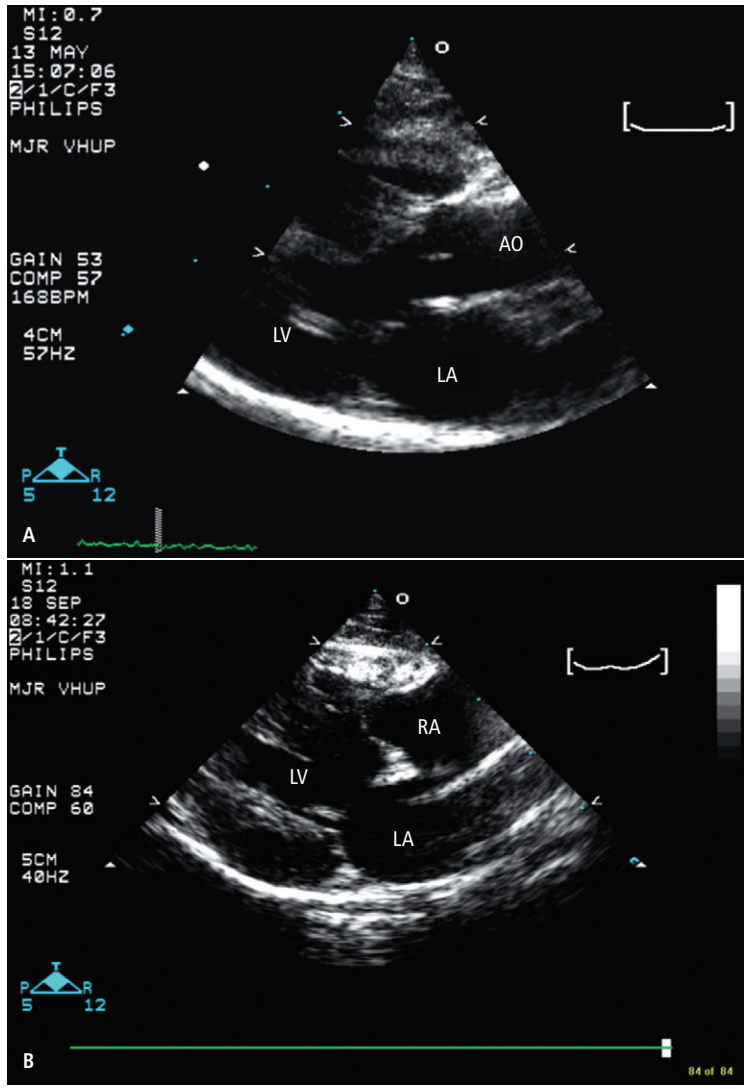


Figure 7.7. **(A)** Right parasternal long-axis echocardiographic image from a normal cat at the left ventricular outflow tract view. Ao = aorta, LA = left atrium; LV = left ventricle. **(B)** Right parasternal long-axis echocardiographic image from a normal cat at the 4-chamber view. RA = right atrium; LA = left atrium; LV = left ventricle.

window is close to the sternum between the 5th and 7th intercostal spaces. The 4-chamber view (Figure 7.8) from this window is oriented vertically with the left side of the heart appearing to the right of the 2D image and the right side of the heart appearing to the left (by convention). In order to obtain this orientation, the probe marker is directed toward the animal's left hip. By tilting the beam slightly cranially from this view, the examiner will bring the aortic valve into view. Hence this view is termed the 5-chamber view because all 4 cardiac chambers and the aortic root are visible. The left apical 2-chamber view is achieved when the ultrasound beam is nearly perpendicular to the long axis of the body and parallel to the long axis of the heart. With this view, the left atrium, mitral valve, and left ventricle are visible in long axis view. The subcostal view, which is commonly used in dogs to obtain the most parallel alignment with the aorta, and therefore the most accurate aortic velocity measurement, is rarely necessary in cats.

The normal aortic spectral Doppler tracing from the 5-chamber view is one single systolic envelope, directed away from the transducer, with a peak velocity of <1.4 m/sec. Normal cats that are excited or stressed may have increased flow velocities up to 2 m/s. However, in any cat with aortic outflows in the upper end of normal, it is important to critically evaluate the mitral valve and left ventricular outflow tract for the presence of systolic anterior motion. Mitral valve inflow is obtained using pulsed-wave Doppler from the apical 4- or 2-chamber view. A small sample volume should be used and placed at the leaflet tips. The diastolic flow pattern (left ventricular filling) is dependent on heart rate. In many cats, the heart rate is rapid enough that early and late filling are combined into one positive wave which follows the

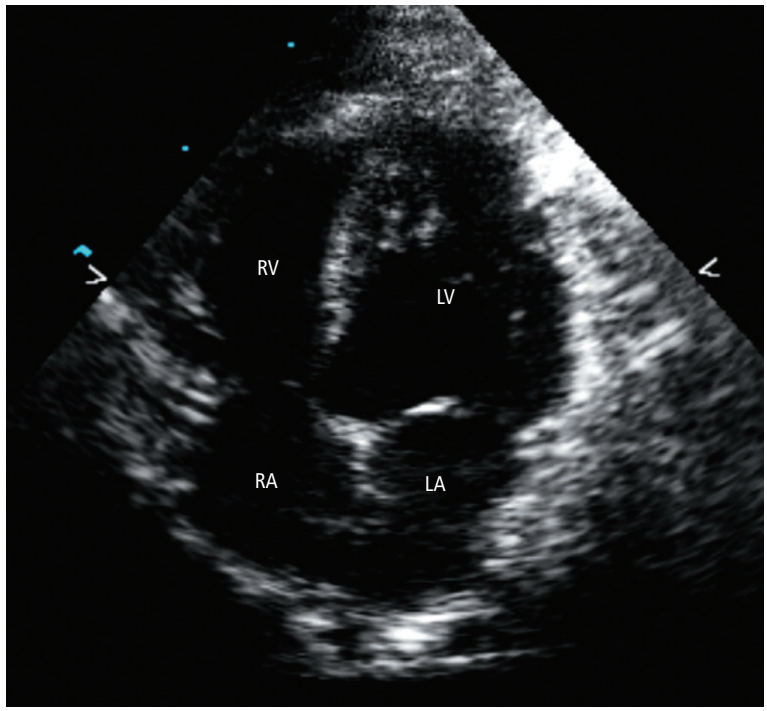


Figure 7.8. A 4-chamber view obtained from the left apical view. Transmitral and transtricuspid flow (ventricular filling) are parallel with the ultrasound beam in this alignment, which optimizes Doppler studies. RA = right atrium, LA = left atrium; LV = left ventricle; RV = right ventricle.

P wave. However, if the heart rate is reasonably slow (<180 bpm), two separate phases of diastolic flow are generally recorded. The E wave corresponds to early, passive filling, and the A wave corresponds to late, active filling (atrial contraction) and follows the P wave on the ECG. Normal values in the cat are listed in Table 7.3. A similar flow pattern is present when evaluating tricuspid inflow. If mitral or tricuspid regurgitation is noted, or any turbulent flow pattern is recognized with color or pulsed-wave Doppler, velocity of the flow should be measured with continuous-wave Doppler. The pressure gradient (PG) across the valve can be estimated by using the modified Bernoulli equation [PG (in mm Hg) = $4 \times V^2$, where V = velocity in m/s]. Normally, the gradient (pressure difference) between atrium and ventricle or between ventricle and great vessel should be close to zero when the valve separating the two structures is open; elevations suggest obstruction (stenosis) between the two structures.

ECHOCARDIOGRAPHIC ASSESSMENT OF DIASTOLIC FUNCTION

Diastolic function is difficult to assess echocardiographically; however, an overview can be ascertained using several Doppler measurements. In the cat, where the most common heart diseases cause diastolic dysfunction, these measurements are critical to obtaining a complete study. Transmitral flow, discussed above, reflects the instantaneous pressure gradient across the mitral valve. In the normal animal, the peak E wave velocity exceeds the peak A wave velocity (E/A >1). With advancing left ventricular myocardial disease, the filling pattern progressively changes. In cats with reduced left ventricular compliance, the early diastolic flow (E wave) is smaller, the rate of deceleration is reduced, and the peak velocity of the A wave increases in absolute and relative terms. Unfortunately, interpretation of transmitral flows can be difficult because of "pseudonormalization" where the E/A ratio returns to normal, although the cat has diastolic dysfunction. With pseudonormalization, increased left atrial pressure causes early opening of the mitral valve and augmented passive filling of the left ventricle (because the LA to LV gradient is increased). Also, ventricular pressure rises more rapidly than normal causing the late diastolic LA to LV gradient to be lower than normal, with a resultant reduction in the transmitral A wave. In humans, this stage is considered "transitional" and occurs when the increased LV stiffness has lead to elevated left atrial (LA) pressure. However, as LV stiffness and LA pressure continue to increase, further changes in the transmitral flow pattern occur, resulting in a "restrictive" transmitral filling pattern. The restrictive pattern is characterized by tall and narrow E waves, small A waves, and shortened isovolumetric relaxation and deceleration times (Bright et al. 1999) (Figures 7.9, 7.10).

In addition to the phenomenon of pseudonormalization, the transmitral flow pattern can also be adversely

Table 7.3. Echocardiographically derived indices of left ventricular diastolic function in normal cats

Parameter	Schober et al.	Chetboul et al.	Bright et al.	Santilli and Bussadori
HR (bpm)	132 ± 15	184 ± 33	191 (127–308)*	
IVRT (ms)	71 ± 17	43 ± 9	46.2 ± 0.76	55.40 ± 13.24
HR (bpm)	137 ± 28			
Peak E (m/s)	0.67 ± 0.14	0.7 ± 0.1	0.70 ± 0.14	0.67 ± 0.13
Peak A (m/s)	0.33 ± 0.11	0.5 ± 0.1	0.65 ± 0.14	0.59 ± 0.14
E:A	2.27 ± 1.00	1.5 ± 0.3	1.12 ± 0.22	1.19 ± 0.30
HR (bpm)	135 ± 35			
Peak S (m/s)	0.25 ± 0.07			
Peak D (m/s)	0.23 ± 0.04			
S:D	1.14 ± 0.32			
HR (bpm)	130 ± 37			
Peak S′ septal (cm/s)	4.19 ± 0.82			
Peak E′ septal (cm/s)	6.42 ± 1.25			
Peak A′ septal (cm/sec)	3.64 ± 1.47			
Peak S′ lateral (cm/s)	3.99 ± 0.41			
Peak E′ lateral (cm/s)	8.34 ± 2.04			
Peak A′ lateral (cm/sec)	4.01 ± 1.65			
PPVs (m/s)			0.48 ± 0.14	0.39 ± 0.12
PPVd (m/s)			0.47 ± 0.10	0.44 ± 0.09
PPVr (m/s)			0.23 ± 0.06	0.010 ± 0.002
BW (kg)			4.6 ± 1.8	3.68 ± 1.28
Age (yr)			4 (0.25–19)*	7.75 ± 4.51

HR = heart rate; IVRT = isovolumic relaxation time; Peak E = peak velocity of early diastolic mitral flow wave (E wave); Peak A = peak velocity of late diastolic mitral flow wave (A wave); Peak S = peak velocity of systolic pulmonary venous flow wave (S wave); Peak D = peak velocity of early diastolic pulmonary venous flow wave (D wave); Peak S′ septal = peak velocity of systolic septal mitral annulus motion (S′ wave); Peak E′ septal = peak velocity of early diastolic septal mitral annulus motion (E′ wave); Peak A′ septal = peak velocity of late diastolic septal mitral annulus motion (A′ wave); Peak Sa lateral = peak velocity of systolic lateral mitral annulus motion (S′ wave); Peak E′ lateral = peak velocity of early diastolic lateral mitral annulus motion (E′ wave); Peak A′ lateral = peak velocity of late diastolic lateral mitral annulus motion (A′ wave); PPVs = peak pulmonary venous systolic velocity; PPVd = peak pulmonary venous diastolic velocity; PPVr = peak pulmonary venous retrograde velocity; BW = body weight.
*variables presented as median and range).

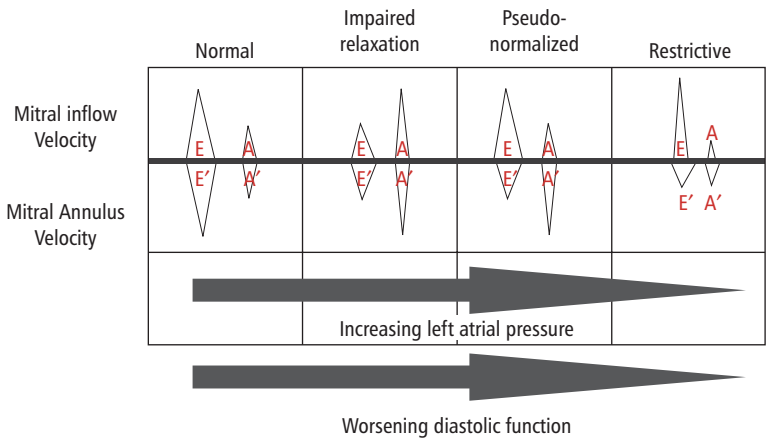


Figure 7.9. An overview of transmitral Doppler echocardiography changes and mitral annulus tissue Doppler changes that occur with progressive diastolic dysfunction and increasing left atrial pressure.

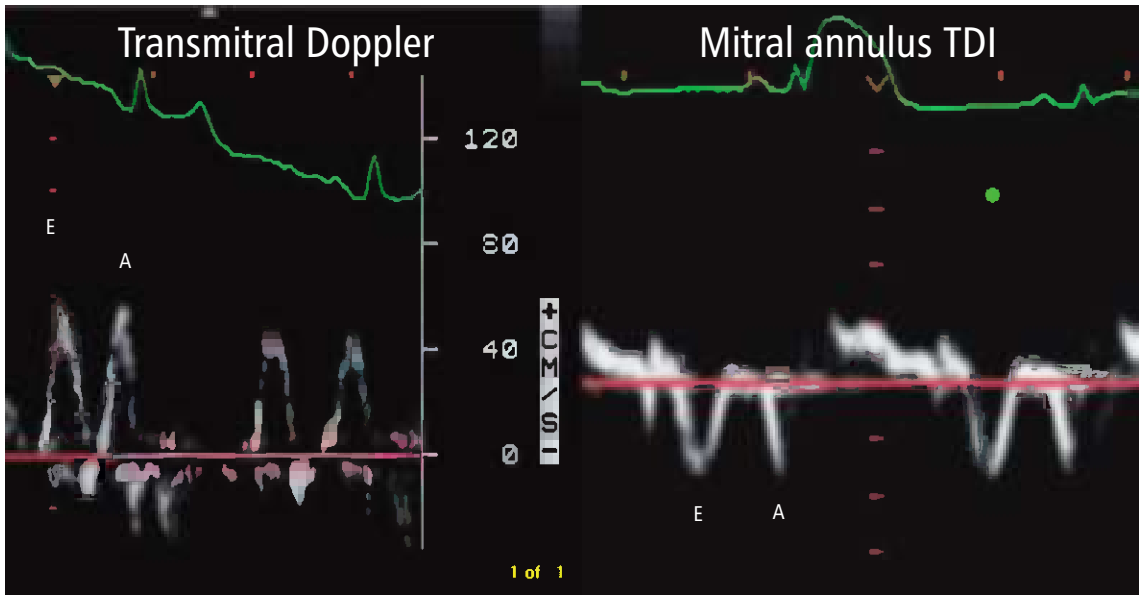


Figure 7.10. Transmitral pulsed-wave spectral Doppler echocardiogram (left side panel) obtained from the left apical 4-chamber with the sample volume placed at the tips of the mitral valve leaflets in a normal cat. Diastolic flow (moving from the left atrium to the left ventricle) is above the baseline and made up of early, passive filling (E wave) and late, active filling (A wave). The right side panel is a spectral tissue Doppler tracing obtained at the mitral valve annulus from a normal cat. Note the similarity to the Doppler pattern obtained from transmitral flow with an early diastolic E wave and a late diastolic A wave. However, diastolic wall motion is away from the transducer, and therefore the waves are below the baseline.

affected by sample volume placement too close to the mitral valve annulus or too far into the left ventricle. Also, many cats have a rapid heart rate that results in summation of the ventricular filling phases and fusion of the two waveforms, precluding their comparison to each other. Therefore, the transmitral flow patterns sometimes cannot be interpreted and should always be considered in the context of other clinical and echocardiographic findings.

Pulmonary venous flow patterns and tissue Doppler imaging (TDI) can be used to help resolve these limitations and better define diastolic function in the feline patient. Although abnormalities in these Doppler techniques have been associated with feline heart diseases (MacDonald et al. 2007, Koffas et al. 2006), their clinical application has not surpassed the value of standard echocardiographic, radiographic, and physical examination information. In general, isolated abnormalities in these Doppler indexes should not be used as the sole determination for initiating therapy, but they can suggest that rechecks would be warranted sooner than otherwise planned, or that such patients might be more intolerant of parenteral fluid therapy than normal cats.

Myocardial tissue velocity can be studied using TDI. This modality is a comparatively newer ultrasonographic technique that permits quantification of regional myocardial function by measurement of radial and longitudinal movement; most often the mitral annulus motion is studied. Unlike conventional Doppler, TDI is minimally affected by left atrial pressure and it can therefore be useful in better evaluating cats in the pseudonormal stage of diastolic disease because early diastolic myocardial velocity is fairly preload-independent (MacDonald et al. 2007; Sohn et al. 1997). Pulsed-wave TDI does not require specialized postprocessing software and can be measured at the time of the examination using many ultrasound systems. The wall motion pattern is similar to transmitral flow in that radial and longitudinal tissue profiles usually have 1 positive systolic wave (S') and 1 (EA) or 2 (E' and A') negative diastolic waves (see Figure 7.10). Various labels have been used for signifying that the derivation of the waveform is mitral annular velocity rather than transmitral (i.e., TDI rather than blood flow). For example, E_a, E', T_E, and EM have all been used for describing early diastolic mitral annular wall motion. Data acquisition in cats is feasible, and results correlate with traditional invasive measures of diastolic function (Oyama 2004). Tissue Doppler imaging provides information regarding relaxation, ventricular compliance and filling pressure, and patients with heart disease demonstrate altered velocities consistent with altered diastolic function (Oyama 2004). Peak systolic and diastolic velocities recorded at the mitral annulus are decreased in cats with HCM, chronic kidney disease, or

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systemic hypertension when compared to normal cats (Koffas et al. 2006; Carlos et al. 2006; Simpson et al. 2009), and systolic velocities are increased over normal in hyperthyroid cats (Simpson et al. 2009). However, fusion of the diastolic waves is common in cats because of high heart rates, making interpretation of TDI more difficult than in dogs or humans. Also, from multiple planes, pulsed-wave Doppler TDI results are not always repeatable, which could lead to unreliable results. Finally, there is substantial overlap between the normal and abnormal published feline TDI ranges, so interpretation of TDI variables can be quite challenging (Simpson et al. 2007). Despite its limitations, this modality can provide useful information, especially when other results are ambiguous or unclear, to add to the entire echocardiographic picture of cardiac function. In general, alterations in TDI indexes suggestive of diastolic dysfunction support a greater frequency of reexamination in breeding animals and/or caution when administering fluid therapy or selecting medications that may cause intravascular volume expansion. However, treatment recommendations should not be made based on tissue Doppler variables alone.

Myocardial velocity gradients can be calculated from basic TDI measurements, and changes in these parameters have also been reported with various forms of cardiomyopathy (MacDonald et al. 2006; MacDonald et al. 2007; Koffas et al. 2006). In normal cats, higher tissue velocities are measured at the valve annulus compared to the apex, and at the free wall compared to the septum (Chetboul 2005) and this gradient has been validated (Koffas et al. 2003; Chetboul et al. 2004; Chetboul et al. 2006). Interestingly, the myocardial gradient has also been shown to be lower than normal in cats with HCM (Koffas et al. 2008). However, these evaluations of myocardial velocity gradients (in contrast to pulsed-wave TDI, described above) require specialized software, which is less commonly available on basic echocardiographic equipment.

Pulmonary venous flow is another Doppler-derived measurement, which yields information regarding cardiac diastolic function. Pulmonary venous flow reflects changes in LV compliance and LV filling pressure (Schober et al. 1998). Obtaining a high-quality pulmonary venous flow tracing can be difficult and color Doppler is often helpful to optimize transducer angle from the apical 4-chamber view. The normal pulmonary venous flow pattern has been described in cats and results from several studies suggest that the pattern, and LV diastolic function, change throughout a cat's life (Santilli et al. 1998; Disatian et al. 2008). However, although age and heart rate were statistically related to pulmonary venous flow changes, the effect was minor, suggesting age and heart rate should not be confounding factors when using the technique for diagnostic purposes in cats with heart disease. Pulmonary venous flow patterns are a useful adjunctive way to interpret diastolic function, but similar to TDI indexes, this tool is in the early stages of its clinical use. See Table 7.3 for a summary of the echocardiographically obtained measurements of diastolic function from normal feline subjects.

Left atrial appendage (LAA) flow velocity has been studied in cats with myocardial disease (Schober and Maerz 2006). Left atrial enlargement, left atrial functional abnormalities, left ventricular diastolic dysfunction, and left-sided congestive heart failure were all associated with decreased LAA flow velocities. Similar to pulmonary venous flow pattern assessment and TDI, LAA flow assessment is in the early stages of clinical utility. However, these techniques allow the clinician to gain insight into a patient's diastolic function, an assessment that can be challenging (yet important in the feline patient).

CONTRAST ECHOCARDIOGRAPHY

Contrast echocardiography is a simple technique for evaluating cardiovascular shunts, which can be very helpful when Doppler echocardiography is not available or when the results remain ambiguous. The principle is to alter the echocardiographic appearance of the blood pool through the injection of agitated saline (which produces microbubbles), iodinated contrast solution, or various other contrast agents (Bonagura 1994). The microbubbles reflect the ultrasound beam, thereby altering the acoustic impedance of blood, and are filtered by capillary beds. When agitated saline is injected into a large vein during echocardiographic examination (after evacuating excess air from the syringe), the echogenic bubbles can be visualized on the echocardiogram entering the right atrium and ventricle and exiting the pulmonary artery. Blood containing these bubbles will enter the right atrium from the cranial (if cephalic or jugular injection) or caudal vena cava (if saphenous injection). If a right to left intracardiac shunt is present, bubbles can be visualized in the left heart (left atrium if an atrial septal defect or left ventricle if a ventricular septal defect). In animals with normal anatomy, the bubbles will be retained by, and dissolve in, the pulmonary capillary bed and will therefore not enter the left heart. A negative contrast effect can be recorded by noncontrast-containing blood (anechoic) shunting into a chamber filled with echogenic bubbles when a left to right shunt exists.

Other adjunctive echocardiographic tests are also available at tertiary care facilities, though not widely

applicable in cats. Transesophageal echocardiography has limited application in feline cardiology. The small patient body size necessitates pediatric transesophageal transducers, which may be cost-prohibitive. Additionally, the patient must be anesthetized for the procedure and one study found that the quality of heart base images was not as consistently superior to transthoracic images in cats as has been reported in dogs using this modality (Kienle et al. 1997).

Another more promising development is 3D ultrasound imaging of the heart. Technologic enhancements in 2D imaging have led to the development of real-time 3D echocardiography. Specific equipment, software, and training are necessary. The technique is particularly useful prior to cardiac surgery to fully define structural abnormalities in advance of the procedure, and it is becoming increasingly available as the technology matures.

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8

Cardiac Biomarkers

Key Points

- Circulating cardiac biomarkers, biologic substances that are associated with cardiac stress, have growing clinical importance in human and veterinary cardiology.
- There are currently feline assays for NT-proBNP and cardiac troponin I (cTnI) on the market, with published normal ranges.
- There are two point-of-care (cage-side) assays available for cTnI but the natriuretic peptides are not available as cage-side tests.
- Biomarkers cannot replace echocardiography for diagnosing the presence and type of heart disease in an individual patient. However, they can be useful tools in certain subsets of patients. For example, biomarker results can help differentiate between primary respiratory vs primary cardiac disease in the critical, dyspneic feline patient.
- There is currently no evidence to support the use of any of these tests for screening clinically normal patients for heart disease.

INTRODUCTION

The National Institutes of Health (NIH) has defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention." This broad definition essentially allows the term to be used for a wide range of measureable indexes in medicine: from radiographic heart size to arrhythmia detection on an electrocardiogram. However, the term has gradually evolved to be used most frequently to describe circulating biomarkers, most often those substances involved in the neurohormonal response to heart failure or those substances released from myocardial tissue in response to injury. Although many of these biomarkers are routinely used in human cardiovascular medicine, they are only beginning to be characterized in the veterinary species. However, the area is attracting a great deal of work and results are encouraging that biomarkers will ultimately play an important role in veterinary cardiology as well. Six main categories have been proposed to describe the various potential circulating biomarkers in human medicine: inflammation, oxidative stress, extracellular matrix remodeling, neurohormones, myocyte injury and myocyte stress (Braunwald 2008).

Numerous circulating biomarkers (enzymes, hormones, and biologic substances) appear to have clinical importance in human heart disease and failure. However, there have been few studies performed in cats. This discussion will focus on those circulating biomarkers that have been evaluated in the feline species. There are several excellent reviews of biomarkers in human and veterinary patients and the interested reader is referred to them for further reading on the topic (Braunwald 2008; Boswood 2009).

HOMOCYST(E)INE AND B VITAMINS

In humans, high plasma homocysteine and low B vitamin levels are risk factors for various vascular diseases. McMichael et al. (2000) evaluated circulating homocysteine, B vitamins and amino acid concentrations in cats with cardiomyopathy and ATE. This group showed that arginine concentrations were lower in cardiomyopathic cats with ATE compared to cardiomyopathic cats without ATE and a group of healthy controls. In addition, both heart disease groups had lower plasma B_6 and

Feline Cardiology, First Edition. Etienne Côté, Kristin A. MacDonald, Kathryn M. Meurs, Meg M. Sleeper.
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B_{12} concentrations than the healthy controls. However, it was unclear whether these changes were secondary or primary and further studies are warranted. A separate group of researchers found that plasma homocysteine was significantly elevated in cats with CHF and ATE compared to normal cats. However, although plasma homocysteine levels were elevated in the CHF (without ATE) group compared to normal cats, it was not significantly different, nor was there a significant difference in plasma homocysteine levels between the CHF groups with and without ATE (Hohenhaus et al. 1999).

ENDOTHELIN I

Endothelin (ET-1) is a powerful stimulant of vascular smooth muscle contraction and proliferation as well as myocardial fibrosis. It also potentiates other neurohormones (Braunwald 2008). ET-1 is produced within endothelial cells in response to various stimuli, including shear stress, hypoxia, and the presence of other circulating vasoactive hormones such as angiotensin II and vasopressin. Along with the RAAS system, ET-1 contributes to pathologic cardiac remodeling by inducing cardiomyocyte hypertrophy and activation of cardiac fibroblasts. After elevated plasma B-type natriuretic peptide levels, an increase in plasma levels of big endothelin (the prohormone that is converted to ET-1) was the most powerful predictor of mortality and hospitalization for heart failure in a human study (Braunwald 2008). Moreover, ET-1 levels correlated with the severity of heart failure class and degree of hemodynamic impairment (Wei 1994), and elevated ET-1 was associated with higher 1-year mortality in people with heart failure, suggesting that routine monitoring may provide important prognostic information in people with mild to moderate heart failure (Pousset et al. 1997). However, several ET-1 receptor antagonists have failed to show clinical benefit in more recent human trials (Rich and McLaughlin 2003).

Several veterinary studies have identified that ET-1 may be a prognostic indicator of early mortality in dogs with heart failure or severe pulmonary disease (O'Sullivan et al. 2007; Tessier-Vetzel et al. 2006). ET-1 was increased in dogs with heart failure compared to normal dogs or dogs with asymptomatic heart disease, but it was not different between asymptomatic dogs and normal dogs (Prosek 2004b). One feline study evaluated ET-1 in healthy control cats (n = 12), asymptomatic cats with various cardiomyopathies (n = 12) and symptomatic cats with heart failure (n = 15) or arterial thromboembolism (n = 4) (Prosek 2004a). ET-1 was increased in asymptomatic cats compared to normal cats and in symptomatic cats compared to normal cats. Although this study validated a human ET-1 ELISA assay in the cat, it also demonstrated that ET-1 was unable to discriminate asymptomatic cats from symptomatic cats with heart failure or arterial thromboembolism (Prosek 2004a).

At this time in veterinary cardiology, the biomarkers that have been best studied in the cat and that are readily available for clinical use are the cardiac troponins and the natriuretic peptides. The remainder of this chapter focuses on these biomarkers.

CARDIAC TROPONINS

Cardiac troponin I and T are specific markers of myocyte injury. Troponins (Tn) are regulatory proteins that are part of the contractile apparatus of skeletal and cardiac muscle tissue. They are not present in smooth muscle tissue. With the proteins actin and tropomyosin, they make up the thin filaments within the myofibrils that are essential for the calcium-mediated regulation of muscle contraction. The troponin complex consists of three interacting and functionally distinct proteins (troponin I, T, and C). Each troponin protein has specific functions that regulate muscle contraction (see Figure 11.1).

Troponin C binds calcium to initiate muscle contraction and is present in two isoforms. Homology between the cardiac isoform and one of the skeletal muscle isoforms reduces the cardiac specificity of TnC and therefore limits its diagnostic usefulness in heart disease (Schreier et al. 1990). Troponin T attaches the troponin complex to tropomyosin and actin (Filatov 1999). In human cardiac tissue four isoforms exist, but only one is characteristic of the adult heart. The other three cardiac isoforms are expressed in fetal tissue. The fetal isoforms may be reexpressed during heart failure or in damaged skeletal muscle. Troponin I inhibits actomyosin ATPase and prevents the structural interaction of myosin with the actin–binding sites. The binding of calcium to troponin C displaces troponin I and causes a conformational change in tropomyosin so that it no longer interferes with myosin/actin binding and muscle contraction can occur. Three isoforms exist for troponin I. Two are present in skeletal muscle and the other is present only in cardiac muscle. Unlike cardiac TnT, cardiac TnI is not expressed in fetal skeletal muscle during development, nor after damage and regeneration in adult skeletal muscle (Bodor et al. 1995).

Troponins are considered leakage markers. Damage to cardiac myocytes resulting in loss of membrane integrity allows the release of cardiac Tn into the circulation. Troponin release kinetics are consistent with two separate intracellular populations. After acute cardiac injury, the cytosolic pool is released resulting in an early rise in

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blood levels. This is followed by the slower release of structurally bound troponin that results in a sustained elevation (Katus et al. 1991; Adams et al. 1994; Jaffe et al. 1996). The half–life of cTnI and its complex in the circulation is about two hours. The exact mechanism for elimination of cTnI is unknown but it is thought to involve clearance by the reticuloendothelial system (Freda cardiac TnI 2002). There is also some evidence that it may be broken down into small fragments that could be excreted renally (Diris cardiac TnI 2004). Elevated cardiac troponin levels indicate myocardial damage but do not provide any information regarding its cause. Cardiac troponins have emerged as sensitive and specific markers of cardiomyocyte injury postmyocardial infarction, and elevations have been reported in numerous canine studies secondary to myocarditis, blunt chest trauma, congestive heart failure, etc. Several feline studies have also shown the test may help identify patients affected with hypertrophic cardiomyopathy or hyperthyroidism (Herndon et al. 2002; Herndon et al. 2008; Connolly et al. 2003; Connolly et al. 2005). However, results from three veterinary studies suggest there may be potential for prognostication or evaluation of therapy response with cardiac troponin I (cTnI) (Oyama and Solter 2004; Côté 2007; Connolly et al. 2005).

Cardiac troponin assays

The currently available tests determine troponin levels by using enzyme–linked immunosorbent assays (ELISA). The difference in amino acid sequences from skeletal muscle and cardiac troponins (specifically TnI and T) has allowed production of antibodies specific for cardiac troponins in these assays (Larue et al. 1992; Muller-Bardorff et al. 1997). The first assays for detection of cTn were developed in the late 1980s. The tests have evolved dramatically since their introduction, with greater sensitivity and improved precision. The turnaround time for results has also decreased from several hours to a few minutes. Point-of-care assays now exist that may be run bedside or in the field, and reference ranges for cats have been developed for at least two bedside analyzers (Adin et al. 2005; Wells [in press]). The first published cTnI reference range for the feline species used the Dade Behring Stratus® with a range of <0.03–0.16 ng/ml (Sleeper et al. 2001). Currently there are at least two cTnI bedside analyzers that have been validated in the feline species, the Biosite Triage Meter® and the Heska I-stat® handheld analyzer with available cardiac troponin I cartridges. See Box 8.1 for normal feline values using these tests. When choosing an assay, it is important to consider the limit of detection. For some assays, the limit is 0.2 ng/ml, which is actually outside the feline (and canine) normal range.

Box 8.1. cTnI Reference Ranges for Normal Cats

Biosite Triage Meter®	<0.05 ng/ml (95th percentile)
Heska i-STAT®	0–0.17 ng/ml (median of 0.02 ng/ml)

Therefore, patients with mild elevations of cTnI could be missed if using these assays. The higher sensitivity cardiac troponin assays hold promise for addressing this problem (Reichlin 2009).

Because of the many assays available for cTnI, there has been some confusion regarding interpretation of results. Tests are not standardized, so manufacturers may design them using proprietary antibodies that target varying amino acid sequences on the cTnI molecule. In the bloodstream, cTnI can be modified or complexed to other proteins, such as cTnC, and the antibodies used in the assays may have differing specificity for each circulating form of cTnI (Apple 1999; Katrukha et al. 1998). There exists no gold standard assay for cTnI at this time. Comparison studies using a number of analyzers have concluded with the recommendation that, until assays are standardized, reference ranges should be established for each individual assay. Therefore, absolute values obtained from different assays cannot be compared (Apple 1999; Panteghini et al. 2004; Adin et al. 2006). Serum, heparinized plasma, or whole blood may be sampled depending on which cTnI assay is used. Studies in dogs have shown that cTnI levels do not significantly change in serum stored at room temperature over a 5-day period nor in serum that has undergone up to five freeze-thaw cycles (Schober et al. 2002; Oyama and Solter 2004).

Only one manufacturer produces an assay for cTnT, which eliminates interassay comparison issues for cTnT. The first-generation cTnT assays used an antibody that cross-reacted with skeletal muscle troponin T, thereby decreasing its specificity for cardiac injury (Katus et al. 1992). Subsequent generations of cTnT assays have replaced this antibody with one that is more specific for cTnT and thereby eliminated the false positives related to skeletal muscle leakage (Muller-Bardorff et al. 1997). However, no published studies to date have evaluated cTnT values in the feline species.

Hypertrophic cardiomyopathy (HCM), the most common form of heart disease in cats, can cause intramural coronary artery disease, leading to microscopic areas of ischemia, and myocardial hypertrophy with cellular necrosis and cTn release into the circulation (Maron et al. 1986; Krams et al. 1998). Although cats

with mild HCM may have normal cTnI levels, several studies have shown that cats with moderate to severe HCM have significantly higher levels of circulating cTnI than normal cats (Herndon et al. 2002; Connolly et al. 2003), and a weak correlation exists between cTnI concentrations and ventricular wall thickness. More recently, several studies have shown that plasma cTnI levels may be clinically useful for differentiating cardiac from non-cardiac causes of dyspnea (Herndon et al. 2008; Connolly et al. 2009; Wells [in press]). Now that several cage-side, point-of-care tests are available, cTnI testing should prove useful for rapid triage of cats presenting with severe dyspnea.

Elevated cTnI levels have also been recognized in groups of cats without hypertrophic cardiomyopathy. Approximately 50% of hyperthyroid cats (without underlying heart disease) in one study were found to have elevated baseline cTnI levels, which generally returned to normal within 2 months of radioactive iodine therapy (Connolly et al. 2005). Although not reaching statistical significance, the cats with cTnI elevations also tended to have higher T_4 levels. The mechanism of troponin release was not determined although it was speculated to result from myocardial cell damage associated with intramural coronary ischemia or from the physiological effects of excess thyroid hormone.

As of the writing of this chapter, two cTnI assays are available as cage-side tests (Heska i-STAT® and Biosite Triage Meter®). Both assays have reasonable lower limits of detection (i-STAT®: 0.00 ng/ml, according to the manufacturer; Triage Meter®: 0.05 ng/ml), and published reference ranges for cats are available for both (see Box 8.1).

NATRIURETIC PEPTIDES (ATRIAL AND B-TYPE NATRIURETIC PEPTIDE; ANP AND BNP)

ANP and BNP are produced by myocardial tissue in response to increased pressure and wall stress and therefore are markers for cardiac dysfunction and heart failure. Pre-proBNP is processed intracellularly to proBNP, which is secreted by the cell. ProBNP then undergoes further processing to yield the active hormone (BNP) and an inactive fragment, NT-proBNP. The pattern for ANP production is similar. The primary stimulus for ANP and BNP production is increased transmural pressure or sudden wall stretch of an atrium [ANP] or ventricle [BNP]. However, sustained elevations are facilitated by increased protein synthesis, which switches from the atria to the ventricles. BNP is principally regulated by ventricular wall stress and pressure load (Connolly et al. 2008). BNP was the first biomarker to prove its value in diagnosis, prognostication, and screening of human congestive heart failure patients in a cost-effective way (Maisel et al. 2006). Mature ANP and BNP have short half-lives, so most clinical assays target prohormones (NT-proANP and NT-proBNP), which are more stable. Depending on the assay being used, heparinized or EDTA plasma or serum is submitted to the appropriate laboratory. Samples should be centrifuged and separated after collection. If analysis is delayed more than a day, samples should be frozen. The natriuretic peptides are cleared by the kidneys. Hypervolemia and hypertension (characteristic of renal failure) enhance its secretion and elevate the levels of BNP (because of increased ventricular pressure), especially NT-pro-BNP. In humans, there is also a moderate increase in the level of circulating BNP with increasing age. One must consider these possible confounding factors when interpreting the natriuretic peptide levels in an individual patient.

Several studies have evaluated the use of these biomarkers in feline heart disease patients. Plasma NT-proANP immunoreactivity was compared between two groups of cats with and without hypertrophic cardiomyopathy, and no significant difference was found between the two groups (MacLean et al. 2006). In this study, the disease group was asymptomatic. In another study using an assay for C-terminal ANP, another group showed C-ANP levels increased from baseline in a model of feline volume overload, and C-ANP concentration was also significantly higher in cats with various forms of cardiomyopathy compared to normal cats. Moreover, cats with CHF had significantly higher C-ANP levels than did heart disease cats without CHF (Hori et al. 2008). Another study evaluated NT-proANP and NT-proBNP in 28 healthy controls and 50 cats with heart disease. The affected group had various forms of heart disease and was farther broken down into those with and without congestive heart failure. Both natriuretic peptides were significantly different between the three groups, with cats in heart failure having the highest levels. Although there was overlap of NT-proANP levels between the three groups, there was no overlap of the NT-proBNP levels suggesting this marker is likely superior (Connolly et al. 2008), although in all of these studies its elevation mirrored the presence and severity of congestive heart failure (which could be diagnosed radiographically with shorter turnaround time). The 7–10-day variability of circulating NT-proBNP in normal and cardiomyopathic cats was demonstrated to be low and unlikely to confound its interpretation (Reynolds et al. 2010). However, 23% of the affected cats (3/13) had normal NT-proBNP values, which could have confounded interpretation of the assay. These three cats were asymptomatic (Reynolds et al. 2010). NT-proBNP has also been used in a clinical trial assessing

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ramipril therapy in asymptomatic cats with HCM. In this study, ramipril did not change left ventricular mass or improve diastolic function (and similarly no significant change was noted in NT-proBNP levels) (MacDonald et al. 2006). A large-scale, single-institution, prospective study evaluating NT-proBNP levels in 425 cats covering the full clinical spectrum (normal to end-stage heart failure) has demonstrated serum NT-proBNP level correlates with stage of cardiovascular disease severity as well as survival. This study also demonstrated that sex, body weight, and blood pressure are not associated with significant differences in circulating levels of NT-proBNP (Ettinger 2010). According to these findings, feline NT-proBNP levels below 100 pmol/l indicate that significant cardiovascular disease is unlikely, whereas a level greater than 270 pmol/l indicates clinically significant disease is highly likely. NT-proBNP levels between 100–270 pmol/l suggest an intermediate result where cardiac disease can neither be ruled in nor ruled out (Ettinger 2010).

At this time there is one assay for NT-proBNP on the market for veterinary use in the United States (Idexx Cardiopet™ proBNP test) and the blood sample must be shipped to the Idexx laboratory for analysis. Two studies focusing on clinical relevancy of the test have shown that NT-proBNP can distinguish between congestive heart failure and noncardiac causes of acute dyspnea in cats (Connolly et al. 2009; Fox et al. 2009). See Table 8.1 for their suggested cutoff values. It is often difficult to distinguish the underlying cause of dyspnea in cats, particularly when the cat's severe respiratory distress limits diagnostic evaluation. These results suggest NT-proBNP levels will be a useful adjunctive diagnostic in these critically ill cats, especially when a rapid, cage-side test is available. However, the test was not useful for screening earlier stages of heart disease: asymptomatic Maine coon or Maine coon crossbred cats with mild or moderate HCM did not have elevated NT proBNP levels, suggesting it is unlikely the test will be useful to screen clinically normal cats (Hsu et al. 2009). The test does not replace a traditional, complete diagnostic evaluation (physical examination, echocardiogram, etc.).

Table 8.1. Proposed feline circulating plasma NT-proBNP cutoff concentrations for discriminating cats with dyspnea caused by heart disease vs respiratory disease

Study	Plasma NT-proBNP (pmol/l)	Sensitivity (%)	Specificity (%)
Fox et al. 2009	265	90.2	87.9
Connolly et al. 2009	220	93.9	87.8

Clearance of natriuretic peptides in mammals is thought to occur renally. In cats with systemic hypertension, since many have concurrent renal disease, interpretation of NT-proBNP may be problematic. In a study that evaluated natriuretic peptides in cats with renal disease, only NT-proANP correlated with creatinine concentrations, with NT-proBNP performing better as a diagnostic test. However, although azotemia was not a confounding factor in the evaluation of NT-proBNP, systemic hypertension, as mentioned above, was associated with an increase in NT-proBNP (Lalor et al. 2009). Systemic hypertension likely stimulates increased production of BNP secondary to elevated cardiac afterload. Therefore, it is possible that elevated NT-proBNP levels caused by systemic hypertension could be misinterpreted as indicative of primary cardiomyopathy if blood pressure is not measured.

Several human studies suggest multiple biomarker strategies are of greater value than using a single marker alone. It is likely the same will be true in veterinary medicine. The search for new biomarkers for human patients is ongoing, and studies using the currently available ones will be essential to better define clinical utility for these tests. The rapid development of this field seen to date will probably continue for the foreseeable future. The possibility exists that these assays will be useful for prognosticating and optimizing medical management of individual feline cases. Until results are rapidly available, they are unlikely to alter emergent care in veterinary medicine and there is currently no evidence they will be useful to screen asymptomatic cats for underlying cardiomyopathy.

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9

Electrocardiography

Key Points

- Electrocardiography is most useful in cats for the following indications, in decreasing order of diagnostic yield: cardiac arrhythmias, metabolic abnormalities, and structural heart disease.
- The position of the limbs can affect the ECG results substantially in cats.
- Recording multiple leads helps the clinician choose the clearest tracing and makes ECG interpretation easier and more accurate.
- Normal values for the feline ECG are listed on the inside covers of this book.

INTRODUCTION

The first feline electrocardiogram (ECG) was performed on a kitten by Augustus Waller in 1887 (Waller 1887, 1888, 1889). Today, the main clinical indication for electrocardiography in cats is to assess the rhythm of the heartbeat, commonly when an irregular or otherwise abnormal rhythm (arrhythmia) is detected during physical exam, a patient is being monitored in the intensive care unit, or during general anesthesia. Additional applications include assessment of cardiac dimensions, for which an ECG is a poor substitute for an echocardiogram, and monitoring of such extracardiac disturbances as hyperkalemia and hypoxemia (Tilley 1992; Côté 2010; Côté and Harpster 2009; Fox and Harpster 1999). The abbreviations ECG and EKG are used interchangeably; EKG was the original Dutch spelling (*elektrokardiogramm*) put forth by the father of electrocardiography, Willem Einthoven, and this has been replaced only partially by ECG in English.

TECHNIQUE

A great deal of the interpretation of a feline ECG depends on ECG quality. The small amplitude of deflections, and numerous potential artifacts, make many interpretations challenging, and a poor quality tracing may not be interpretable by even the most skilled cardiologist. Using multiple ECG leads provides additional information that may be missed on a single-lead strip, and by convention a complete ECG in the cat displays 10 leads (see Figure 9.1). Recording multiple leads provides additional information where lead II, or any other single lead, may be inadequate (see Figure 9.2).

A cat's ECG may be obtained with the patient in any position, but the standard technique requires the cat to be in right lateral recumbency. Left lateral and sternal recumbencies have been evaluated in feline ECGs (Harvey et al. 2005; Gompf and Tilley 1979; Calvert and Coulter 1981), with conflicting results. Some studies identified little difference between recumbencies (Gompf and Tilley 1979; Calvert and Coulter 1981), whereas a more recent study demonstrated significantly smaller R waves when the ECG is recorded with cats in left lateral or sternal recumbency compared to right lateral recumbency and a mean electrical axis that is significantly different in left versus right lateral recumbency (Harvey et al. 2005). At least part of the explanation for this discrepancy likely relates to the position of the electrodes on the limbs. As demonstrated in an

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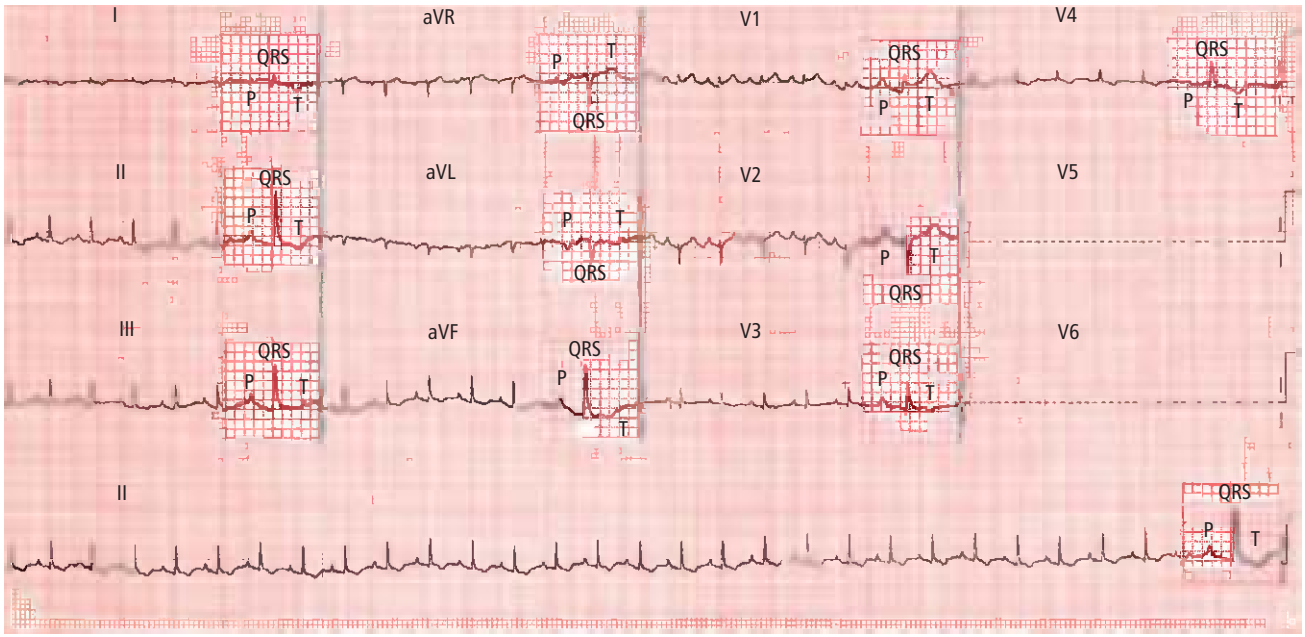


Figure 9.1. Normal sinus rhythm in a cat. Ten-lead tracing with zoomed inserts for each lead identifying the components of the heartbeat. The heart rate is 160 beats/minute and the mean electrical axis is +90°. 25 mm/sec, 1 cm = 1 mV.

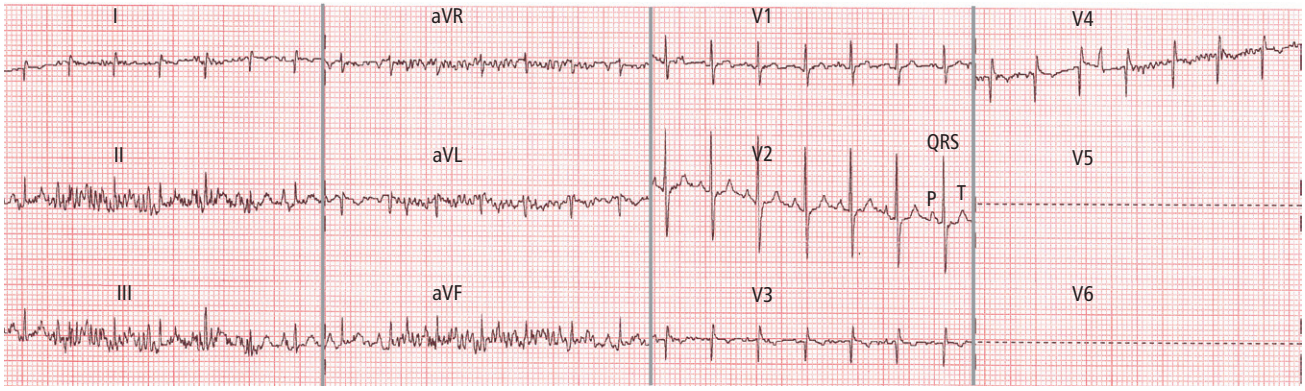


Figure 9.2. Advantage of multiple leads: the limb leads (I, II, III, aVR, aVL, aVF) are difficult to interpret due to severe motion artifact. In this cat, the precordial leads are much clearer, especially lead V2 (P, QRS, T labeled). 25 mm/sec; 1 cm = 1 mV.

elegant and striking case report, the natural tendency of cats, when in lateral recumbency, to flex the elbows and shoulders into a tucked, crouched posture changes the position of the ECG electrodes, which in turn can dramatically alter the amplitude of ECG deflections and the resulting mean electrical axis (Bond 2005) (Figure 9.3). Any recumbency will do if only the rhythm is being assessed, but if dimensions of waves and complexes are being measured in an attempt to infer cardiac size and structure, right lateral recumbency and proper restraint and positioning are required. An optimal tracing is most likely to result when the cat is gently held recumbent on a comfortable, nonconductive surface (e.g., rubber-coated foam mat) in a quiet area. For right lateral recumbency, an assistant holds all four limbs pointing away from himself/herself, toward the clinician recording the tracing. Typically the assistant holds the forelimbs in the right hand, with an index finger between right and left paws for comfort, and the hindlimbs in the same manner in the left hand. The right wrist lies gently over the cat's neck and the left forearm may rest over the cat's left lateral thigh. An Elizabethan collar is recommended for most cats as a precaution against the cat's quick turning and biting the assistant's wrist. The ECG electrodes, which are typically alligator-type clips, should be of the minimally traumatic type (Figure 9.4), and these are placed immediately distal to the right (RA) and left (LA) elbows and right (RL) and left (LL) stifles.

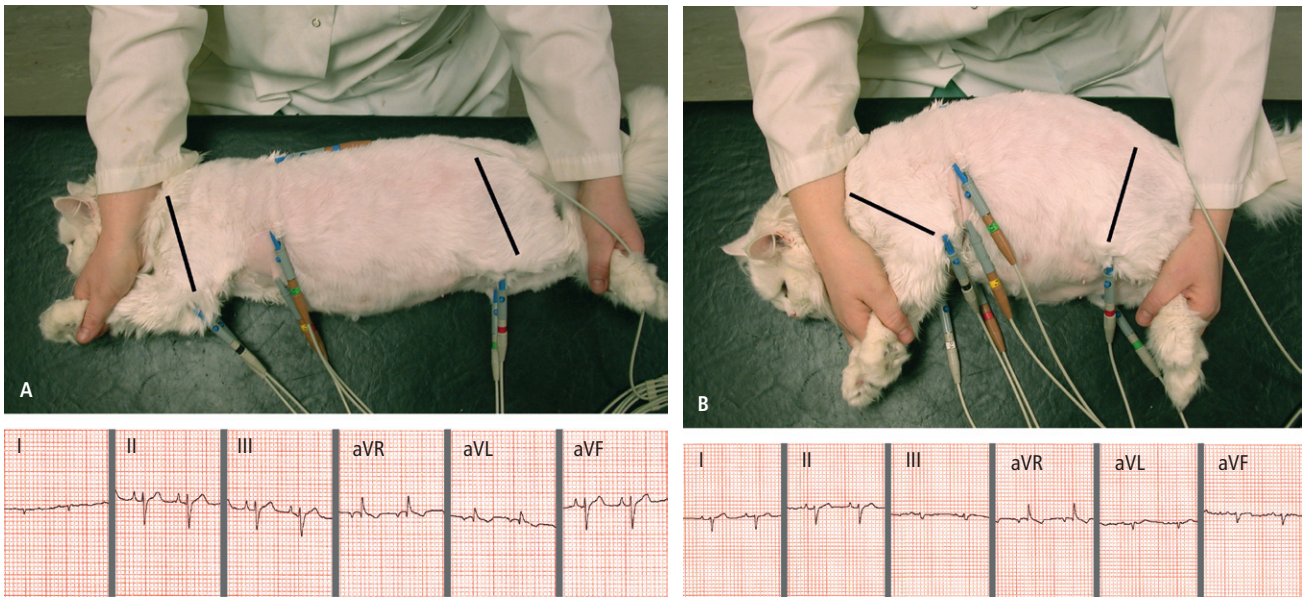


Figure 9.3. Correct and incorrect technique for obtaining the ECG in a cat, illustrating the effect of limb position as described by Bond (2005). The standard position involves placing the cat in right lateral recumbency, with the forelimbs pointing toward the clinician recording the ECG. **(A)** Correct technique. The limbs are held properly, with both humeri and both femurs (black bars) perpendicular to the long axis of the body. The mean electrical axis is −100°. The tracing is easily interpreted in all leads. **(B)** Incorrect technique. The cat is allowed to flex the shoulders and elbows naturally, which alters the location of the ECG electrodes. This posture is common and needs to be gently changed with steady traction to the limbs to produce the position shown in (A). The tracing associated with the crouched posture is difficult to interpret in several leads due to decreased P wave and QRS complex amplitude. The apparent mean electrical axis is altered by 50° (now −150°). This form of artifact may explain at least part of the poor sensitivity and specificity of mean electrical axis for identifying changes in ventricular size and structure in the cat compared to the dog and human. 25 mm/sec, 1 cm = 1 mV.

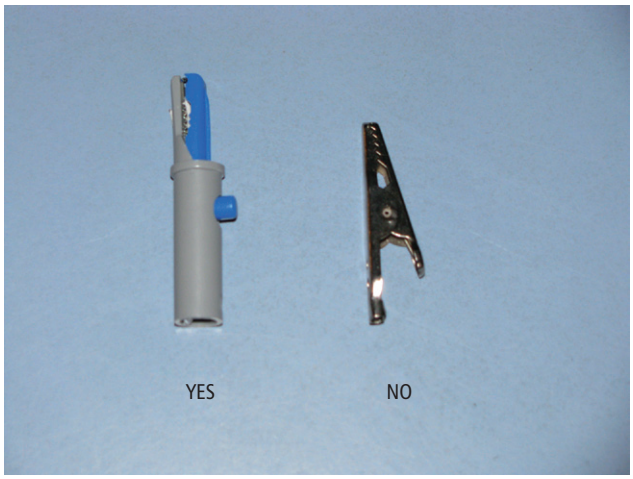


Figure 9.4. Close-up of a minimally traumatic ECG clip (YES) and a metal alligator clip (NO) for connecting the ECG to the patient. The alligator-type clip has fallen out of favor due to tissue trauma and the discomfort it causes to patients.

Electrodes to derive the 4 precordial leads are placed at the right 4th intercostal space just to the right of the sternum (rV2, marked "V1" on the clip; formerly CV5RL), at the left 5th intercostal space just to the left of the sternum (V2; formerly CV6LL), at the 5th intercostal space at the costochondral junction (V4, marked "V3"; formerly CV6LU), and over the seventh thoracic vertebra on the dorsal midline (V10, marked "V4"). The advantage of these precordial leads is that they may provide ECG information that is otherwise confusing or absent from the limb leads (I, II, III, aVR, aVL, aVF) (see Figures 9.1, 9.2). Contact between patient and electrode must be optimized, usually by applying isopropyl alcohol to the point of contact between the electrode and the skin; ultrasound gel may be applied simultaneously to maintain good contact if prolonged ECG monitoring is anticipated (e.g., general anesthesia). A complete ECG should always display all 6 leads and at least 1 precordial lead, so the clinician may pick the clearest one for accurate interpretation. Lead II is less reliably the clearest lead in cats compared to dogs, and P waves, or even QRS complexes, often may be difficult to distinguish in lead II but clearly apparent in another lead (Figure 9.5; see Figure 9.2). Typically the duration of recording is 1 minute, with 12–15 seconds of recording in multiple leads and a rhythm strip that records 1, 3, or more leads simultaneously at 10, 25, or 50 mm/sec for the remainder of the minute. The expected results in normal cats have been well documented (Blok and Boeles 1957; Hamlin et al.; Massmann and Opitz 1954;

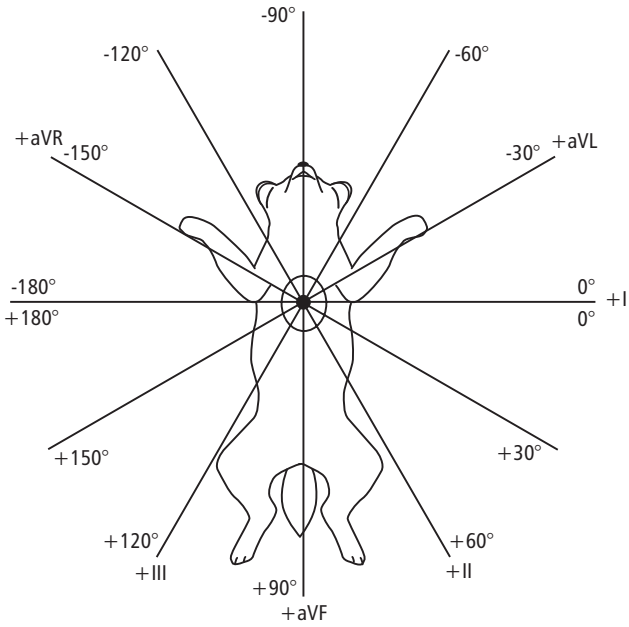


Figure 9.5. Hexaxial lead system diagram.

Robertson et al. 1976) and are listed in the inside covers of this book.

NORMAL EVOLUTION OF THE ECG THROUGH LIFE

At birth, a kitten's heart rate is slightly higher (247 beats/minute) than at 30 days of age (237 beats/minute). As might be expected with postnatal changes of the pulmonary circulation during the first 30 days of life, the mean electrical axis shifts leftward toward a more normal adult position, from the –150° to ± 180° segment to the +120° to +150° segment (Gomes-Lourenço and Ferreira 2003).

HOLTER AND EVENT MONITORING

If an arrhythmia occurs only intermittently, it may not be apparent on an ECG even though it is detected on physical examination, is suspected to be responsible for a cat's clinical signs, or both. In these instances, telemetric (wireless) monitoring may be useful. Three forms of telemetry are available for cats: in-hospital cage-side ECG, Holter monitoring, and cardiac event recording. In-hospital cage-side ECG monitoring, typically performed for 24 or 48 hours, introduces the element of a foreign environment, which may cause sympathetic stimulation that abolishes bradycardias (false negative result). However, it is valuable for the patient whose clinical signs or severity of episodes indicate a possible life-threatening recurrence and the risk of death at home. Ideally, ECG patch electrodes and a small transmitter pack are attached to the cat and the cat can move and behave normally in his/her cage in the intensive care unit.

A superior alternative is Holter monitoring. Modern Holter monitors weigh 300–400 grams (<1 lb), and they record the ECG continuously for periods ranging from 24 hours (most commonly) up to 6 days, usually on multiple leads simultaneously (Côté 2010; Petrie 2005). The information is stored digitally, although in older models an audiocassette inside the monitor may be used for data recording. Veterinarians can rent Holter monitors from various suppliers, including such online sources as www.vetheart.com, www.albamedical.com, www.labcorp.com, www.vetcardio.com, www.idexx.com, and www.pdsheart.com. Owners need to maintain a diary of the patient's activities—and lack thereof—during the entire monitoring period to provide a context for analysis of the tracing. For example, a heart rate of 90 bpm is normal for a sleeping cat, but it would be an important finding if it occurred during physical activity. A feline patient's Holter report, if produced through human cardiology software, should be reviewed carefully. Automated reviewing is attractive because manual review of Holter studies in cats has been documented to take up to 2 hours of interpretation per hour of recording. However, in automated review, over- and underinterpretation are common, because software designed for automated analysis of feline Holter recordings does not exist at this time. It remains the veterinarian's obligation to assess the abnormal ECG segments shown in the Holter report and to decide whether the interpretation correlates well with the rest of the patient's information.

The third type of telemetric ECG monitor is the cardiac event monitor (Figure 9.6). Event monitors continuously receive ECG information into a loop memory system, which can only retain the information temporarily. When an episode of clinical signs is observed, the owner needs to trigger the event monitor. Doing so saves an exact segment of ECG information in the monitor's memory. Several episodes can thus be recorded over a number of days and the ECG can then be printed out either at the veterinary hospital or, in the case of external event monitors (Figure 9.6), transtelephonically.

External event monitors are approximately the size of a deck of cards (1 × 5 × 10 cm) and provide 7 to 30 days of monitoring time (Bright and Cali 2000; Côté 2009). External event monitors are connected to patients using two or three wires attached to cutaneous ECG electrode patches, one on each side of the chest over the heart (modified precordial lead). The memory capacity of external event monitors ranges from 5 to 18 minutes,

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Figure 9.6. Cardiac event monitors. **(A)** External event monitor (left) and implantable event recorder (upper right) with its external, owner-operated activator (lower right). **(B)** Cat instrumented with an external event monitor. The monitors are light (100 g; less than 1/4 lb.) and tolerated by most cats when lightly wrapped using roll gauze and elastic wrap. Courtesy of Dr. Christopher Rocchio, Cottonwood Images, and Veterinary Learning Systems.

and the monitors are programmed beforehand to save a selected amount of ECG information (e.g., 45 seconds preceding the push of the button and 15 seconds after it for each triggered episode). They are available for use from various sources, including many of those listed previously for Holter monitors.

Internal event monitors (implantable loop recorders [ILRs], Reveal® monitors) are for extended periods of ECG assessment. These units consist of two parts: the monitor and the patient (owner) activator (see Figure 9.6). The monitor itself is implanted subcutaneously in the patient, whereas the owner-activated remote control is a handheld device that can be applied over the skin where the monitor lies in order to trigger the monitor at the time of a clinical event. These monitors can also be programmed so that they are triggered to record



Figure 9.7. Cat instrumented with Holter monitor. With a light but secure wrap, modern Holter monitors are sufficiently light that they can be worn comfortably by cats. Photograph courtesy of Dr. Fiona Campbell.

when they sense significantly low or elevated heart rates (the triggering rates are chosen by the programmer). Internal event monitors measure 0.5 × 2 × 7 cm, about the size of a man's thumb; have a battery life of approximately 7 months; and have a memory capacity of about 1 hour of ECG recording. The information they capture is retrieved after the episode is over, using a pacemaker interrogator unit placed over the area of skin where the monitor is located (requires a return trip to the veterinary hospital). The use of both types of event monitors is of proven diagnostic value in humans; both external, and to a lesser extent so far, internal, monitors are in accepted use in cats (Bright and Cali 2000; Côté 1999; Krahn et al 1999). Each form of ambulatory ECG monitoring has its relative merits (Côté 2010). Holter monitors are superior for screening the number of abnormal heartbeats on the ECG in a fixed 24- or 48-hour period, such as for assessing a cat's arrhythmia before and during treatment with an antiarrhythmic drug (Figure 9.7). Conversely, external event monitors also have a number of advantages: they are smaller and lighter (3.5 oz [100 g], compared with up to 14 oz [400 g] for a Holter monitor), making them especially practical for cats; they have a longer memory (at least 1 week, and up to 30 days in certain models), which is useful for episodes occurring less frequently; they eliminate some uncertainty of interpretation by directly associating the ECG information with an owner-observed event; and external event monitors can transmit the acquired ECG information transtelephonically, allowing the monitor to be reset and a new monitoring period to begin without a return visit to the hospital.

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SECTION C

Congenital Heart Disease

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10

Congenital Heart Malformations

Key Points

- Congenital heart malformations occur in a small proportion of feline cardiology patients (<10% of cases).
- In general, echocardiography will be needed to diagnose the exact malformation because there is a tremendous amount of overlap between physical examination, electrocardiographic, and radiographic findings for most malformations.
- Treatment is generally directed at controlling clinical signs that may develop due to heart failure or arrhythmias because treatment of the primary defect is not usually possible.

INTRODUCTION

Congenital heart malformations are developmental defects of the heart that are present at birth. They may be inherited or may develop spontaneously without any known familial pattern.

In general, feline congenital heart disease is much less common than acquired heart diseases like the cardiomyopathies. Approximately 5% of cats examined by the cardiology service at the School of Veterinary Medicine at the University of California-Davis over a 10-year period were diagnosed with a congenital heart malformation (MacDonald 2006). A recent study from two veterinary cardiology services in Switzerland identified that 12% of the feline cardiology cases had congenital heart disease (Riesen et al. 2007). A prospective study of circulating biomarkers in cats presented to a private referral practice revealed a ratio of myocardial disease to congenital heart malformations of 23:1 (Ettinger 2010).

The most commonly reported feline congenital heart malformations are mitral and tricuspid valve malformations and ventricular septal defects, although which defect is actually more common seems to vary depending on the study. Less commonly reported feline heart malformations are patent ductus arteriosus, aortic stenosis, tetralogy of Fallot, atrial septal defect, common atrioventricular canal, and pulmonic stenosis (Riesen et al. 2007).

HISTORY AND CHIEF COMPLAINT

Many kittens and cats with congenital heart malformations are asymptomatic, but in others, clinical signs may be intermittent and include exercise intolerance, syncope, and dyspnea. Animals that have progressed to the point of development of congestive heart failure may show other vague clinical signs including loss of appetite, depression, and exercise intolerance.

PHYSICAL EXAMINATION

In many cases, careful evaluation of a juvenile cat with a congenital heart malformation defect will identify a heart murmur and/or arrhythmia, although some cases may not have any auscultatory abnormalities. The location and timing of the murmur can help to narrow the differential diagnosis list substantially (see Chapter 1). Cyanosis may be noted in some cases.

Feline Cardiology, First Edition. Etienne Côté, Kristin A. MacDonald, Kathryn M. Meurs, Meg M. Sleeper.
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Innocent Murmurs

Young kittens (<16 weeks) can have "innocent" murmurs. These murmurs are generally soft (≤3/6), are usually heard best at the left base of the heart (rib spaces 3–4) and may increase or decrease in intensity or tone with the position of the kitten or an increase in heart rate.

The presence of loud heart murmurs or heart murmurs that persist beyond 16 weeks of age is suggestive of a congenital heart malformation, and additional diagnostic tests are recommended to identify the cause of the heart murmur and the severity of the defect if one is present. Although information about the presence or absence of congestive heart failure can be obtained from thoracic radiographs, echocardiography is typically needed to identify the actual defect. Circulating biomarkers may help in this respect: a series of 10 cats with congenital heart malformations uniformly had elevated plasma NT-proBNP levels compared to healthy controls (Ettinger 2010). If an arrhythmia is present, an electrocardiogram is indicated to determine the type of arrhythmia.

COMPLICATIONS AND MONITORING

Some patients can remain asymptomatic and live comfortably for years with their particular malformation. However, the outcome of many malformations is the development of left and/or right heart failure (e.g., pulmonary edema, pleural effusion, or both).

Once the initial diagnosis is made, the best method for long-term monitoring of these patients with cardiac malformations should be carefully considered. Repeated visits to the veterinary clinic likely result in more stress for the cat with cardiac disease (as well as the owner); therefore, it is useful to limit repeated visits to when they are most needed. Some follow-up can be done with simple phone communication with an owner regarding the cat's behavior at home and the owner's records of the at-rest respiratory rate. Owners may be instructed to monitor the respiratory rate at home once a day when the cat is in a resting state. Most resting cats have a respiratory rate well below 20 breaths/minute. An increase in respiratory rate may be a sign of the development of or recurrence of pulmonary edema or pleural effusion and may indicate the need for thoracic radiographs or an alteration in dosage of medication.

Some aspects of cardiac disease do require at least a brief visit to the hospital for monitoring even in the absence of overt clinical signs. Cats with tachyarrhythmias may require physical examination or an electrocardiogram to be sure that the heart rate is well controlled. Blood pressure monitoring may be helpful to make sure that the patient is not hypotensive, either spontaneously or as a result of medications. Periodic (2 weeks after starting medication, 6 weeks, 3 months) renal profiles to monitor BUN, serum creatinine, and serum electrolyte levels are also helpful for cats receiving furosemide and an angiotensin converting enzyme inhibitor. Owners should be instructed to watch for the development of depression, anorexia, or vomiting, which may suggest complications with the medications or progression of heart failure.

Once a diagnosis is made, echocardiography is usually necessary only annually or if the patient's clinical status changes dramatically and there is concern for the status of myocardial function or development of an embolus.

ATRIOVENTRICULAR VALVE MALFORMATIONS: TRICUSPID VALVE MALFORMATION

Characteristics of tricuspid valve malformation include a spectrum of tricuspid valve abnormalities made up of focal or diffuse thickening of the valve leaflets, underdevelopment of the chordae tendinae and papillary muscles, incomplete separation of the valve components from the ventricular wall, and focal agenesis of the valve tissue (Liu and Tilley 1976).

Tricuspid valve dysplasia (TVD) has been recognized in cats both as a primary abnormality and commonly in coexistance with mitral valve dysplasia or ventricular septal defects in the cat (Liu 1977; Chetboul et al. 2004) Pulmonic stenosis, aortic stenosis, and endocardial cushion defect have also been noted in some affected cats (Liu 1977; Kornreich and Moïse 1997; Chetboul et al. 2004).

Etiology, Pathophysiology, and Gross Pathology

Etiology

The etiology of tricuspid valve dysplasia is unknown. Although there is no conclusive evidence that it is familial, a retrospective study identified that tricuspid valve malformations occurred significantly more frequently in European short-haired cats (odds ratio = 11.37) and Chartreux cats (odds ratio = 27.24) compared to the general feline hospital population (Chetboul et al. 2004).

Pathophysiology

The malformation results primarily in tricuspid valve regurgitation, which leads to right atrial and right ventricular dilation. Right-sided heart failure (e.g., pleural effusion) may develop secondary to the dilated right atrium and elevated right atrial pressure. Supraventricular arrhythmias may develop and thromboemboli may form in the right atrium secondary to the atrial dilation.

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Gross Pathology

Tricuspid valve dysplasia is characterized by long, thickened septal valve leaflets, which can be focal or diffuse (Liu and Tilley 1976). The leaflets may adhere directly to the septum with absent or short, abnormal chordae tendinae. The papillary muscles may be hypertrophied and attach directly to the valve leaflet (Liu 1977).

Signalment

There are no known breed predispositions. The breeds reported in the literature include the domestic shorthair, Siamese, Birman, Persian, and Chartreux (Lord 1968; Liu and Tilley 1976, Fossum et al. 1994; Kornreich and Moïse 1997; Chetboul et al. 2004).

History and Chief Complaint

There is a spectrum of clinical presentations. Some kittens or even adult cats are diagnosed at the time of a routine evaluation when a heart murmur is detected and a thorough evaluation is performed. One cat presented with exercise-induced tachypnea and two have been reported to present for syncope (Chetboul et al. 2004). Some cats are only diagnosed when they have progressed to congestive heart failure and present with tachypnea and dyspnea (Liu 1977).

Physical Examination

Cats with tricuspid valve malformation would be expected to have a holosystolic murmur over the 3rd–5th intercostal spaces on the right thorax. However, in some cases the degree of the abnormality may be so severe that right atrial and ventricular pressures seem to equilibrate and the heart murmur may be very soft or even not detectable. Additionally some cats have multiple congenital cardiac malformations and have murmurs that characterize their other defects.

Cats with severe tricuspid valve dysplasia that have progressed into heart failure may have distended jugular veins and tachypnea associated with pleural effusion. In rare cases, cyanosis can develop if a stenotic tricuspid valve or severe tricuspid regurgitation leads to elevated right atrial pressure and a patent foramen ovale results in a right-to-left shunt at the atrial level.

Differential Diagnosis

Cats with arrhythmogenic right ventricular cardiomyopathy (ARVC) can have a similar echocardiographic appearance. However feline ARVC is generally observed in older cats and should have a lesser degree of tricuspid regurgitation noted on echocardiography. Additionally, the morphology of the tricuspid valve should be normal in a cat with ARVC.

Diagnostic Testing

Electrocardiography

Cats with tricuspid valve dysplasia may have a normal sinus rhythm, a normal axis, and normal QRS morphology. Alternatively, they may also have a splintered (notched) QRS or evidence of right ventricular enlargement (with a right axis shift of >160° and prominent S waves in leads I, II, III and aVF) (Liu and Tilley 1976; Kornreich and Moïse 1997). Occasional atrial or ventricular premature beats have been observed (Chetboul et al. 2004).

Radiography

Depending on the severity of the defect and the age of the cat, the radiographs may be normal or may demonstrate signs of right-sided or generalized cardiomegaly (Chetboul et al. 2004). A dilated caudal vena cava and pleural effusion suggest right heart failure (Figure 10.1).

Echocardiography

Two-dimensional echocardiography should identify the abnormal, thickened appearance and movement of the tricuspid valve and its abnormal attachment to the papillary muscles or wall of the ventricle. Right atrial and ventricular dilation can be observed as well. In milder cases, only a small amount of tricuspid regurgitation may be noted on color-flow Doppler examination as the sole abnormality. Ebstein's anomaly, a malformation of the tricuspid valve where the basal attachment of the valve is more apically placed than normally, is another differential for the abnormal appearance of the tricuspid valve and may be considered as well. Ebstein's malformation is a specific type of tricuspid valve dysplasia, and it appears to be uncommon in the cat. Color-flow Doppler should indicate the presence of tricuspid valve regurgitation in virtually all cases. Valvular stenosis appears to be uncommon.

A staging scheme for tricuspid valve dysplasia based on echocardiographic identification of tricuspid regurgitation was suggested by Chetboul et al. (2004):

- Stage 1: Tricuspid valve is structurally abnormal but the right atrium and right ventricle appear normal.
- Stage 2: Tricuspid valve is structurally abnormal and right atrial dilation is present.
- Stage 3: Tricuspid valve is structurally abnormal and both right atrium and ventricle are dilated.

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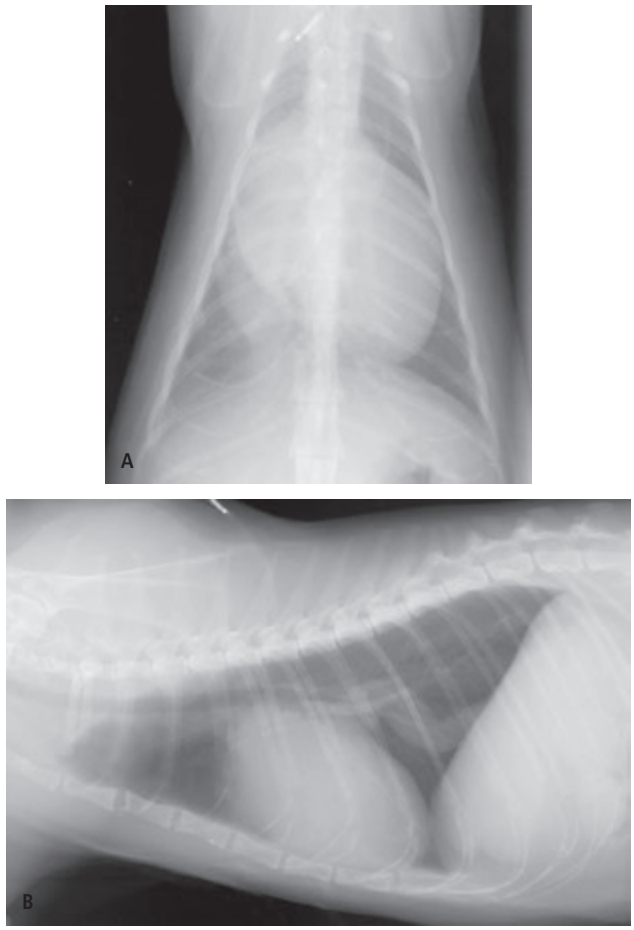


Figure 10.1. Radiographs from a cat with tricuspid valve malformation. Note the enlarged right atrium, auricle, and right ventricle on the ventrodorsal view **(A)**. A dilated and tortuous caudal vena cava is apparent on both views **(B)**.

All cats in stage 1 were asymptomatic. The staging did not correspond to murmur loudness and it has not yet been studied to see whether stage of disease correlates with progression (Chetboul et al. 2004).

Tricuspid valve dysplasia has been observed to coexist with additional congenital heart malformations; therefore, a thorough echocardiographic evaluation should be performed.

Diagnosis

The physical examination and electrocardiographic and radiographic findings can overlap with many other cardiac malformations and diseases, and therefore an echocardiogram is needed to confirm the diagnosis.

Treatment

Because a dysplastic tricuspid valve is not generally stenotic in the cat, interventional (cardiac catheter, surgical) procedures are not typically beneficial. Medical therapy to control signs of right heart failure or signs caused by arrhythmias should be considered if they are present (see Chapter 18). Additionally, because right atrial dilation may predispose a cat to thromboembolic disease, preventative measures should be considered in cats with moderate or marked right atrial dilation (see Chapter 20).

Outcome and Prognosis

The prognosis for tricuspid valve dysplasia is likely dependent on the severity of the valve malformation and the presence of concurrent defects, and it is best determined for each individual case based on echocardiography. Extent of valve dysplasia, concurrent heart defects, arrhythmias, and congestive heart failure appear to be negative prognostic indicators in the cat (Chetboul et al. 2004).

MITRAL VALVE MALFORMATION/DYSPLASIA

Mitral valve malformation is considered to be one of the most common congenital malformations in the cat. As with tricuspid valve dysplasia, this defect may be observed as an isolated malformation or with other defects, including tricuspid valve dysplasia.

Etiology, Pathophysiology, and Gross Pathology

Etiology

The etiology of this malformation is not known, and there is no evidence of a familial etiology at this time.

Pathophysiology

Mitral valve malformation results in mitral valve regurgitation, and left atrial and left ventricular enlargement. Elevated pressures in the left atrium can result in pulmonary venous congestion and the development of pulmonary edema. Pulmonary hypertension and right ventricular failure can occur as well.

Gross Pathology

Mitral valve dysplasia is characterized by an enlarged mitral valve annulus; short, thickened leaflets; short, stout chordae tendinae; and malposition of the papillary muscles that can result in valve dysfunction, primarily valve insufficiency (Liu 1977) (Figure 10.2).

Signalment

There are no known breed predispositions.

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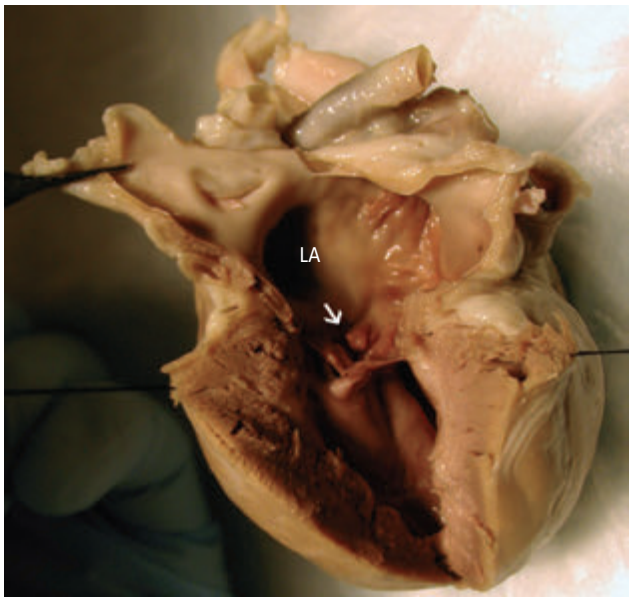


Figure 10.2. Heart from a cat with mitral valve dysplasia. Note the abnormal, shortened thickened mitral valve leaflets (arrow). LA = left atrium.

History and Chief Complaint

Clinical presentation may include the young, apparently normal kitten that presents for routine evaluation at which time a murmur is detected. However, affected cats in which a heart murmur is initially missed or not evaluated may present later with vague clinical signs suggestive of the development of heart failure including lethargy, anorexia, and dyspnea.

Physical Examination

Cats with mitral valve dysplasia should have a holosystolic murmur over the left caudal sternal border. Mitral valve dysplasia is sometimes identified in conjunction with other cardiac malformations, so heart murmurs that characterize those malformations may also be noted. Cats with severe mitral valve dysplasia that have progressed to congestive heart failure may be tachypneic and tachycardic.

Diagnostic Testing

Electrocardiography

The electrocardiogram of a cat with mitral valve dysplasia may have a normal sinus rhythm and a normal electrical axis and QRS morphology. However, they may also have evidence of left atrial enlargement defined by a widened P wave (>0.04 seconds) and/or left ventricular enlargement defined by a tall R wave (>0.9 mV). Arrhythmias including occasional atrial or ventricular premature beats may be observed.

Radiography

Depending on the severity of the defect and the age of the cat, the radiographs may be normal or may exhibit left-sided (atrial and/or ventricular) or generalized cardiomegaly. Evidence of heart failure with patchy pulmonary edema and pulmonary venous congestion may be observed. In some cases, pulmonary artery congestion may be observed, suggesting the development of pulmonary hypertension.

Echocardiography

Two-dimensional echocardiography should identify the abnormal, thickened appearance and movement of the mitral valve. Left atrial and ventricular dilation can be observed if the degree of dysplasia and valve regurgitation is substantial. Color-flow Doppler should indicate mitral valve regurgitation. Systolic anterior motion of the mitral valve resulting in left ventricular outflow tract obstruction may be present. Due to possible other congenital defects, a thorough evaluation should be performed.

Diagnosis

Although the diagnosis may be suggested based on a left apical or sternal murmur in a kitten or young cat, an echocardiogram is needed to confirm the diagnosis and rule out the presence of concurrent defects.

Treatment

Unless the valve is stenotic (described below), which is rare, interventional therapy (surgery or cardiac catheterization) is not indicated. Medical therapy to control signs of heart failure are warranted (see Chapter 19). Additionally, cats with moderate or marked atrial enlargement are at risk of developing an atrial thrombus and antithrombotic therapy may be considered as described for tricuspid dysplasia.

Outcome and Prognosis

The prognosis is dependent on several factors. The severity of the defect is important, and small defects with minimal valve regurgitation are compatible with few or no clinical signs, whereas markedly dysplastic valves can be associated with progression to congestive heart failure even at a young age. The presence of concurrent defects may be a negative prognostic indicator, particularly if such defects act synergistically with the hemodynamic disturbance created by mitral regurgitation (e.g., aortic

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stenosis). Progression to left heart failure is also a likely negative prognostic indicator, and it appears to be the most likely outcome of cats with this defect if the cat experiences clinical decompensation.

MITRAL VALVE STENOSIS

Mitral valve stenosis, a narrowed annulus of the mitral valve or subvalvular or supravalvular area, is described much less commonly than mitral valve dysplasia in the cat. Valvular or supravalvular mitral valve stenosis has been reported in at least 6 cats (Fine et al. 2002; Stamoulis and Fox 1993; Matsuu et al. 2007; Takemura et al. 2003).

Etiology and Pathophysiology

Etiology

Mitral valve stenosis is an uncommon feline malformation. The small number of reported cases has prevented any studies of etiology.

Pathophysiology

The stenotic area at the supravalvular, valve, or subvalvular region impedes normal diastolic (filling) function, resulting in elevated left atrial pressures, increased pulmonary venous congestion, and pulmonary edema. The valve may be insufficient as well as stenotic.

Signalment

Reported cases have occurred only in adult cats, ranging from 3 years of age (Fine et al. 2002) to 16 years of age (Stamoulis and Fox 1993) (median = 9 years of age), leading to speculation that mitral valve stenosis may be an acquired, rather than congenital disorder in the cat (Takemura et al. 2003) as it often is in humans. Alternatively, since the auscultatory findings of mitral valve stenosis may be subtle or nonexistent (see below), the defect may simply escape notice until congestive heart failure occurs (Stamoulis and Fox 1993). Four domestic shorthairs (3 male, 1 female) and 2 Siamese cats (1 male, 1 female), all neutered, have been reported.

History and Chief Complaint

The chief complaint for all 6 cats with mitral stenosis was dyspnea and/or tachypnea referable to pulmonary edema, pleural effusion, or both. In 2 cats, signs of aortic thromboembolism were also present. In a young kitten or one with a mild malformation, it may be assumed that overt clinical signs would not be apparent (Fine et al. 2002; Stamoulis and Fox 1993; Matsuu et al. 2007; Takemura et al. 2003).

Physical Examination

Cats with primary mitral valve stenosis should have a low-frequency diastolic murmur or diastolic rumble caused by low-velocity turbulence of blood entering the left ventricle through the stenotic valve. This type of murmur is often very difficult to hear due to its soft intensity, low frequency, and—in the cat—high heart rate; concurrent pericardial or pleural effusion, or pulmonary edema, makes a soft diastolic murmur virtually impossible to hear. It was not reported in any of the 6 feline cases. However, a left apical systolic murmur may be ausculted (3 of 5 cats in which auscultation was described) (Stamoulis and Fox 1993; Fine et al. 2002) if mitral regurgitation is present (n = 4 of 5 cats in which color Doppler echocardiographic studies were reported) (Stamoulis and Fox 1993; Fine et al. 2002; Matsuu et al. 2007).

Differential Diagnosis

Supravalvular mitral valve stenosis can be confused with cor triatriatum sinister (see below). Differentiation is based on the level of the obstruction. In supravalvular mitral stenosis, the left auricle is proximal to the obstructing membrane, but with cor triatriatum sinister the left auricle is distal to the dividing membrane.

Diagnostic Testing

Electrocardiography

The electrocardiogram of a cat with mitral valve stenosis would be expected to be similar to those of mitral valve dysplasia and could include evidence of left atrial enlargement defined by a widened P wave (>0.04 seconds) and/or left ventricular enlargement defined by a tall R wave (>0.9 mV).

Radiography

Depending on the severity of the defect and the age of the cat, the radiographs may be normal or may reveal left-sided (atrial or ventricular) or generalized cardiomegaly. Signs of heart failure with patchy pulmonary edema and pulmonary venous congestion are expected when affected cats are dyspneic. In some cases, pulmonary artery congestion may be observed as well, suggesting the development of pulmonary hypertension.

Echocardiography

Two-dimensional and M-mode echocardiography may show abnormal movement of the mitral valve during diastole if the stenosis is at the valve level. Specifically, tethering of the valve leaflets and concordant movement

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of the leaflets during diastole may occur. The diagnosis is established via Doppler echocardiography, which demonstrates increased mitral valve inflow velocities demonstrating the existence of a pressure gradient across the mitral valve during diastole (normal E wave velocity = 0.7 ± 0.1 m/s in the cat; see the inside covers of this book), with mitral valve E wave velocities typically >1 m/s unless severe diastolic dysfunction is also present. In most cases (4/5), mitral valve insufficiency is also noted. In the case of supravalvular stenosis, a stenotic membrane is observed proximal to the mitral valve on 2D echocardiography.

Treatment

Depending on the location and severity of stenosis, balloon valvuloplasty may possibly be beneficial. This should be considered after careful consultation with a cardiologist. Medical therapy to control signs of heart failure if present are warranted (see Chapter 19). Additionally, cats with significant atrial enlargement are at risk of developing an atrial thrombus, and antithrombotic therapy may be considered as described for tricuspid dysplasia.

Outcome and Prognosis

Reported cats have presented at very advanced stages of disease and have lived between a few hours (critical dyspnea at presentation) to 7 months (good response to treatment) (Stamoulis and Fox 1993) after diagnosis. Presumably a stenotic defect that is detected before a cat shows overt clinical signs carries a better prognosis, although physical exam limitations make such early detection difficult as discussed above.

VENTRICULAR SEPTAL DEFECT

A ventricular septal defect (VSD) is a common feline congenital malformation. It is characterized by an opening in the ventricular septum that occurs due to failure of the ventricular septum to complete formation. During ventricular septal development, the septum develops by growing upward from the apical area of the ventricle. Defects that result from incomplete development of the ventricular septum are called *ventricular septal defects*. The most common location for a ventricular septal defect in the cat is the perimembranous area. On a long-axis, two-dimensional echocardiographic view, this area is located immediately apical to the aortic valve in the left ventricle and adjacent to the region of the septal tricuspid valve leaflet in the right ventricle.

Etiology, Pathophysiology, and Gross Pathology

Etiology

The VSD is not known to be a familial trait in the cat although extensive etiology studies have not been performed. There are no known breed predispositions.

Pathophysiology

Due to the pressure difference between the left and right ventricles, blood typically shunts across the septal defect from the left ventricle to the right. Most of the blood is immediately pushed out of the right ventricle into the pulmonary artery, to the lungs via the peripheral pulmonary arteries, and returns to the left atrium again via the pulmonary veins. The pulmonary arteries, veins and left side of the heart (atrium and ventricle) experience the majority of the volume load. Left heart failure with pulmonary artery and venous congestion may result depending on the size of the defect. In some cases, the septal defect is so large that the right and left ventricular pressure may almost equilibrate with the two ventricles largely openly connected.

Some patients develop elevated pulmonary artery pressure, likely due to the impact of the increased blood volume on pulmonary vasculature (Eisenmenger's physiology). The elevated pulmonary pressures result in elevated right ventricular pressures and may become high enough to cause a reversal of the direction of the shunt, now becoming right to left. These patients may develop polycythemia and cyanosis as the deoxygenated blood from the right ventricle is shunted to the left and out the aorta. Irreversible changes in the pulmonary vasculature may develop.

Because the defect is most commonly located at the perimembranous region, directly under the aortic valve, the defect may weaken the support structure of the aortic valve and result in aortic valve insufficiency. Finally, in a small number of patients, the ventricular septal defect may become partially or completely covered with a thin fibrous membrane, in essence closing itself (Thomas 2005).

Gross Pathology

The defect is generally observed just apical to the aortic valve within the membranous part of the basal (upper) ventricular septum (Liu 1977). Left ventricular and atrial dilation may be observed.

Signalment

A specific breed or gender predisposition has not been noted.

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History and Chief Complaint

In many cases, the diagnosis is made after auscultation of a murmur in an asymptomatic kitten or adult cat at the time of a routine evaluation. In other cases, the diagnosis is made after a cat presents for signs consistent with congestive heart failure including tachypnea, dyspnea, anorexia, or depression.

Physical Examination

Physical examination findings should include the presence of a heart murmur typically ausculted at the right sternum or parasternal area (4th–5th intercostal space) as blood shunts from the left ventricle to the right. Sometimes a murmur of mitral regurgitation may also be heard at the left apex or the sternum because the left ventricle and atrium may be dilated with volume overload and lead to valve regurgitation.

Diagnostic Testing

Electrocardiography

Cats with a VSD may have a sinus rhythm and normal axis. In cases with larger defects, evidence of left ventricular eccentric dilation may be noted based on the identification of a tall R wave (>0.9 mV) in lead II.

Radiography

Depending on the severity of the defect and the age of the cat, the radiographs may be normal or may have evidence of left-sided or generalized cardiomegaly. Signs of left heart failure with pulmonary venous congestion and patchy pulmonary edema may be observed. Cats with large defects that are developing pulmonary hypertension secondary to their left-sided volume overload may show evidence of pulmonary arterial hypertension with dilated peripheral pulmonary arteries as well.

Echocardiography

Echocardiography with Doppler is the diagnostic test of choice. Two-dimensional echocardiography should identify the septal defect, most commonly in the perimembranous region immediately below the aortic valve on a long-axis 5-chamber view or on a right parasternal short-axis view. Doppler echocardiography should be used to measure the pressure gradient across the defect. If one assumes that the normal left ventricular systolic pressure is 125 mm Hg and the right ventricle is 25 mm Hg, the pressure gradient or difference between the ventricles should be approximately 80–100 mm Hg. With a small ventricular septal defect that is "restricted" (a small shunt), the pressure gradient should remain in this "normal" range (i.e., 80–100 mm Hg). Larger defects would be expected to allow the ventricular pressures to equilibrate more and a lower pressure gradient would be observed.

Treatment

Some small, restricted ventricular septal defects are well-tolerated and the cat may remain asymptomatic for years. Treatment for cats with large ventricular septal defects is generally thought of as surgical or medical.

Surgical therapy could include surgical closure of the defect, which would require cardiopulmonary bypass, something that is technically possible in a full-sized cat and very difficult in an immature cat with a large defect. Interventional procedures that implant a device across the VSD by a catheter would be technically challenging in a cat because of the small body size. Interventional or surgical options for a kitten with a large defect should be discussed with a cardiologist or surgeon because new techniques and devices are becoming increasingly available.

However, because there are currently very limited surgical interventions feasible for cats with large defects (particularly small cats), most animals that develop clinical signs are simply managed with heart failure medication as described (see Chapter 19).

Prognosis

The prognosis is largely dependent on the size of the defect. Some cats with a small VSD will remain asymptomatic for years and live a normal life; others with larger defects and/or concurrent defects develop congestive heart failure very quickly. Finally, in a small number of patients with small defects the ventricular septal defect may become partially or completely covered with a thin fibrous membrane; this outcome is thought to be most likely in the first year of life (Thomas 2005).

AORTIC STENOSIS

Aortic stenosis is a narrowing or stenotic region that can occur at the subvalvular, valvular, or supravalvular level (Liu 1977; Stepien and Bonagura 1991; Margiocco and Zini 2005).

Etiology and Pathophysiology

Etiology

The etiology is unknown. A breed predisposition has not been noted, although one report described the malformation in 2 Himalayans and 3 mixed-breed cats (Stepien and Bonagura 1991). Several early reports also described subvalvular aortic stenosis in the Siamese cat (Liu 1977; Stepien and Bonagura 1991).

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Pathophysiology

The stenosis results in increased left ventricular pressure and may lead to the development of left ventricular concentric hypertrophy, left atrial dilation, and the development of left-sided heart failure.

History and Chief Complaint

The most common clinical presentations are associated with the development of congestive heart failure and include tachypnea, dyspnea, and crackles (Stepien and Bonagura 1991). Syncope has also been described (Margiocco and Zini 2005).

Physical Examination

The heart murmur of aortic stenosis might be expected to be loudest at the left base over the aortic valve, but in some cases the murmur may be loudest at the sternum. A gallop rhythm may be ausculted.

Differential Diagnosis

Systemic hypertension, hypertrophic cardiomyopathy, and hyperthyroidism can all cause concentric hypertrophy of the left ventricle similar to that observed with aortic stenosis.

Diagnostic Testing

Electrocardiography

A sinus rhythm and normal axis may be observed, but left atrial enlargement (wide P wave) or left ventricular chamber enlargement patterns (tall R waves) may be observed. R waves of 2.1 mV were observed in 1 cat (Margiocco and Zini 2005).

Radiography

Radiographs may appear to be normal or may show evidence of left atrial or ventricular enlargement. A poststenosis dilation bulge may be observed within the aorta. Evidence of left heart failure with pulmonary venous congestion and patchy pulmonary edema may be observed.

Echocardiography

Echocardiography from the right parasternal long-axis view may reveal an echogenic band below the aortic valve (subvalvular), thickened aortic valve (valvular), or supravalvular stenosis. Secondary findings could include hypertrophy of the left ventricular walls and papillary muscles. The left atrium may appear dilated. Continuous-wave Doppler echocardiography should be used for assessing the severity of the stenosis from a position that is parallel to flow of the aortic outflow (see Chapter 7). Systolic anterior motion of the mitral valve may be observed.

Treatment

Interventional therapy for aortic stenosis might be considered depending on the location of the stenosis and other aspects of the individual case. For the many cases that are not candidates for interventional therapy, medical therapy is recommended with atenolol (6.25–12.5 mg orally q 12 hours); such treatment should be initiated only if the cat is not in acute congestive heart failure (which beta-blockade can worsen).

Prognosis

Cats with mild disease can live a normal life span. Cats with a more severe defect determined by Doppler echocardiography are at increased risk of sudden cardiac death, or possibly the development of heart failure. Cats that have subvalvular aortic stenosis (SAS) could possibly be at increased risk of developing endocarditis as in the dog, so prophylactic antibiotics might be warranted prior to surgical procedures. In the dog, SAS is familial, so it should be considered that it also might be in the cat, particularly if a breed or genetic line appears to have several affected individuals.

ATRIAL SEPTAL DEFECT

Atrial septal defects are openings between the right and left atrium that result from abnormal atrial septation during development. During this process, the septum forms by growing apically (downward) from the base of the heart and dorsally (upward) from the endocardial cushion region where the atrioventricular valves develop. There are three types of atrial septal defects: sinus venosus (uncommon; in the dorsal septal region), septum primum (at the lower/basal septal region), and septum secundum, which are defects at the level of the foramen ovale.

Etiology, Pathophysiology, and Gross Pathology

Etiology

A specific etiology is not known. The defect may be a spontaneous developmental abnormality. A familial nature has not been observed in the cat.

Pathophysiology

Because the pressure in the right and left atria are very similar, shunting from the left atrium to the right atrium occurs mainly due to the greater compliance of the right ventricle and sucking of blood from the right atrium

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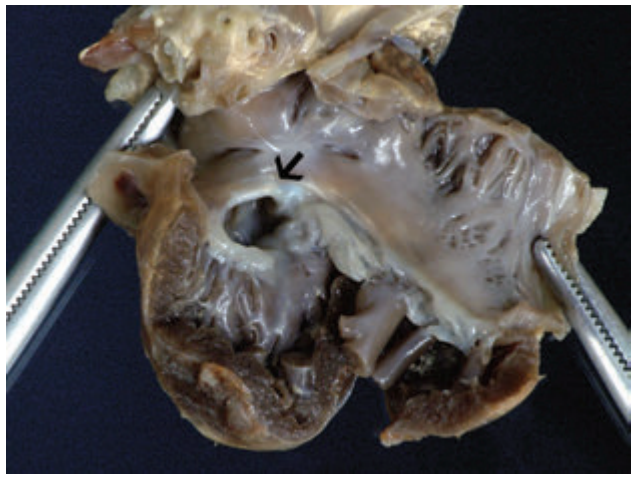


Figure 10.3. Heart from a cat with an ostium primum atrial septal defect (arrow), left-sided view. The proximal attachment of the septal leaflet of the mitral valve is seen along the ventral border of the defect. The left atrium (opened) appears enlarged.

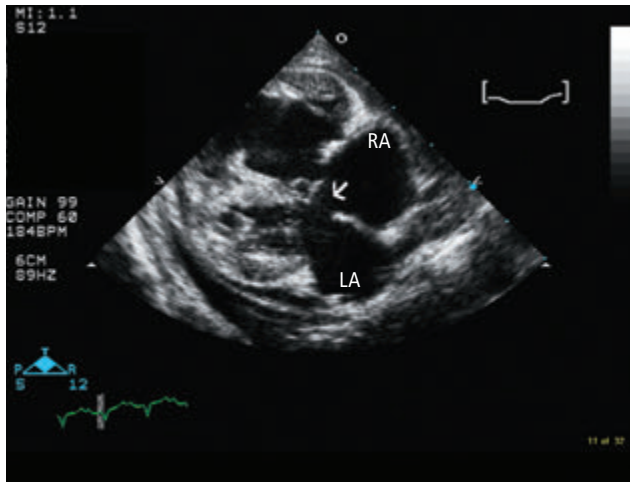


Figure 10.4. Right-sided long-axis 4-chamber echocardiogram from a cat with an ostium primum atrial septal defect (arrow). The location is characteristic of ostium primum defects. Echo dropout artifact is unlikely due to location: typically, dropout occurs more dorsally, in the mid-interatrial septum (in the location of the fossa ovalis). Marked right ventricular eccentric hypertrophy and a small amount of pericardial and pleural effusion are also present. LA = left atrium; RA = right atrium.

into the right ventricle and, therefore, from the left atrium to the right atrium.

Gross Pathology

A defect of the atrial septum should be noted at the top of the septum (sinus venosus), at the foramen ovale level (ostium secundum), or at the level of the atrioventricular valves (ostium primum) (Figure 10.3).

Signalment

A specific signalment is not known, although one study found certain breeds to be overrepresented (domestic shorthair, Persian, and Chartreux) (Chetboul et al. 2004).

History and Chief Complaint

In the majority of cases, the atrial septal defect is an incidental finding observed at necropsy without any clinical signs. However, in one study 1/14 cats presented with a history of exercise intolerance and 2/14 had syncope (Chetboul et al. 2004).

Physical Examination

A heart murmur is frequently not detected. If a heart murmur is present with an atrial septal defect it is typically ausculted at the left base of the heart. It may be a systolic murmur resulting from relative pulmonic stenosis associated with increased blood volume (due to the interatrial shunt) crossing a normal-sized pulmonic valve. One study of both dogs and cats with atrial septal defects found that those animals with a left systolic heart murmur had a significantly larger atrial septal defect than those without a heart murmur (Chetboul et al. 2006).

Diagnostic Testing

Electrocardiography

Cats with an atrial septal defect generally have a normal sinus rhythm and normal axis. However, changes associated with right atrial and ventricular enlargement can be observed.

Radiography

Evidence of increased volume in the right atrium and ventricle may be observed by increased chamber size and an overcirculation pattern of the pulmonary vasculature. With smaller atrial septal defects the radiographs may appear normal.

Echocardiography

Echocardiography can be used to image the defect (Figure 10.4). Doppler echocardiography can be used to identify the abnormal flow crossing the atrial septum. Diagnosis without Doppler can be challenging though due to natural echo dropout of the atrial septum with two-dimensional echocardiographic imaging of this area.

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Treatment

Because the majority of cats with atrial septal defects remain asymptomatic, treatment is not generally needed. Cats with large defects and volume overload may benefit from angiotensin-converting enzyme inhibitors such as enalapril or benazepril. Large defects may result in the development of heart failure and should be treated as described (see Chapter 19).

Prognosis

The prognosis is typically dependent on the size of the defect. Cats with small atrial septal defects may remain asymptomatic for life.

COMMON AV CANAL (ENDOCARDIAL CUSHION DEFECT)

This developmental malformation is characterized by absence of the lower/basal atrial septum, higher/dorsal ventricular septum, and malformation of the atrioventricular valves (mitral and tricuspid).

Pathophysiology

The resultant abnormality leads to communication between all the chambers and results in heart failure usually by 1 year of age.

COR TRIATRIATUM SINISTER

Cor triatriatum sinister is an uncommon defect in the cat (Gordon et al. 1982; Wander et al. 1998; Koie et al. 2000; Heaney and Bulmer 2004). It is characterized by the presence of a band of tissue that divides the left atrium resulting in 2 left atrial chambers, which communicate through a small opening. One chamber receives the pulmonary venous flow and the second chamber communicates with the mitral valve.

Pathophysiology

Because of the small communication between the two, obstruction of blood flow occurs between the two chambers. The pressure in the proximal chamber becomes elevated, the chamber dilates, and increased pressure is reflected to the pulmonary veins. Left-sided heart failure usually results.

Physical Examination

A heart murmur is typically detected on the left side. Both systolic and diastolic murmurs have been reported (Wander 1998; Heaney and Bulmer 2004).

Differential Diagnosis

The clinical, radiographic and echocardiographic findings of supravalvular mitral valve stenosis are very similar to those of cor triatriatum sinister. The position of the obstructing membrane relative to the left auricle as noted on a two- dimensional echo, 4-chamber, right parasternal view may help differentiate the two. Cor triatriatum should be suspected if the left auricle is located distal to the dividing membrane and supravalvular stenosis should be suspected if the left auricle is located proximal to the dividing membrane (Fine et al. 2002).

Diagnostic Testing

Electrocardiography

A right axis shift was observed in one case (Koie et al. 2000).

Radiography

Radiographs may indicate signs of left heart failure including pulmonary venous congestion and pulmonary edema.

Echocardiography

Echocardiography should identify a double chamber left atrium with a dilated proximal chamber (Figure 10.5). The atrium should appear to be divided by a membrane with a small communication between the two chambers. The left auricle should be associated with the distal chamber as noted on a two-dimensional, 4-chamber, right parasternal view echocardiogram.

Treatment

Kittens with cor triatriatum often present with clinical signs of congestive heart failure that should be addressed as described (see Chapter 19). Surgical correction of cor

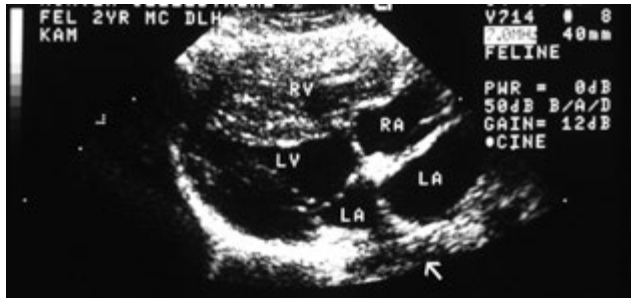


Figure 10.5. Right-sided long-axis 4-chamber echocardiographic view from a cat with cor triatriatum sinister. Note the double chamber left atrium (LA in 2 locations, separated by the partitioning membrane [arrow]), with a dilated proximal chamber. LV = left ventricle; RA = right atrium; RV = right ventricle.

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triatriatum has been reported but is challenging (Wander et al. 1998).

Prognosis

The prognosis for cor triatriatium is generally poor, with kittens generally succumbing to the signs of congestive heart failure. Pulmonary hypertension may develop.

DOUBLE CHAMBER RIGHT VENTRICLE

Double chamber right ventricle is a congenital defect characterized by the presence of anomalous muscle bundles that spread from the septal wall of the right ventricle to the parietal wall, dividing the right ventricle. A breed predisposition has not been noted. One report noted it in 4 domestic shorthairs, 1 domestic longhair, and 1 each Birman, Bengal, Maine coon, and Manx (Koffas et al. 2007).

Pathophysiology

The right ventricle is divided into two smaller compartments by the muscle bundles. The proximal compartment is exposed to higher pressure due to the obstruction caused by the muscle bundles and may have right ventricular hypertrophy. The distal chamber has normal pressures.

History and Chief Complaint

Reported clinical signs are fairly nonspecific and have included lethargy, exercise intolerance, and chylothorax, but some cats remain asymptomatic (MacLean et al. 2002; Koffas et al. 2007).

Physical Examination

A systolic heart murmur is most commonly heard on the left hemithorax, but it may be loudest on the right. Progression of the disease can include the development of right heart failure, so jugular venous pulses may be observed.

Differential Diagnosis

Because pulmonic stenosis can also lead to the development of right ventricular hypertrophy, it should be considered.

Diagnostic Testing

Electrocardiography

A sinus rhythm is expected, but a right axis shift or an arrhythmia could be observed. Atrial tachycardia has been noted as well.

Radiography

Right-sided enlargement is a common finding. Pleural effusion may be observed.

Echocardiography

A fibromuscular bundle should be noted crossing the right ventricle, most commonly at the midventricular level. Right ventricle hypertrophy should be noted proximal to the lesion but not below it. The pulmonic valve should appear normal. Doppler echocardiography should reveal an increased pressure gradient across the fibromuscular band (high velocity of blood flow across the communicating aperture in the band). Flow across the pulmonic valve should be normal. In some cases a small perimembranous ventricular septal defect was noted as a concurrent finding (Koffas et al. 2007).

Treatment

Treatment for heart failure, if present, should be initiated as described (see Chapter 19). A beta blocker such as atenolol (6.25–12.5 mg PO q 12 hours) might be beneficial if heart failure is not present. Surgical treatment with a patch graft was successfully performed in one case (Koffas et al. 2007). Balloon valvuloplasty was attempted in one case, not successfully, likely due to the fibrous bundles not being responsive to valvuloplasty (i.e., they stretch and deform rather than breaking or tearing) (MacLean et al. 2002).

Prognosis

Many cats remain asymptomatic for years, but others may progress to the development of heart failure, with chylothorax a possible outcome.

PATENT DUCTUS ARTERIOSUS

Patent ductus arteriosus (PDA) is an uncommon defect in the cat. A patent ductus arteriosus occurs when the embryologic ductus that allows shunting of blood between the pulmonary artery and the ascending aorta fails to close (Figure 10.6).

Etiology and Pathophysiology

Etiology

Although the patent ductus arteriosus is well known for being a familial trait in the dog, heritability has not been demonstrated in the cat.

Pathophysiology

As long as the ductus is patent, blood will shunt from the descending aorta to the pulmonary artery since the

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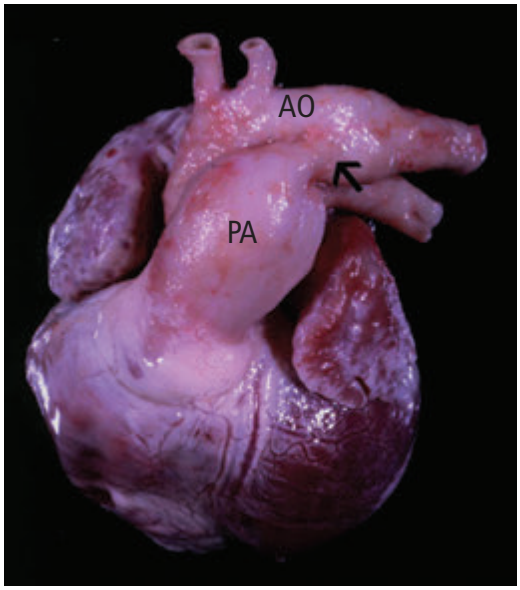


Figure 10.6. Heart from a cat with a patent ductus arteriosus (PDA). The arrow indicates the patent ductus connecting the descending aorta (Ao) and the pulmonary artery (PA). Moderate right ventricular enlargement is also seen.

pressure in the aorta is naturally always higher (120/80 mm Mg) than the pulmonary artery (25/12 mm HG). Shunting of blood occurs both though systole and diastole and is, therefore, a continuous shunt. The shunting of blood from the aorta to pulmonary artery results in left-sided volume overload as the blood circulates through pulmonary artery and veins, back to the left atrium and ventricle, and through the aorta and pulmonary artery again. Left heart failure may develop.

Some cats develop elevated pulmonary artery pressure, likely due to the impact of the increased blood volume on pulmonary vasculature (Eisenmenger's physiology), as described for ventricular septal defects. The elevated pulmonary pressures may become high enough to result in a reversal of the direction of the shunt, now shunting from pulmonary artery to the descending aorta. These patients may develop polycythemia and differential cyanosis as the deoxygenated blood from the pulmonary artery is shunted to the descending aorta. Irreversible changes in the pulmonary vasculature may develop.

Signalment

Specific breed predispositions or genders with increased predisposition have not been noted.

The patent ductus arteriosus is an uncommon defect in the cat; therefore, specific signalment prevalences have not been defined.

History and Chief Complaint

In one study, the most common clinical presentation included abnormal respiration, exercise intolerance, and poor growth (Hitchcock et al. 2000).

Physical Examination

Although the heart murmur of a patent ductus arteriosus is typically continuous, in about 1/3 of the feline cases in one study, only the systolic component of the murmur was heard (Hitchcock et al. 2000). In some cases, the continuous murmur is heard best ventrally. Hyperkinetic pulses were identified in about 1/3 of feline cases.

Diagnostic Testing

Electrocardiography

A normal sinus rhythm and normal axis may be observed, but left ventricular chamber enlargement patterns may be observed.

Radiography

The most commonly reported radiographic abnormality is cardiomegaly. Left-sided enlargement would be expected, with pulmonary overcirculation also commonly expected. The cardiac apex may be displaced to the right.

Echocardiography

Echocardiography is needed to confirm the diagnosis. Doppler echocardiography should in the region of the pulmonic valve and ductus should show continuous flow shunting into the pulmonary artery from the ductus (Figure 10.7). It can be quite challenging to image the actual ductus in a cat, particularly a kitten. Cats that develop pulmonary hypertension may show signs of right ventricular hypertrophy.

Treatment

Because patients with patent ductus arteriosus may develop left heart failure and pulmonary hypertension, repair is almost always advised. Surgical ligation of the defect is most common, but transvenous embolization with a detachable coil has also been reported in 2 cats (Schneider and Hildebrandt 2003; Summerfield and Holt 2005). Uncommonly an older cat may present with a patent ductus arteriosus that was not diagnosed at a young age. In some cases, if the patent ductus arteriosus is small with little volume overload, surgical correction may not be needed.

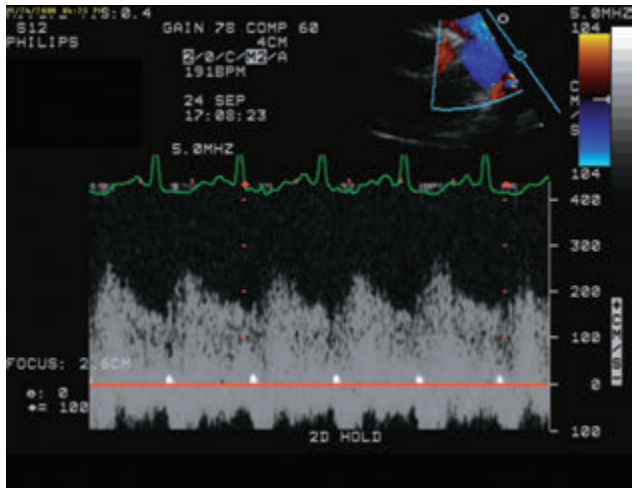


Figure 10.7. Doppler echocardiograph from a cat with a patent ductus arteriosus (PDA). Continuous flow is noted to be shunting into the pulmonary artery from the ductus.

Prognosis

The prognosis for patent ductus arteriosus, particularly if diagnosed early, is very good. Once cats develop pulmonary hypertension and reversal of shunting, the prognosis becomes guarded to poor.

PULMONIC STENOSIS, PULMONARY ARTERY STENOSIS

Pulmonic stenosis is a narrowing or a stenosis that can occur at the subvalvular, valvular, or supravalvular level (Keirstead et al. 2002; Johnson and Martin 2003). Additionally, pulmonary artery stenosis, a stenosis of the main or branched pulmonary artery, has also been recently reported in several cats (Schrope and Kelch 2007).

A breed predisposition has not been noted. These defects have been reported in 1 Devon Rex, several domestic shorthairs, and 1 Persian (Johnson and Martin 2003; Schrope and Kelch 2007).

Pathophysiology

Pulmonic stenosis or stenosis of the pulmonary artery, (main pulmonary artery or a peripheral pulmonary artery) results in similar hemodynamic effects. Increased right ventricular systolic pressure resulting in right ventricular concentric hypertrophy, septal flattening, right atrial dilation, and the development of right heart failure can all be observed.

History and Chief Complaint

Clinical signs appear to be rare, with many animals remaining asymptomatic for many years. One cat presented for exertional dyspnea (Schrope and Kelch 2007). Syncope and exercise intolerance could also be expected.

Physical Examination

The heart murmur of pulmonic stenosis should be a systolic murmur ausculted loudest at the left base over the pulmonic valve but it may radiate widely (Johnson and Martin 2003; Schrope and Kelch 2007). Tricuspid regurgitation associated with right ventricular hypertrophy and pressure overload may result in a systolic murmur ausculted over the right hemithorax.

Differential Diagnosis

A double chambered right ventricle may produce similar clinical findings. An echocardiogram with Doppler should differentiate the two defects.

Diagnostic Testing

Electrocardiography

A normal sinus rhythm and normal axis may be observed, or a right axis shift consistent with right ventricular hypertrophy may be present. Right atrial enlargement (tall P wave) may be noted.

Radiography

Radiographs may appear to be normal in many cases. Alternatively, evidence of right atrial or ventricular enlargement may be noted. A bulge due to poststenotic dilation may be observed within the pulmonary artery.

Echocardiography

Two-dimensional echocardiography may demonstrate some degree of right ventricular and/or papillary muscle hypertrophy, flattening of the interventricular septum, right atrial enlargement, and/or dilation of the pulmonary artery above the stenosis. Doppler echocardiographic studies should demonstrate an increased velocity across the stenotic area. The severity of the stenosis is typically based on Doppler velocity across the narrowing and the calculated pressure gradient.

Treatment

Interventional therapy for pulmonic stenosis might be considered on a case-to-case basis. Balloon valvuloplasty has been successfully performed in a cat with pulmonic stenosis (Johnson and Martin 2003). Surgical palliation, including placement of a patch graft, might also be considered in some cases. Medical therapy with atenolol (6.25–12.5 mg orally q 12 hours), a beta blocker, may also be considered if the patient is not a candidate for valvuloplasty and is not in congestive heart failure.

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Prognosis

The prognosis may depend on the severity of the defect, but some cats appear to do quite well and remain asymptomatic or with only mild symptoms for some time.

TETRALOGY OF FALLOT

Tetralogy of Fallot is an uncommon congenital defect in the cat. It is characterized by a ventricular septal defect, obstruction of the right ventricular outflow tract (pulmonic stenosis), an overriding (dextropositioned) aorta (arising from both ventricles), and secondary right ventricular hypertrophy. Shunting of blood through the ventricular septal defect is typically right to left or mixed due to the obstruction of the pulmonary artery and elevated right ventricular pressures.

History and Chief Complaint

Affected cats have been reported to be small and possibly stunted. They may present with dyspnea, exercise intolerance, cyanosis, or syncope.

Physical Examination

Cyanosis associated with a right-to-left shunting ventricular septal defect is generally noted, but not always. A systolic murmur consistent with pulmonic stenosis may be ausculted at the left base of the heart, but it may radiate generally and be heard over the right thorax as well.

Differential Diagnosis

Radiographs may be suggestive of pulmonic stenosis, but the poststenotic pulmonary artery dilation typically seen with pulmonic stenosis would not be expected. Echocardiography should be used to determine the etiology of the outflow obstruction.

Diagnostic Testing

Electrocardiography

A right axis shift would be expected but is not always present.

Radiography

Right ventricular enlargement may be noted. Pulmonary vascularity may be small, or the lungs may appear undercirculated.

Echocardiography

Right ventricular hypertrophy, a ventricular septal defect, a dextroposition of the aorta, and right ventricular outflow obstruction should be noted. Color Doppler examination should identify the right-to-left shunting across the ventricular septal defect (Fruganti et al. 2004).

Additional Testing

Polycythemia is expected when substantial right-to-left shunting of blood is present.

Treatment

Surgical therapy including the development of a shunt from the systemic to the pulmonary system has been successfully performed but is challenging in a cat (Miller et al. 1985). Medical therapy with a beta blocker, particularly propranolol (2.5–5 mg/cat PO q 8h; begin low and titrate up to desired effect of preventing tachycardia) may be helpful. In this case, propranol may be more helpful than atenolol, which is cardioselective. Phlebotomy may be needed periodically to try to maintain the PCV below 68% if polycythemia occurs.

Prognosis

Tetralogy of Fallot generally carries a poor prognosis, though the specific prognosis depends on the combination of size of ventricular septal defect, degree of pulmonic stenosis, and degree of dextroposition of the aorta. Therefore, the diagnosis of tetralogy of Fallot does not by itself indicate a definitive prognosis; the extent of the primary lesions, and their effects (overt clinical signs, polycythemia, etc.) must be considered in order to provide an accurate prognosis.

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SECTION D

Cardiomyopathies

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11

Hypertrophic Cardiomyopathy

Key Points

- Hypertrophic cardiomyopathy (HCM) is the most common heart disease in cats. Fifteen to thirty-four percent of overtly healthy cats have echocardiographic evidence of left ventricular concentric hypertrophy (increased ventricular wall thickness) attributed to HCM.
- HCM is caused by a primary defect within the heart muscle cells, which causes the ventricle to become thick (i.e., concentric hypertrophy) and develop excess scar tissue (i.e., fibrosis), which makes the ventricle stiff and unable to relax normally.
- HCM ranges in severity from mild to severe disease. Pathophysiologic sequelae to severe HCM may be development of diastolic congestive heart failure (i.e., pulmonary edema and/or pleural effusion), arterial thromboembolism, or sudden death.
- Diagnosis of HCM requires an echocardiogram, which demonstrates increased left ventricular free wall and/or papillary muscle and/or interventricular septal end-diastolic wall thickness, and sometimes left atrial dilation, with normal systolic function.
- Congestive heart failure is diagnosed by clinical signs and thoracic radiographic evidence of cardiomegaly, pulmonary edema and/or pleural effusion, and often pulmonary venous distension. Atrial enlargement is also often present.
- Electrocardiography is not indicated to screen for HCM, but it is important in cats with an arrhythmia or history of episodic weakness or collapse.
- Hyperthyroidism, systemic hypertension, subaortic stenosis, acromegaly, and pseudohypertrophy due to dehydration are differential diagnoses for increased left ventricular wall thickness.
- Treatment of cats with HCM is dependent on many variables, which may include presence of left atrial dilation, severity of systolic anterior motion of the mitral valve, tachycardia, severity of left ventricular hypertrophy, and client and patient motivation and ability to chronically administer medications. Treatment options for asymptomatic cats include atenolol, or less preferably diltiazem. If elected, atenolol is the treatment of choice for moderate or severe systolic anterior motion of the mitral valve (left ventricular to aortic pressure gradient measured on echocardiography of ≥50 mm Hg), in the appropriate clinical context.
- Congestive heart failure is treated with furosemide and an ACE inhibitor. Anticoagulant therapy with clopidogrel, aspirin, or low molecular weight heparin is necessary in cats currently or previously suffering from arterial thromboembolism, cats with echocardiographic evidence of spontaneous contrast or thrombus, and may be considered in cats with moderate to severe left atrial dilation (left atrial to aortic ratio of >1.9 and/or evidence of atrial blood stasis).
- Prognosis of mild and/or asymptomatic HCM is good, and cats many live for many years without problems. The prognosis worsens once cats develop congestive heart failure, with average survival times ranging from 92–654 days. Cats with HCM and ATE have the poorest prognosis, with average survival times ranging from 61–184 days.

Feline Cardiology, First Edition. Etienne Côté, Kristin A. MacDonald, Kathryn M. Meurs, Meg M. Sleeper.
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INTRODUCTION

Key Points

- Hypertrophic cardiomyopathy (HCM) is a primary myocardial defect diagnosed by presence of increased left ventricular wall thickness, in the absence of secondary causes of concentric hypertrophy.
- HCM is the most common heart disease of cats and is the most common form of feline cardiomyopathy.
- HCM is inherited in Maine coon cats and Ragdoll cats as an autosomal dominant trait with incomplete penetrance. This means that HCM affects all individuals that have the mutation, but to varying degrees. For example, homozygous affected cats typically show obvious phenotypic abnormalities, and heterozygous affected cats have much more variability in penetrance and may demonstrate only mild phenotypic abnormalities.
- Hypertrophic obstructive cardiomyopathy (HOCM) indicates that there is dynamic systolic anterior motion of the mitral valve (SAM) accompanying HCM.

Hypertrophic cardiomyopathy (HCM) is the most common cardiac disease in cats, and is defined as concentric hypertrophy of the left ventricle (i.e., thick ventricular wall) in the absence of other causes of concentric hypertrophy including systemic hypertension, aortic stenosis, hyperthyroidism, or acromegaly. HCM is a primary myocardial disorder, indicating that the myocardial abnormality is due to a defect most often within the sarcomere (i.e., individual contractile element within the heart) of the cardiomyocytes, and not secondary to other causes (Figure 11.1). Approximately two-thirds of people who develop HCM have an autosomal dominant heritable defect (with incomplete penetrance pattern) in one of 11 sarcomeric proteins. Currently there are hundreds of mutations in dozens of genes, and this number is expected to expand with discoveries of additional novel mutations (for updated information, access the human gene mutation database at hgmd.cf.ac.uk). Often individual families have novel mutations, which makes widespread genetic screening difficult, even in human medicine (Marian et al. 2001). Familial HCM has been described in cats, and is caused by mutations in myosin binding protein C in Maine coon cats and Ragdoll cats (Meurs et al. 2005, 2007). The etiology of HCM in other cats remains unknown and may be caused by unrecognized mutations.

Initial veterinary reports in the 1960s and 1970s often named HCM as idiopathic cardiomyopathy, primary myocardial disease, or feline cardiomyopathy. At that time, the similarities between feline and human HCM in clinical features and pathology were beginning to be recognized, and feline HCM was identified as a model for human disease (Tilley et al. 1977). The term "hypertrophic cardiomyopathy" became more prevalent in the

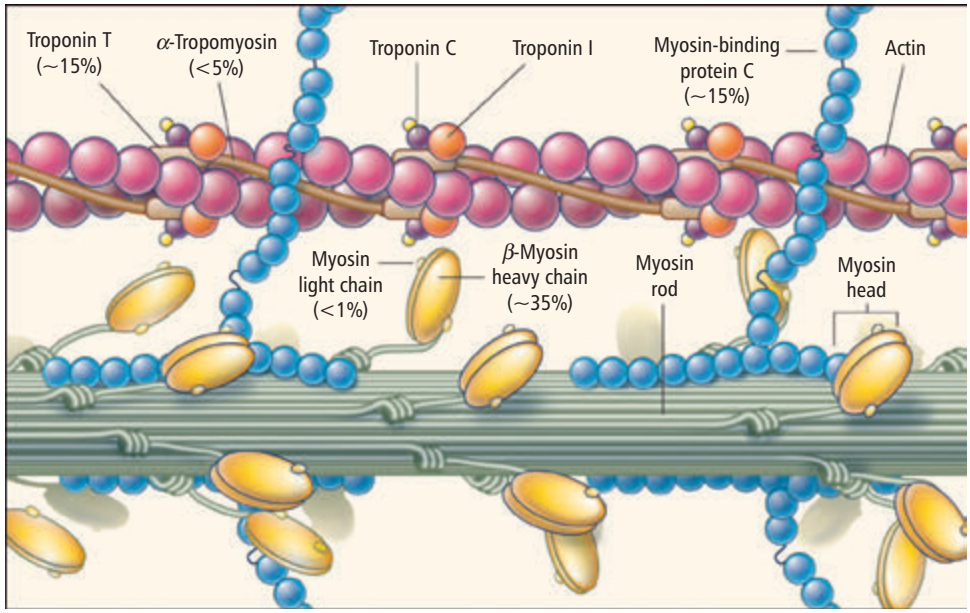


Figure 11.1. Sarcomeric proteins found to have mutations that cause familial hypertrophic cardiomyopathy in people. HCM is a primary myocardial disease caused by mutations in sarcomeric proteins within the cardiomyocytes. Mutations of all sarcomeric proteins displayed in the figure, as well as titin (not shown), have been shown to cause familial HCM in humans. Two missense mutations of myosin binding protein C (the blue protein in the figure) have been found to cause familial HCM in Maine coon cats and Ragdoll cats, and a screening test is now available. Obtained with permission; Spirito et al. N Eng J Med 336:776, 1997.

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veterinary literature in the 1980s, when it was recognized that there are other forms of cardiomyopathies in cats in addition to HCM, and that there are secondary causes of concentric hypertrophy of the left ventricle that should not be labeled as HCM. HCM is a primary and likely heritable myocardial disorder that is not secondary to diseases such as hyperthyroidism or systemic hypertension, which cause a secondary, compensatory increase in ventricular muscle thickness (i.e., concentric hypertrophy). Unlike HCM, successful treatment of secondary causes of left ventricular concentric hypertrophy leads to regression of the ventricular hypertrophy. The term "hypertrophic cardiomyopathy secondary to hyperthyroidism" is therefore, inappropriate because the changes are not primary but compensatory, and the correct term is "thyrotoxic heart disease" or "concentric ventricular hypertrophy secondary to hyperthyroidism."

In the 1960s, dynamic obstruction of the left ventricular outflow tract (later termed *systolic anterior motion of the mitral valve*) was identified in people with left ventricular hypertrophy and had several names, including muscular subaortic stenosis, idiopathic hypertrophic subaortic stenosis, or dynamic subaortic stenosis. Today, *hypertrophic obstructive cardiomyopathy (HOCM)* is the term used to describe presence of systolic anterior motion (SAM) of the mitral valve accompanying HCM, and for the remainder of the chapter HOCM will be included in the category of HCM. SAM causes a dynamic obstruction of the left ventricular outflow tract that worsens throughout systole and will be discussed later.

Prevalence

HCM is the most common cardiac disease in cats, and is highly prevalent in the general feline population. Prevalence rates of left ventricular hypertrophy identified on echocardiography, attributed to HCM, in clinically healthy cats range from 14.5% to 34%, although hydration, thyroxine concentration, and systolic blood pressure were not measured in all cats in these studies (Paige et al. 2009; Wagner et al. 2010). However, presence of a murmur is not diagnostic for cardiomyopathy (in the first study), with a low sensitivity of 31% and specificity of 87%, and murmurs may be benign (i.e., innocent) or caused by other heart diseases. In contradiction, the latter study found that 31–62% of cats with a murmur had left ventricular hypertrophy based on different hypertrophy classification schemes. This study found that a murmur grade of 3 or higher was moderately specific (70%) and sensitive (61%) for left ventricular hypertrophy. The absence of a murmur does not rule out HCM, because 69% of cats with asymptomatic HCM in one study did not have a murmur (Paige et al. 2009). Approximately 68% of cats referred for a cardiac workup at a referral institute were diagnosed with HCM (Riesen et al. 2007). When excluding other forms of heart disease and only including cats with cardiomyopathy, 58% of cats were diagnosed with HCM, followed by restrictive cardiomyopathy (21%), dilated cardiomyopathy (10%), and unclassified cardiomyopathy (10%) (Ferasin et al. 2003). Echocardiographic evidence of concentric hypertrophy was present in 10% of asymptomatic breeding Swedish Maine coon cats, but hypertension, hyperthyroidism, or other secondary causes of concentric hypertrophy were not ruled out, and the genetic status of the cats is unknown since they were not screened for the mutation of myosin binding protein C gene (MYBPC3) (Gundler et al. 2008). A mutation in the myosin binding protein C gene (MYBPC3) has been found to cause HCM in some Maine coon cats, and this mutation is highly prevalent (identified in 34% of Maine coon cats worldwide (Fries et al. 2008) Similar to Maine coon cats, echocardiographic screening of healthy British shorthair cats revealed a prevalence of 8.2% for HCM, but this was based on an increased left ventricular wall thickness of ≥5.5 mm rather than the usual criteria of ≥6 mm, which will overestimate the prevalence (Granstrom 2010).

ETIOLOGY

Key Points

- Familial HCM occurs in Maine coon cats and Ragdoll cats as a dominant heritable defect with incomplete penetrance.
- Two missense mutations in cardiac myosin binding protein C gene (MYBPC3) have been identified to cause HCM in some families of Maine coon cats and Ragdoll cats, and a commercial assay is available for genetic screening.
- Heterozygous cats may not have phenotypic evidence of disease (i.e., no concentric ventricular hypertrophy) but may transmit the defect to progeny.
- Some Maine coon cats and Ragdoll cats develop HCM in the absence of the MYBPC3 mutation and likely have another sarcomeric defect yet to be identified. Similarly, in other breeds of cats and mixed-breed cats, a multitude of genetic mutations is likely present, which also explains the variable expression (i.e., age of onset, distribution and severity of ventricular hypertrophy, and rate of progression) of HCM in cats.
- A sarcomere is the smallest individual contractile unit within a muscle cell. The initial sarcomeric defect is hypothesized to cause sarcomeric dysfunction, which increases cell stress and activates signaling cascades

Continued

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and compensatory mechanisms to lead to the final phenotype of concentric hypertrophy, myofiber disarray, and myocardial fibrosis.
- Environmental influences, including nutrition and air- or waterborne factors, are not known to cause HCM in cats, but have only been sparsely investigated.

Familial Hypertrophic Cardiomyopathy in Cats

HCM is a heritable disease in Maine coon cats, Ragdoll cats, and American shorthair cats, and many other purebred cats are predisposed (Meurs et al. 1997, 2005, 2007). Although heritable, it is not a congenital disease that is present at birth. Rather, it is a developmental disease that occurs as the cat ages, at any time during its life span ranging from adolescent to geriatric.

HCM is an autosomal dominant inherited disease with incomplete penetrance in Maine coon cats (Kittleson et al. 1999). A missense mutation in the myosin binding protein C gene (MYBPC3) has been identified in some Maine coon cats, which results in a change from the conserved amino acid alanine to proline, thus altering protein conformation (Meurs et al. 2005). A second mutation of MYBPC3 has been found in Ragdoll cats with familial HCM (Meurs et al. 2007). This missense mutation results in a change in the conserved amino acid from arginine to tryptophan, which alters the structure of myosin binding protein C (MBPC). The acronym *MBPC* indicates the sarcomeric protein, and the acronym *MYBPC3* represents the actual genetic mutation of the myosin binding protein C that alters the structure of the protein. MBPC is a sarcomeric protein located at the transverse band within the A band of the sarcomere and attaches to titin and β-myosin heavy chain (see Figure 11.1). Its role is believed to be both structural and regulatory (Marian et al. 2001; Harris et al. 2002). The axial alignment of MBPC along the beta myosin heavy chain (β-MHC) backbone and the interaction of MBPC with titin are necessary for ordered, stabilized arrangement of the sarcomere. Consequently, absence of MBPC in transgenic MBPC knockout mice results in malignment of sarcomeric striations, a classic histopathologic abnormality seen in HCM (Harris et al. 2002). MBPC also interacts with the β-MHC head, and acts as a braking mechanism between the interaction of actin and β-MHC. When MBPC is phosphorylated, it undergoes a conformational change in the C_0–C_1 linker region that releases the myosin head to be in a favorable position to bind with actin (Weisberg and Winegrad 1996). The mutation of MBPC in Maine coon cats is localized to the C_0 and C_0–C_1 linker region involved with binding to myosin and/or actin (Meurs et al. 2005). In an experimental model of interrupted MBPC and myosin interaction in ventricular myocytes, there were increased calcium sensitivity, force of contraction, and time to half-relaxation (Calaghan et al. 2000). Similarly, in a knock-in mouse HCM model missing the linker between motifs C_0–C_1, there was an increased calcium sensitivity to force production (Witt et al. 2001). These experimental findings of diastolic impairment closely parallel those seen in cats with naturally occurring HCM and may help identify possible pathophysiologic mechanisms of familial HCM in cats with mutations of MBPC (Bright et al. 1999). The pathway that links a defective, dysfunctional sarcomere to development of the final phenotype of concentric hypertrophy involves many factors that increase the cell's machinery to synthesize more muscle cells that compensate for the dysfunctional ones, at the expense of increased muscle stiffness and decreased ventricular diastolic relaxation.

A family of American shorthair cats has also been found to have an autosomal dominant heritable form of HCM, consisting mostly of systolic anterior motion of the mitral valve (Meurs et al. 1997). Anecdotal evidence suggests that other purebred cats may have an inherited form of HCM, including British shorthair, Norwegian forest cat, Turkish van, Scottish fold, Bengal, Siberian, Sphynx, and Rex. A heritable form of HCM was suspected in a family of mixed-breed domestic shorthair cats, which also appears to be observed in clinical practice (Nakagawa et al. 2002; see also Chapter 10). Aside from the familial heritable forms of HCM, the remaining cases of spontaneously developing HCM are possibly due to de novo sarcomeric mutations, as they are in approximately 1/3 of humans with HCM (Marian et al. 2001). Since these "unknown cause" cases do not have mutations in the genes found to cause HCM in people, little is known about their etiology, and there may be environmental or other influences, or just unrecognized familial mutations, underlying them. An individual that develops a "spontaneous" de novo sarcomeric mutation may then pass on that mutation to offspring as a heritable trait. This process likely occurs in cats, because one Maine coon cat (with severe HCM but without the MYBPC3 mutation) from a colony of familial HCM sired many progeny affected with HCM without the MYBPC3 mutation (K. MacDonald, personal observation).

Etiology of HCM in Humans and Molecular Mechanisms of Disease

To help understand etiology and pathophysiology of feline HCM, it is helpful to examine the pertinent genetic and molecular mechanisms of disease in humans and other animal species with familial HCM. The sarcomere

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is the basic unit of muscular contraction and relaxation in a muscle cell (myocyte). The primary components are the myofilaments, actin and myosin, which interact in a ratcheting-type mechanism referred to as cross-bridge cycling during muscle contraction. The fibers slide against each other, bringing the two ends of the sarcomere closer to shorten the muscle during contraction. Release of myosin from actin allows the sarcomere to elongate and relax in a resting state. Muscle relaxation is not passive but active, and it requires ATP for normal relaxation. Defects in cellular energetics or calcium handling impact both contraction (systole) and relaxation (diastole) of the muscle. The cardiomyocyte consists of thousands of sarcomeres that are anchored together by a cytoskeletal framework necessary to maintain coordinated contraction and relaxation. Cardiomyopathies involve defects in sarcomeric proteins (actin, myosin, etc.), cytoskeletal proteins, nuclear membrane proteins, or mitochondrial energetics.

Molecular techniques have made it possible to identify mutations in proteins within the cardiomyocytes of patients with various cardiomyopathies including HCM, dilated cardiomyopathy, or other inherited cardiomyopathies (Spaendonck-Zwarts et al. 2008). Two-thirds of people with HCM develop the disorder due to familial inherited, sarcomeric mutations (see Figure 11.1) (Marian et al. 2001). In a large study of a genotyped population of people with familial HCM, there was incomplete, age-related penetrance that was greater in males than in females (Charron et al. 1997). This means that the severity of ventricular hypertrophy is highly variable, occurs more frequently in older people and is typically more severe in males. This closely parallels the characteristics of feline familial HCM. Mutations in people have been identified in a number of sarcomeric protein genes including those for β-MHC, essential and regulatory light chains, α-cardiac actin, α-tropomyosin, troponin I (TnI), troponin T (TnT), MBPC, and titin (see Figure 11.1) (Towbin and Bowles 2002). The most common mutations in people involve β-MHC or MBPC genes. Of the β-MHC mutations identified to date in humans, many are associated with an earlier onset of disease, more extensive hypertrophy, and a higher incidence of sudden cardiac death than other mutations. β-MHC mutations mostly involve the portion of the gene that encodes for the myosin head or head-rod junction, where the altered protein decreases the ability of myosin to dislocate from actin (Marian et al. 2001). Mutations in MBPC occur in approximately 20% of familial HCM cases in people, and often cause aberrant transcripts that result in truncated peptides that lack the myosin binding domain. MBPC mutations often cause a delayed onset of hypertrophy after age 40, with an incomplete penetrance pattern (Marian et al. 2001). The troponin (Tn) complex and tropomyosin behave like a calcium switch that regulates the interaction of actin and β-MHC, which is necessary for cross-bridge cycling and power generation. TnT mutations are a fairly common (20%) cause of familial human HCM cases. Sudden cardiac death with minimal hypertrophy is typical for mutations in this gene (Marian et al. 2001). Actin mutations involve the region near the β-MHC binding site and result in heterogeneous phenotypes ranging from mild hypertrophy to severe septal hypertrophy and systolic anterior motion (SAM) of the mitral valve (Marian et al. 2001). Mechanical performance (i.e., ability to contract) of muscle fibers is reduced when there are mutations in β-MHC, TnT, and tropomyosin (Marian et al. 2001). Most sarcomeric protein mutations also result in an enhanced calcium sensitivity of the contractile apparatus, which may lead to diastolic dysfunction (Marian et al. 2001). In vitro, the majority of mutant sarcomeric proteins assemble into sarcomeres and then myofilaments, and do not cause immediate sarcomere dysgenesis or myofibrillar degeneration, but cause systolic and/or diastolic dysfunction at a cellular level (Marian et al. 2001). If sarcomeric protein mutations are expressed in a very high concentration, there may be sarcomere dysgenesis and myofibrillar disarray. It is hypothesized that the initial expression (phenotype) of HCM at the sarcomeric level is a functional defect, and there are intermediary pathways that connect the initial defect to the final phenotype of LV hypertrophy, myocardial fibrosis, and myofiber disarray (Figure 11.2) (Marian et al. 2001). The mutated sarcomeric proteins are often termed "poison peptides," which exert a dominant negative effect following incorporation into the myofibrils (Marian et al. 2001). The impaired mechanical function leads to increased myocyte stress and activation of stress responsive intracellular signaling kinases, calcium sensitive signaling molecules, and trophic factors (Marian et al. 2001). Transcriptional machinery of the myocyte is activated, which leads to myocyte hypertrophy, collagen synthesis, and myocyte disarray (Marian et al. 2001). LV hypertrophy is a compensatory process occurring later in the disease (Marian et al. 2001). Gene transfer studies in adult cardiac myocytes document myocyte dysfunction prior to development of myofibrillar disarray (Marian et al. 1997). Likewise, in humans and transgenic animals with sarcomeric mutations for familial HCM and no LV hypertrophy, there is reduced velocity of myocardial contraction and relaxation, documenting early systolic and diastolic dysfunction (Nagueh et al. 2000, 2001). Together these findings indicate that HCM is not a monomorphic disease but is caused by a variety of mutations of different sarcomeric

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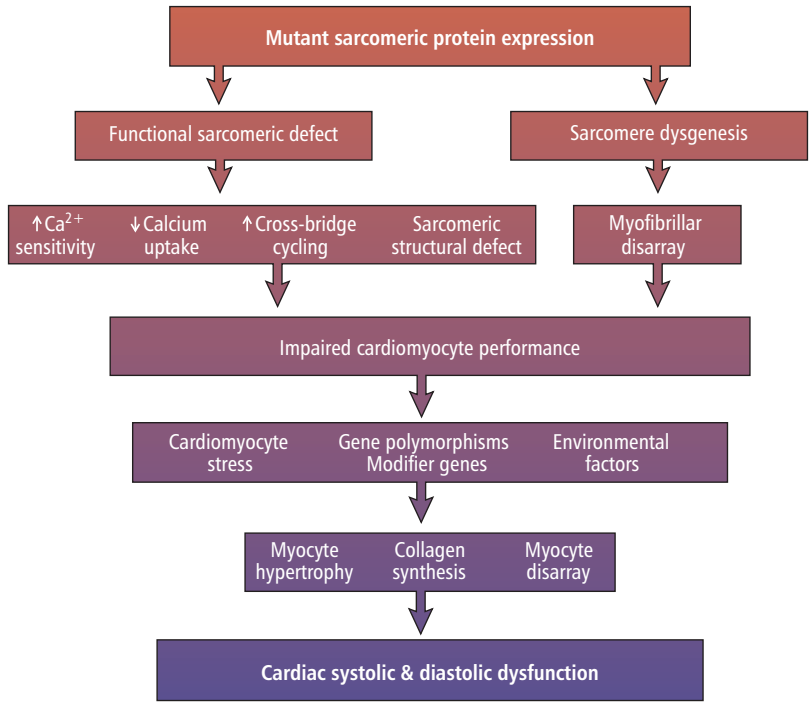


Figure 11.2. Pathophysiologic mechanisms of hypertrophic cardiomyopathy. The initial sarcomeric defect in HCM leads to cardiomyocyte dysfunction, which activates cell stress responses. Increased cell transcription leads to development of cardiomyocyte hypertrophy, increased collagen formation, and myofiber disarray. The final phenotype is concentric left ventricular hypertrophy, myocardial fibrosis, and myofiber disarray, which lead to diastolic and possibly systolic dysfunction.

proteins, which cause a wide range in phenotypic abnormalities including degree of fibrosis, ventricular hypertrophy, or sudden death. The initial defects are impossible to clinically recognize as they occur on a cellular level, and often phenotypic abnormalities are only identified much later once left ventricular hypertrophy or global diastolic dysfunction have occurred closer to the end-stage of the disease. Likewise, some individuals may not ever display phenotypic abnormalities despite being genotypically affected, or they may develop abnormalities much later in life. This is paralleled by our clinical experience in cats, where even within families of cats with HCM, there is great variability in the time of onset of the disease, the extent of ventricular hypertrophy and atrial dilation, and the clinical course where some cats remain asymptomatic yet relatives may decompensate over a short time.

Other factors involved in phenotypic expression in people with HCM include environmental factors, polymorphisms in other genes that modify left ventricular hypertrophy, and concomitant diseases. These factors have been largely neglected in the study of feline HCM. There are no environmental, nutritional, amino acid deficiencies (i.e., taurine deficiency), infectious, or immunologic factors that are implicated to cause HCM in cats, nor have vaccinations been implicated as a causative factor. Viral myocarditis has been hypothesized to be a factor in development of cardiomyopathy in people, and has been investigated in cats with cardiomyopathy. Feline panleukopenia virus was present in the myocardium of 32% (10/31) of cats with various cardiomyopathies (58% had HCM), and 80% of cats with panleukopenia virus in the myocardium had concurrent myocarditis (Meurs et al. 2000). The presence of panleukopenia virus and myocarditis does not establish a causal relationship with HCM, but it is possible that it may contribute to the pathology of HCM or its final common pathway. Likewise, it is not clear whether the panleukopenia virus could be merely present in the myocardium secondary to vaccination with a modified live panleukopenia virus vaccine.

There are several examples of polymorphisms in genes that modify the severity of phenotypic expression of HCM in people, i.e., the extent of gene penetrance and ensuing LV hypertrophy are increased or decreased by the expression of other genes. For example, tumor necrosis factor (TNF-α) is an important modifier of HCM phenotype. The polymorphism that causes the AA genotype, which is known to produce greater amounts of TNF-α, is associated with greater LV mass index and clinical diagnosis at an earlier age when compared to the GA and GG genotypes (Patel et al. 2000). The presence

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of this polymorphism accounts for approximately 6% of the variability of LV hypertrophy in humans. TNF-α provokes a dose-dependent increase in hypertrophy by increasing synthesis of actin and myosin in the cardiomyocyte. TNF-α also interacts with the renin-angiotensin-aldosterone system (RAAS) and increases expression of angiotensin II receptor type 1.

There are four polymorphisms in genes that encode for proteins in RAAS that are associated with higher activation of RAAS and have been identified as "pro-left ventricular hypertrophy" genotypes in some familial HCM-related mutations (Ortlepp et al. 2002). These polymorphisms are an insertion/deletion polymorphism of angiotensin converting enzyme (ACE) gene, a T/C exchange in the angiotensinogen gene, an A/C polymorphism of the angiotensin II receptor type I gene, and a C/T exchange of the aldosterone synthase gene (Ortlepp et al. 2002; Kupari et al. 1998). The ACE-DD polymorphism causes a higher tissue concentration of ACE, and has been associated with more severe LV hypertrophy in patients with β-MHC mutations. Approximately 15% of the variability of LV mass index in humans with familial HCM is due to the type of ACE genotype present in an individual (Lechin et al. 1995). However, the relationship of the RAAS system and ACE in feline HCM is not clear, given the lack of any measurable improvement in left ventricular hypertrophy in asymptomatic Maine coon cats with HCM given an ACE inhibitor daily for 1 year (MacDonald et al. 2006b). The angiotensinogen CC polymorphism results in greater production of angiotensinogen, the catalytic enzyme that converts renin to angiotensin I. The angiotensin II receptor type I CC polymorphism is associated with higher receptor responsiveness. All four prohypertrophic RAAS polymorphisms are independently related to the degree of penetrance and severity of LV hypertrophy in humans with familial HCM due to a MBPC mutation (Ortlepp et al. 2002). Given the highly variable nature of feline HCM, it is an intriguing hypothesis that these RAAS polymorphisms exist in cats. Given the wide spectrum of HCM phenotype and clinical course in cats, it is possible that there are different modifiers (gene, environment, etc.) that occur, which makes it impossible to extrapolate results of clinical therapeutic studies in a group of cats (maybe within a specific breed or family) to apply to all cats with HCM.

Experimental Animal Models of Familial HCM

There are several transgenic or knockout mice with mutations in β-MHC, tropomyosin, TnT, TnI, MBPC, and essential light chains, as well as a transgenic TnT mutation rat model (Marian et al. 2001). Often there is a substantial discrepancy between the phenotype of rodent models compared with the phenotype seen in familial HCM in humans. Aside from the Maine coon cat model, the transgenic β-MHC rabbit model most closely approximates human HCM. Transgenic rabbits have myocyte disarray involving 10–20% of the LV, 2–3-fold increase in interstitial fibrosis, concentric LV hypertrophy, sudden cardiac death, and diastolic dysfunction (Marian et al. 1999). This mirrors the same pathologic abnormalities and clinical correlates described in cats with HCM (Fox 2003a; Fox et al. 1995). A spontaneously developing, moderately heritable model of HCM has been identified in pigs from a breeder farm in Taiwan (Huang et al. 1996; Dai et al. 1996). Pigs develop similar phenotypic abnormalities to those of Maine coon cats and humans, including concentric LV hypertrophy, SAM, and left atrial enlargement (Lin et al. 2002). Like people and cats, these pigs also develop the hallmark histopathologic abnormalities of HCM including myofiber disarray, intramural coronary arteriosclerosis, and myocardial fibrosis (Dai et al. 1996). Therefore, these pigs may serve as models for feline HCM, and future diagnostic and therapeutic discoveries could possibly be relevant to cats with HCM.

Relationship Between HCM and Other Cardiomyopathies

Although cardiomyopathies are classified into specific and very different functional categories (i.e., dilated, restricted, hypertrophic), there are many similarities of molecular genetic mechanisms in humans with various cardiomyopathies. Historically, it was hypothesized that the different functional classes were manifestations along a continuum of one disease, spanning HCM at one extreme, DCM as end-stage myocardial failure at the other, and *intermediate cardiomyopathy* (currently recognized as restrictive or unclassified cardiomyopathy) as a transitional stage from HCM to DCM (Harpster 1977). Continued research (molecular genetic studies, clinical observation), however, has not supported this hypothesis and the different cardiomyopathies are now considered distinct entities (Spaendonck-Zwarts et al. 2008; Maron et al. 2006). However, while transition from HCM to RCM/UCM to DCM does not represent the natural evolution of cardiomyopathy in the cat, mutations in many of the same sarcomeric proteins linked to familial HCM have been shown to cause familial dilated cardiomyopathy or restrictive cardiomyopathy in people (Maron et al. 2006). Since mutations affect some of the same proteins in HCM and DCM – two clinically distinct diseases with opposite pathophysiology – the mutations likely confer different structural and functional consequences to explain the disparate phenotypes. Although previously described as idiopathic, RCM is now known to be a familial heritable disease in

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people: approximately 1/3 of RCM cases are familial and caused by mutations in cardiac troponin I, cardiac troponin T, and α-cardiac actin genes (Kaski et al. 2008). Another study found that six of nine cases of "idiopathic" RCM were actually caused by mutations in cardiac troponin I (Mogensen et al. 2003). Familial RCM is a collection of heterogeneous disorders with a spectrum of cardiac phenotypes, including HCM or DCM in family members. Histopathologic abnormalities in idiopathic RCM often resemble HCM because greater than 40% of cases have myocyte disarray, interstitial fibrosis, and hypertrophy identical to histopathologic abnormalities seen in HCM (Kaski et al. 2008). Although RCM, HCM, and DCM have distinct clinical differences, the causative mutations in familial cases often involve the same sarcomeric mutations. In vitro, cardiac troponin T mutations causing RCM lead to greater calcium sensitivity and more severe diastolic impairment than the mutations causing familial HCM, likely leading to the restrictive phenotype (Gomes et al. 2005; Yumoto et al. 2005). It is likely that variations in the location of the mutation within the specific functional domain of the sarcomeric disease genes can result in different clinical phenotypes of dilated, restrictive, or hypertrophic cardiomyopathy in people. The importance of differentiating between the cardiomyopathies lies in the potential of identifying different clinical features that relate to prognosis, treatment recommendations, and expectations for clinical response, breeding recommendations, and may also define future diagnostic approaches targeted at the specific mechanisms of the disease.

Recognition that left ventricular hypertrophy can be primary (hypertrophic cardiomyopathy) or can be secondary to other diseases such as systemic hypertension or hyperthyroidism is essential for patient workup and management. Before recognition of primary and secondary causes of left ventricular hypertrophy, cats with thyrotoxic heart disease were often diagnosed with "cardiomyopathy due to hyperthyroidism" or "hypertrophic cardiomyopathy due to hyperthyroidism," which we now understand are incorrect terms. Distinguishing between hypertrophic cardiomyopathy (a primary heart muscle disease) and reversible, secondary compensatory left ventricular hypertrophy due to hyperthyroidism or systemic hypertension is essential for both treatment and prognostic implications, because successful treatment of secondary causes of hypertrophy leads to regression of the hypertrophy. In contrast, patients with "primary" hypertrophic cardiomyopathy may progress over time to develop heart failure, sudden death, or arterial thromboembolism and require continued monitoring and possibly lifelong medical therapy for the heart disease.

GROSS PATHOLOGY

Key Points

- Left ventricular concentric hypertrophy (i.e., increased ventricular wall thickness) is seen on gross pathology and leads to increased heart weight of 29–37 grams compared to normal of <20 grams. A heart weight to body weight ratio can also be used, with normal defined as 4.8 ± 0.1 g/kg compared to 6.3 ± 0.1 g/kg in cats with HCM.
- Hallmark histopathologic abnormalities include cardiomyocyte hypertrophy, myofiber disarray, interstitial and replacement fibrosis, and small coronary arteriosclerosis.

Postmortem evaluation to identify whether HCM was present and the cause of death should include obtaining the heart weight, subjective assessment of left atrial dilation, evaluation of intracardiac thrombus, and evaluation for congestive heart failure based on presence of pleural effusion or pulmonary edema (Box 11.1). Postmortem wall thickness measurements reflect an end-systolic time frame (and reflect the echocardiographic measurement of end-systolic wall thickness) due to the rigor process, and do not reflect the end-diastolic ventricular wall thickness that is used to determine presence of concentric ventricular hypertrophy by echocardiography. Sudden death due to a malignant ventricular arrhythmia may be a possible cause of death in cats with HCM with pathologic evidence of increased heart weight and concentric hypertrophy without heart failure or a massive intracardiac thrombus. Cats with HCM have gross (subjective) evidence of concentric LV hypertrophy, which may be diffuse or asymmetrical (Figure 11.3). Asymmetrical hypertrophy can involve either the interventricular septum or the LV free wall. Papillary muscle hypertrophy is a consistent finding in Maine coon cats with HCM, and usually is the first region of the LV to become hypertrophied (Kittleson et al. 1999). Absolute and relative heart weights are increased in cats with HCM that die of their disease compared to normal cats (29–37 g [HCM] versus <20 g [normal]; ≥6.4 ± 0.1 gram heart weight/kg of body weight [HCM] versus ≤4.8 ± 0.1 g/kg [normal]) (Kittleson et al. 1999; Fox 2003a; Liu 1983; Liu et al. 1993).

Cats with severe HCM often have gross evidence of left atrial enlargement and congestive heart failure (CHF). Edematous lungs are heavy, red, and sink when placed in water or formalin. Pulmonary edema may be identified as frothy fluid exuding from the cut surface of the lung or filling the trachea or smaller airways. Pleural effusion may be readily identified upon opening the thorax, but it

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BOX 11.1. Cardiac Necropsy Techniques in Cats Suspected of Dying from Heart Disease

In cats dying from possible cardiac disease, a comprehensive necropsy is done including both gross (preferably with photographs for the medical record) and histopathologic analyses. Typically, the following postmortem examination procedure is recommended:

- The chest is opened laterally with transection of the dorsal and ventral extensions of all ribs on the left side, and all the parasternal soft tissue attachments. The thoracic wall is reflected dorsally, exposing the entire thorax from the left side. Pleural and pericardial effusion are noted if present, and samples obtained for analysis as clinically indicated.
- Before dissecting the pluck (lungs, trachea, heart, and associated vessels) from the esophagus and removing the pluck from the body, attention should be paid to the cranial and caudal mediastinum and the structure, location, and integrity of vascular connections, notably the aorta, cranial and caudal venae cavae, azygos vein, and thoracic duct.
- To remove the pluck after dissection from the esophagus, the cranial and caudal mediastina are removed, the trachea is transected at the thoracic inlet, and the cranial and caudal venae cavae, and azygos vein are transected 5–10 mm from their junction with the heart. The proximal descending section of the aorta is transected, and the brachiocephalic trunk and left subclavian artery are also transected 3–5 mm distal to their branching from the aorta.
- The lungs are removed from the pluck, paying special attention to the pulmonary veins and arteries for size (venous enlargement is expected with congestive heart failure), stenosis, and location (anomalous connections; rare).
- The heart may be opened one of two ways: according to echocardiographic planes (single long-axis incision) or sequentially following the path of a red blood cell from right atrium to aorta. With either method, a systematic assessment of all 4 chambers and 4 valves is essential, including chamber content (i.e., identification of an intracardiac thrombus), wall thickness and symmetry between the septum and the free wall, valve structure, and integrity of endothelium and chamber walls.
- Samples for histologic analysis are obtained from the interventricular septum, right and left ventricular free walls, and one or both atria, as well as visibly abnormal lesions. Full thickness tissue blocks from the ventricular wall and septum should be taken in the transverse plane perpendicular to the long axis of the ventricle. Ideally, several myocardial samples of the left ventricle are obtained including the basilar and mid-interventricular septum, the anterolateral left ventricular free wall, and the posterior free wall between the papillary muscles, for evaluation of myocyte disarray, fibrosis, and small coronary artery disease (Liu et al. 1993).
- Samples for histologic analysis are placed in 10% buffered formalin, fresh samples for DNA or RNA extraction should be deep frozen (–80°C) or preserved in a purpose-made medium (e.g., RNALater®), and samples for electron microscopy (which should be harvested within 20 minutes of death) are placed in glutaraldehyde.
- Extracardiac examination typically includes the lungs for gross and histologic assessment for pulmonary edema or noncardiac pulmonary parenchymal disease; the distal aorta, renal arteries, and proximal femoral arteries to assess for arterial thromboembolism; the liver for evidence of congestion; and the eyes, kidneys, and other organs as suggested by clinical findings.

is less common than pulmonary edema in cats with HCM (20% of cats had pleural effusion versus >50% of cats having pulmonary edema on pathologic examination) (Fox 2003a). This parallels the clinical observation that only 15% of cats with HCM and heart failure have dyspnea due to pleural effusion; the majority of cats are dyspneic due to pulmonary edema (Rush et al. 2002).

Hallmark histopathologic myocardial lesions in cats with HCM include myofiber disarray, small coronary arteriosclerosis, and interstitial and replacement fibrosis (Figure 11.4) (Kittleson et al. 1999; Liu et al. 1993). Histopathologic abnormalities seen in the lungs of cats with heart failure include presence of pulmonary edema fluid within alveoli, thickened alveolar membranes, and ruptured alveoli. All eight Maine coon cats with severe HCM that died in one study had moderate to marked myofiber disarray of the LV wall and interventricular septum, moderate to severe intramural coronary arteriosclerosis, moderate to severe interstitial fibrosis, and severe concentric hypertrophy of the papillary muscles along with portions of the LV walls (Kittleson et al. 1999). In a study comparing morphologic abnormalities of humans and cats with HCM, only 30% of cats had evidence of myofiber disarray of the septum, whereas the majority (92%) of people had disarray (Liu et al. 1993). The majority of cats in this study were domestic shorthair, and only 1 Maine coon was included. It is possible that earlier pathologic studies were not as thorough to search for myofiber disarray, or that Maine coon cats with HCM more often have myocyte disarray than other breeds of cats. Abnormal intramural coronary arteries are commonly found in people (66%) and cats (74%) with HCM and are mostly found within or at the margins of fibrous regions (Liu et al. 1993). In people with HCM, 13% of the septum and 10% of the LV free wall consist of fibrosis, and the amount of

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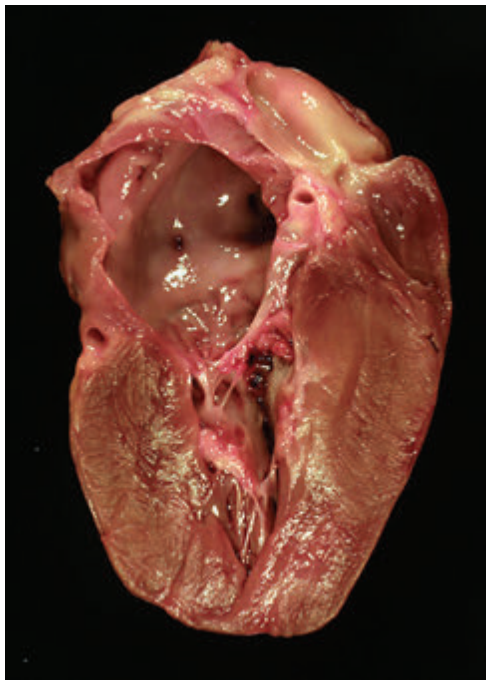


Figure 11.3. Gross pathologic specimen of a Maine coon cat with severe hypertrophic cardiomyopathy. This long-axis section of the left ventricle of a cat with severe HCM and congestive heart failure shows severe global concentric hypertrophy of the interventricular septum and free wall. There is also severe left atrial dilation and a large region of myocardial fibrosis of the interventricular septum where the anterior mitral valve leaflet contacts it due to SAM of the mitral valve.

fibrosis is not correlated with LV mass (Tanaka et al. 1986). Apoptotic cell death is also present within the myocardium of people with HCM (approximately 19% of cardiomyocytes from LV endomyocardial biopsies in one study), but its role in the pathophysiology of feline HCM is yet to be determined (Kavantzas et al. 2000). No other infiltrative substrates, such as amyloid or glycogen, have been demonstrated on histopathologic evaluation of myocardium in cats with HCM.

PATHOPHYSIOLOGY

Key Points

- The cardinal pathophysiologic characteristic of hypertrophic cardiomyopathy is impaired diastolic filling of the left ventricle, due to abnormal relaxation of the heart muscle and increased ventricular muscle stiffness.
- Diastole is comprised of active isovolumic relaxation, rapid passive filling, diastasis, and atrial systolic filling.
- Cats with HCM have abnormal relaxation and increased stiffness that impairs passive ventricular filling.
- Impaired relaxation is caused by abnormal calcium handling, increased myofilament sensitivity to calcium, intracytosolic calcium overload, altered left ventricular loading conditions, and myocardial ischemia from small coronary artery disease.
- Increased ventricular stiffness is caused by concentric left ventricular hypertrophy, myofiber disarray, and myocardial fibrosis.
- Delayed relaxation and increased ventricular stiffness increase LV diastolic filling pressure, which may lead to development of left heart failure.
- Pulmonary edema and/or pleural effusion develop as the main manifestations of left-sided congestive heart failure in cats with HCM.
- Systolic anterior motion (SAM) of the mitral valve develops secondary to anterior-ventrally displaced, hypertrophied papillary muscles that pull the mitral valve into the left ventricular outflow tract during systole. Other factors that may exacerbate or worsen SAM of the mitral valve include severe basilar septal concentric hypertrophy, increased contractility, and tachycardia.
- Moderate or severe SAM of the mitral valve greatly increases left ventricular systolic pressure, which increases severity of concentric LV hypertrophy and potentiates the vicious circle of hypertrophy and the potential for worsened diastolic function.
- Arterial thromboembolism may occur in cats with left atrial enlargement. Factors involved in development of a left atrial thrombus include blood stasis, possible endothelial disruption, and a possible procoagulable state with increased platelet aggregation and markers of hypercoagulability.

Diastolic Dysfunction

HCM produces diastolic dysfunction, a decreased ability of the heart to normally fill with blood during relaxation and passive filling. Diastolic dysfunction may lead to development of heart failure, since left ventricular filling pressures are increased for any given volume of blood in the ventricle, which is transmitted back to elevated pressure in the left atrium and pulmonary veins. Once the pulmonary venous pressure (and left ventricular diastolic filling pressure) exceed ~25 mm Hg, cardiogenic pulmonary edema develops.

Diastole is divided into 4 phases: isovolumic relaxation (IVR), rapid passive filling, diastasis, and atrial systolic filling. IVR is the earliest stage of diastole, consisting of active, ATP consuming, ventricular relaxation without an increase in chamber volume. Isovolumic relaxation is a clinically challenging variable to measure, but it represents a complex set of interactions within the contractile apparatus of the cardiomyocyte. During this active process, calcium is released from TnC, which reduces actin and myosin cross-bridge formation, calcium is actively (ATP requiring) transported into the sarcoplasmic reticulum, and calcium is extruded from the cyto-

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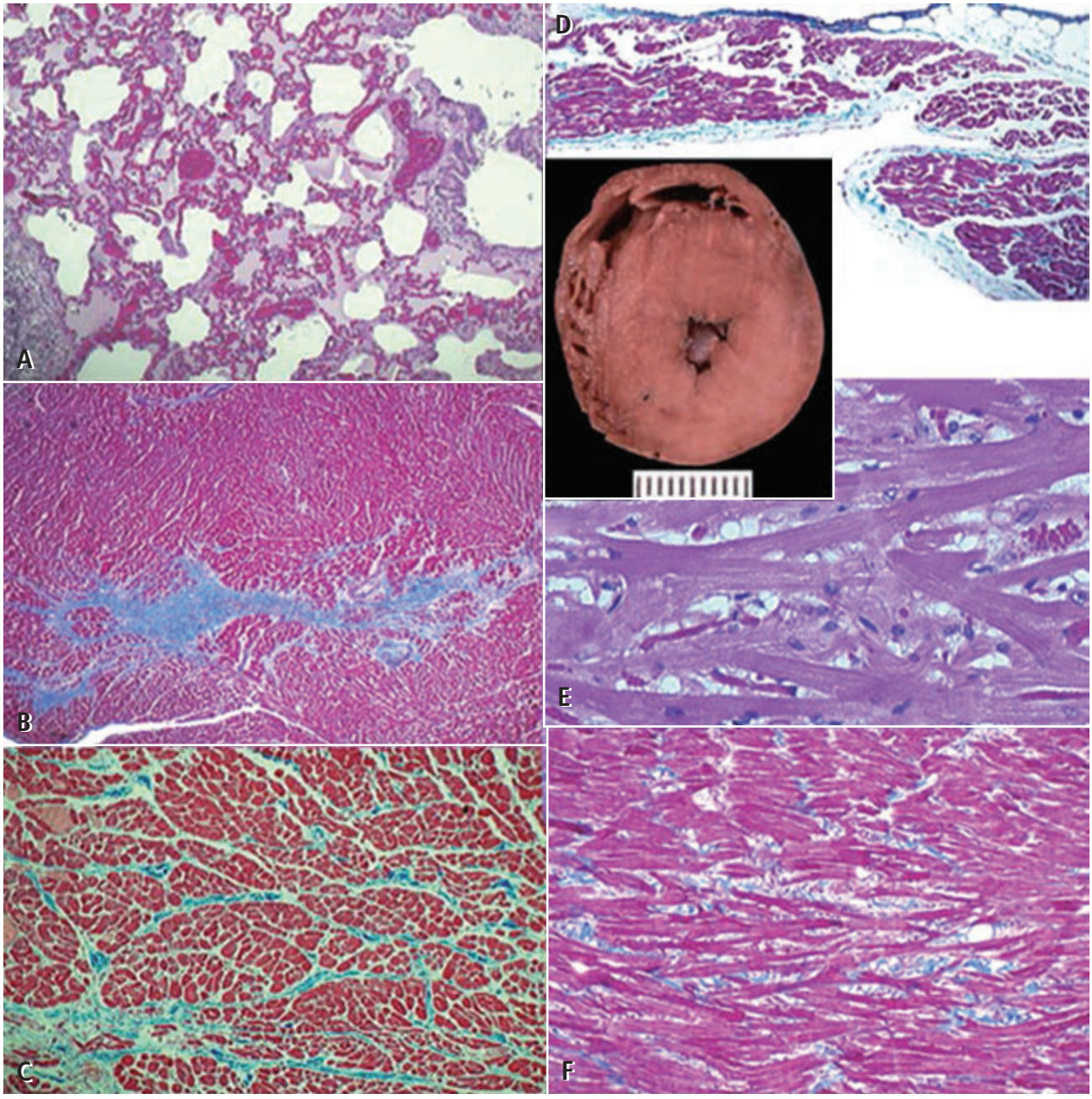


Figure 11.4. Histopathologic examination of the heart and lungs of a Maine coon cat with severe hypertrophic cardiomyopathy. The heart of a Maine coon with severe hypertrophic cardiomyopathy is shown in cross section (center), where there is severe concentric hypertrophy of the left ventricle, and end-systolic cavity obliteration. Histopathologic evaluation of the lungs **(A)** reveals pulmonary edema caused by left-sided congestive heart failure. **(B)** and **(C)** demonstrate severe replacement fibrosis and interstitial fibrosis of the left ventricular myocardium, respectively. **(D)**, **(E)**, and **(F)** are different magnifications of the myocardium showing myocyte disarray, a pathognomonic feature of HCM. Histopathologic images courtesy of Dr. Philip Fox.

plasm by a sodium/calcium exchanger, which causes a release of the myosin heads from actin. Increased cAMP and protein kinase A lead to phosphorylation of phospholamban, which causes the sarcoplasmic reticulum (SR) calcium ATPase pump to sequester calcium into the SR. During IVR, the LV pressure quickly declines, and once the LV pressure is less than LA pressure, the mitral valve opens and the early rapid filling phase begins. LV and LA pressures influence early rapid filling. Increased LA pressure increases early rapid filling and shortens IVR time (IVRT). Elastic recoil also affects passive filling. Diastasis occurs when the LA and LV diastolic pressures

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equilibrate, and is represented as the pause between the first and second heart sounds. Slower heart rates cause a longer diastasis period, which may aid in ventricular filling in a stiff ventricle. Atrial systole contributes the remaining 20% of diastolic LV volume. In rapid heart rates, as seen in cats, the diastolic phases may merge.

Compliance is a major factor in the passive filling of the LV, and is defined as the change in volume for any given change in pressure. The inverse of compliance is stiffness. The greater the stiffness, the greater the diastolic pressure for a given diastolic volume. Other variables involved in diastolic function include heart rate, atrial contractility, pericardial restraint, and left and right ventricular interaction (Mandinov et al. 2000). At rapid heart rates, the three diastolic phases may merge. In atrial fibrillation or atrial standstill, there is a loss in atrial systolic filling at the end of diastole.

Isovolumic Relaxation and Early Diastolic Filling in HCM

In the normal heart, changes in relaxation exert the dominant influence on diastolic function. Beta adrenergic activation results in increased cAMP and exerts positive lusitropic effects (increased relaxation). Impaired relaxation occurs in HCM, where there is a shift in LV filling toward end-diastole (Golden and Bright 1990). In patients with HCM, delayed relaxation may be caused by abnormal calcium handling, altered loading conditions, and myocardial ischemia.

Impaired early relaxation in HCM is caused by altered calcium handling, increased calcium sensitivity, and calcium overload (Figure 11.5). In a study of isolated ventricular muscle from people with HCM, there was abnormal calcium handling consisting of impaired sarcolemmal and sarcoplasmic reticulum calcium channel regulation, which led to increased intracellular calcium concentrations and impaired active relaxation (Gwathmey et al. 1991). Additionally, there may be enhanced calcium sensitivity of myofilaments in models of familial HCM (Marian et al. 2001). During fast heart rates, there is less time for reuptake of calcium into the SR, and accumulation of cytosolic calcium occurs. In a study using isolated muscle strips from humans with HCM, pacing at higher rates (equivalent to 60–120 bpm) resulted in reduced developed tension (i.e., systolic dysfunction) and increased resting (diastolic) tension (Gwathmey et al. 1991). This illustrates that high heart rates may worsen diastolic dysfunction in patients with HCM.

Myocardial ischemia occurs in people with HCM, and may lead to angina, syncope, LV systolic and diastolic dysfunction, and sudden death. It is likely that myocardial ischemia also occurs in cats with HCM. Causes of myocardial ischemia in HCM are multifactorial and include decreased coronary flow reserve, systolic compression of coronary branches, degree of LV outflow tract obstruction, small-vessel disease of intramyocardial coronary arteries, and inadequate capillary density relative to the increase in myocardial mass (Kofflard et al. 2007; Cannon et al. 1985). Regional impairment of coronary flow has been identified in areas of most severe hypertrophy. Like in people, a majority (74%) of cats with HCM have abnormal intramural coronary arteries, based on a comparative pathology study (Liu et al. 1993). Most of the abnormal coronary arteries were located within or at the margins of fibrotic areas. Diastolic dysfunction and elevated diastolic pressure are further exacerbated by reduced coronary flow reserve and calcium overload secondary to ischemia (Cannon et al. 1985). To worsen matters, the effects of hypoxia on ventricular stiffness are exaggerated in the hypertrophied heart, resulting in impaired or incomplete relaxation. Alterations in afterload may also contribute to impaired early diastolic relaxation. Concentric LV hypertrophy reduces end-systolic wall stress and afterload. Counterintuitively, there is improved early diastolic function in people with HCM when afterload is increased (Hausdorf et al. 1989). When afterload is high, there is greater cytosolic calcium, which causes a greater rate of fall of calcium during relaxation, as long as there is adequate sarcoplasmic reticulum function, and explains the faster rate of relaxation. It may be inferred

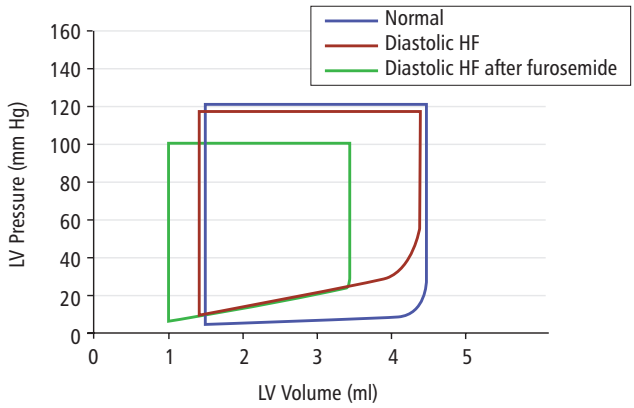


Figure 11.5. Pressure volume curves of a normal cat and a cat with severe hypertrophic cardiomyopathy and congestive heart failure before and after treatment with a diuretic. Increased left ventricular stiffness is reflected by the upward shift in the diastolic pressure volume relationship in this cat with HCM. For each incremental increase in LV volume, the stiff ventricle has a greater increase in diastolic pressure compared to the normal compliant LV. Congestive heart failure occurs once the left ventricular end-diastolic pressure increases over ~24 mm Hg. Diuretic therapy decreases preload and left ventricular chamber volume, which causes a leftward shift of the pressure-volume loop and decreases left ventricular filling pressure.

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that impaired ventricular relaxation in people with HCM may be influenced by a reduced afterload present in the thick ventricle. However, when the afterload is increased in human patients with HCM, the end-diastolic diameter and overall diastolic function is not increased or improved, since the viscoelastic properties of the hypertrophied ventricle remain abnormal (i.e., the heart was still stiff). Delayed relaxation, or regional heterogeneity of relaxation due to geometric distortion or myofiber disarray, also contribute to increased early diastolic filling pressure (Mandinov et al. 2000). In people with HCM, the magnitude of regional nonuniformity of relaxation correlates with the severity of global diastolic dysfunction (Bonow et al. 1987).

In summary, delayed relaxation, a hallmark pathophysiologic abnormality in HCM, may be caused by abnormal calcium handling, altered LV loading, and myocardial ischemia (see Figure 11.5). Delayed or incomplete relaxation not only negatively impacts early diastole, but may impair passive filling due to the continuing interaction of contractile elements and persistent development of myocardial tension.

Passive Diastolic Filling in HCM

Increased myocardial stiffness is an important component of diastolic dysfunction in HCM. Stiffness is represented by the slope of the diastolic pressure-volume curve (Figure 11.5). The diastolic pressure-volume relationship is curvilinear, and pressure increases as chamber volume increases. Myocardial hypertrophy, fibrosis, and myocyte disarray increase myocardial stiffness, which shifts the LV end-diastolic pressure volume relationship upward (see Figures 11.5, 11.6) (Mandinov et al. 2000). Therefore, for any given diastolic volume, the diastolic pressure is greater in a stiff ventricle. Interstitial fibrosis, myocyte hypertrophy, and myocyte disarray all contribute to diastolic dysfunction, but myocyte disarray was found to be the most important factor related to diastolic dysfunction in people with HCM (Ohsato et al. 1992).

Elevated LV diastolic pressure results in elevated left atrial filling pressure and elevated pulmonary capillary wedge pressure (PCWP). In cats with HOCM, SAM of the mitral valve leads to mitral regurgitation, which further elevates left atrial diastolic pressure. Left atrial enlargement occurs secondary to elevated left atrial pressure. The final result is transudation of plasma into the alveoli and development of pulmonary edema once LV diastolic pressure exceeds ~24 mm Hg (Guyton and Lindsey 1959). Reducing LV end-diastolic volume with medical treatment (i.e., a diuretic) shifts the pressure volume loop leftward, and results in lower end-diastolic pressure (see Figure 11.5) (Zile and Brutsaert 2002). Severe LV concentric hypertrophy along with increased myocardial stiffness may reduce end-diastolic volume and reduce stroke volume. Consequently, reduced renal perfusion activates RAAS, leading to increased circulating blood volume and further increased diastolic filling pressure (Taugner 2001).

Congestive Heart Failure

CHF occurs secondary to severe diastolic dysfunction in cats with severe HCM (see also Chapter 19). CHF occurs once the PCWP exceeds approximately 24 mm Hg in cats. In a retrospective study of 260 cats diagnosed with HCM, 46% had CHF as evidenced by pulmonary edema on thoracic radiographs (Rush et al. 2002). Half of the cats with CHF had concurrent pulmonary edema and pleural effusion (Rush et al. 2002). The etiology of pleural effusion in cats with left-sided CHF is debatable. Visceral pleural veins, which collect venous blood from the pleural surface of the lungs, drain into the pulmonary veins in cats. Elevated pulmonary venous pressure secondary to left heart failure may lead to formation of pleural effusion through elevation of hydrostatic pressure and transudation of plasma through the walls of

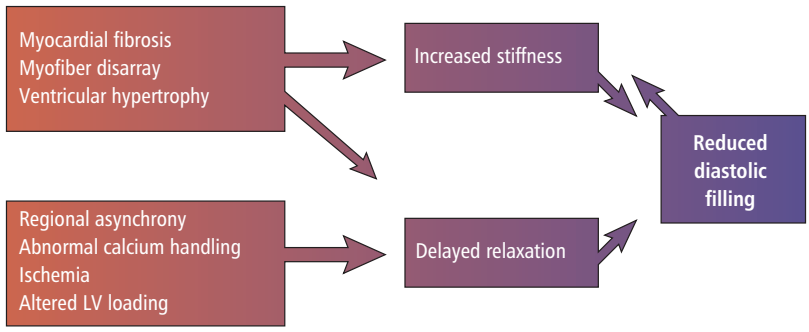


Figure 11.6. Factors causing diastolic dysfunction and diastolic heart failure. Cats with HCM have diastolic dysfunction including delayed or incomplete relaxation as well as impaired passive diastolic filling due to increased chamber stiffness. These abnormalities lead to increased diastolic filling pressure. Congestive heart failure develops when the left ventricular end-diastolic pressure exceeds ~24 mm Hg.

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these veins. Curiously, the visceral pleural veins also drain into the pulmonary veins in dogs, who do not develop pleural effusion secondary to isolated left-sided CHF (Miller 1907). Like cats, people with left heart disease may develop pleural effusion in the absence of pulmonary hypertension or elevated right atrial pressure (Wiener-Kronish et al. 1987).

Systolic Anterior Motion of the Mitral Valve

Systolic anterior motion of the mitral valve (SAM) is a common feature of HCM in cats and humans and has been reported to occur in 67% of cats with HCM (Fox et al. 1995). The anterior mitral valve leaflet is displaced anteriorly into the left ventricular outflow tract (LVOT), creating a dynamic obstruction to ejection of blood out the aorta during mid- to late systole. The magnitude of LVOT obstruction varies from trivial to severe (pressure gradients obtained from Doppler echocardiography may range from 10–100 mm Hg). Mitral regurgitation arising from the displaced mitral leaflet occurs with variable severity and may contribute to increased left atrial pressure. There was once a debate over the actual pathophysiologic mechanisms that cause SAM (Sherrid 2006). The Venturi theory states that an increased blood flow velocity of the narrowed LVOT lifts the anterior mitral leaflet into the LVOT and obstructs systolic blood flow (Sherrid et al. 1988). This theory has been disproven by proponents of the "displacement" theory, stating that papillary muscle hypertrophy anteriorly displaces the chordae tendinae and the anterior mitral leaflet into the LVOT, which obstructs systolic blood flow (Levine et al. 1995; Sherrid et al. 2000). The LVOT is made more narrow by significant basilar septal hypertrophy, which may contribute to development of SAM. Increased contractility and increased acceleration of LV ejection worsens LVOT obstruction (Sherrid et al. 1998). Moderate or severe SAM of the mitral valve greatly increases systolic left ventricular pressure and often leads to anginalike pain in people. Although identification of pain in cats can be challenging, anecdotal experience suggests that cats with moderate or severe SAM may be reluctant to exert themselves vigorously or may demonstrate dyspnea or abrupt cessation of activity associated with vigorous play, and some seem to feel better when the SAM is reduced with beta blockade. However, there may be little impact of SAM on overall survival of asymptomatic cats with HCM (DeFrancesco et al. 2005). Cats with SAM lived longer than cats without obstruction, although this may be due to the earlier detection of HCM in cats with SAM; a systolic murmur is readily audible in these cats and may not be present in cats with more significant HCM without SAM, who may be missed until there are fulminant clinical signs of heart failure (DeFrancesco et al. 2005).

Arterial Thromboembolism

Cats with severe HCM and moderate to severe left atrial enlargement are at risk for developing a thrombus in the left atrium/auricle, which often dislodges to the distal aortic trifurcation. The incidence of arterial thromboembolism (ATE) in cats with HCM is approximately 12–17% (Rush et al. 2002; Atkins et al. 1992; Peterson et al. 1993). In one study of ATE in cats, the left atrium was severely enlarged in 57%, moderately enlarged in 14%, and mildly enlarged in 22%, with only 5% having a normal left atrial size (Laste and Harpster 1995). Thrombus formation may occur when there is an abnormality in one or more of the components of Virchow's triangle, which include: hypercoagulability, endothelial disruption, and blood stasis. When the left atrium becomes moderately to severely dilated, the blood flow velocity is reduced, resulting in red cell aggregation, platelet activation, and subsequent thrombus formation. Blood stasis appears to be an important factor for red blood cell aggregation in cats with significant cardiac disease. Left auricular blood flow velocity is reduced in cats with echocardiographic evidence of spontaneous contrast and red blood cell aggregation (Schober and Maerz 2006). There are contradicting studies regarding whether cats with cardiac disease tend to be hypercoagulable. One study documented that 45% of asymptomatic cats with HCM had evidence of hypercoagulability (Bedard et al. 2007). It is debatable whether there is platelet hyperreactivity in cats with cardiac disease, because some studies document increased platelet reactivity and others report no change in platelet function in cats with heart disease (Helenski and Ross 1987; Jandrey et al. 2008; Welles et al. 1994). Platelet endothelial cell adhesion molecule-1 and endothelin–1 were elevated in asymptomatic Maine coon cats with familial HCM compared to normal control cats, indicating the potential for a prothrombotic state (Jandrey et al. 2009). Endothelial damage and disruption likely occurs in cats with cardiac disease, and endothelial damage and fibrin adherence to the subendothelium has been documented on pathologic examination in several cats with congestive heart failure (Liu 1970). It is likely that a combination of mechanisms leads to development of a left atrial thrombus in cats with significant cardiac disease.

Once the thrombus becomes dislodged from the left atrium, it travels through the arterial blood system and becomes lodged in an artery depending on the size of the thrombus, with the most common location being the aortic trifurcation (71%). More important than the

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physical obstruction of blood flow in the artery, the thrombus releases vasoactive amines including thromboxane and serotonin that cause massive vasoconstriction of the collateral arteries, leading to lack of perfusion to the limb (Schaub et al. 1977, 1982). Approximately 50% of cats regain partial or complete motor control without the aid of thrombolytic therapy in 1–6 weeks (Fox 1987). Other studies estimate survival with our without thrombolytic therapy to be 30–40% (Laste and Harpster 1995; Smith et al. 2003).

End-stage Hypertrophic Cardiomyopathy

Although rare, some cats develop end-stage HCM (i.e., "burnt-out" HCM) characterized by systolic myocardial failure, dilation of the left ventricle, and thinning of the septum and left ventricular wall (Cesta et al. 2005). Congestive heart failure is a consistent feature of end-stage HCM, and may include pulmonary edema and/or pleural effusion. Intracardiac thrombi or arterial thromboembolism appears to be very common in this subset of cats. It is likely that cats with end-stage remodeling suffer from decreased myocardial perfusion, possibly due to coronary arterial thromboembolism and small vessel coronary artery disease, with histopathologic evidence of myocardial infarctions and fibrosis.

Resolution of Left Ventricular Hypertrophy in Some Cats

Although unusual, some cats diagnosed with HCM experience regression, rather than progression or plateau, of left ventricular hypertrophy over time when evaluated by echocardiography. This may be seen as a spontaneous change, or secondary to antihypertrophic therapy (i.e., atenolol, diltiazem, etc.). Regression of hypertrophy in absence of pharmacologic intervention is poorly understood, and mechanisms have not been defined. Possible explanations may be the disappearance of a modulating factor (ill-defined) responsible for stimulating or maintaining hypertrophy, correction of dehydration and normalization of pseudohypertrophy (i.e., wall thickness measured too thick but was due to decreased chamber volume), or potentially a transition to end-stage cardiomyopathy with diffuse small vessel myocardial infarctions and ischemia causing atrophy and fibrosis. However, the end-stage remodeled ventricle typically does not contract normally and may have hyperechoic myocardium due to myocardial fibrosis, rather than reversion to normal ventricular wall thickness, echotexture, and function. The more common cause of regression of ventricular hypertrophy is successful treatment of secondary causes of hypertrophy such as hyperthyroidism or systemic hypertension.

SIGNALMENT

Key Points

- The average age of diagnosis of HCM is ~6 years but may vary from 6 months to geriatric.
- Predisposed breeds include Maine coon cats, Ragdoll cats, American shorthair, British shorthair, Siberian, Turkish Van, Scottish fold, Sphynx, Persian, Himalayan, and Birman. However, the domestic shorthair cat is the most common breed diagnosed.
- Purebred cats, especially the Ragdoll, may develop rapidly progressive, severe HCM at a young age.

There is a wide range of patient characteristics in feline HCM, with any age being possible for HCM to develop. Historically, cats were typically first diagnosed at early to middle age, with mean ages ranging from 5.5–6.5 years in several large-scale studies; but at present, both asymptomatic and decompensated HCM is routinely recognized in cats ranging from young juvenile to geriatric (Ferasin et al. 2003; Rush et al. 2002; Atkins et al. 1992). Although unusual, cats may even be diagnosed with HCM as young as 3 months of age, especially in genetically predisposed purebred cats (Meurs et al. 2007). In a family of Maine coon cats with familial HCM, cats homozygous for the MYBPC3 mutation causing HCM developed phenotypic echocardiographic evidence of LV hypertrophy between 4–6 months of age, and severe LV hypertrophy by 7–12 months of age (Kittelson et al. 1999). Heart failure usually developed by 20 months of age, and most of these cats died by 4 years of age (Kittelson et al. 1999). Male Maine coon cats that were homozygous for the MYBPC3 mutation typically develop more severe disease at an earlier age. Heterozygous affected Maine coon cats may live many years with moderate left ventricular hypertrophy and atrial dilation without development of CHF or sudden death. Ragdoll cats can develop a severe, early-onset form of familial HCM, with a mean age of diagnosis of 15 months in one study (ages range from 6 months to 2 years) (Lefbom et al. 2001). In a genetic study, Ragdoll cats that were homozygously affected with the MYBPC3 mutation developed HCM 18 months earlier than heterozygously affected cats (Meurs et al. 2007). These findings support the hypothesis that gene dosage may affect the penetrance and phenotype of HCM in genetically affected cats.

Although there is no sex-linked heritability pattern, approximately three-fourths of cats diagnosed with HCM are male neutered, which has been described in

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purebred families as well as in the general feline population in an echocardiographic screening study (Wagner et al. 2010; Ferasin et al. 2003; Rush et al. 2002; Atkins et al. 1992). Despite several purebred predilections for HCM, the most common type of cat diagnosed is the domestic shorthair cat (42–65% of cases), followed by the domestic longhair cat (22–42%) (Ferasin et al. 2003; Rush et al. 2002; Atkins et al. 1992). Of purebred cats, the Persian is the most common breed (3–15% of cats with HCM), followed by Himalayan, Maine coon, Ragdoll, and Birman (Ferasin et al. 2003; Rush et al. 2002; Atkins et al. 1992). Other predisposed breeds include the American shorthair cat, British shorthair cat, Sphynx, Bengal, Siberian, and Scottish fold. Cats with HCM were found to have a larger body somatotype (i.e., larger vertebrae, longer radial bone length, larger skull size) than control cats; however there is not one pathognomic characteristic that distinguishes an abnormal somatotype from normal. Although cats with HCM had larger somatotype, there was no difference in serum insulin growth factor-I between normal cats and cats with HCM, making acromegaly an unlikely link (Yang et al. 2008). One potential explanation for a larger somatotype in cats with HCM is the high representation of Maine coon cats and Maine coon cross cats in the feline population, and these cats require only one copy of the MYBPC3 mutation to develop HCM. There is no known link between HCM and other physical traits or concurrent heritable defects in cats.

HISTORY AND CHIEF COMPLAINT

- Approximately half of cats with HCM are diagnosed incidentally and are asymptomatic. The most common reason asymptomatic cats are clinically evaluated for cardiac disease is the presence of a heart murmur or gallop heart sound on routine physical examination.
- Approximately half of cats diagnosed with heart failure secondary to HCM had an identifiable precipitating event; the most common include fluid administration, anesthesia and surgery, and corticosteroid (methylprednisolone) administration.

A large number of cats (at least 33–55%) diagnosed with HCM are asymptomatic and have no abnormal history or chief complaint (Rush et al. 2002; Atkins et al. 1992). By far the most common clinical context for incidental discovery of HCM in cats is during routine examination for other purposes (annual health exam, or medical concern not related to the heart), in which a heart murmur or gallop heart sound is noted (see Chapter 1). Alternatively, HCM is sometimes first suspected during diagnostic imaging for other purposes such as the incidental detection of cardiomegaly on thoracic radiographs. Finally, sudden cardiac death may be the first clinical complaint in some cats with severe disease that were never previously clinically detected and are diagnosed with HCM on necropsy. The diagnosis of HCM in these sudden-death cases may occur at any age, but appears more common in the younger cat (<5 years of age).

Respiratory difficulty due to congestive heart failure is the most common presenting clinical complaint, occurring in 32–46% of cats diagnosed with HCM (Rush et al. 2002; Atkins et al. 1992). A precipitating event was identified in approximately half of cats diagnosed with CHF in one study (Rush et al. 2002). The most common precipitating event was fluid administration (28%), followed by anesthesia/surgery (25%), and recent corticosteroid administration (21%) with methylprednisolone (70% of cats) or injectable form of triamcinolone (30% of cats) given 1–2 weeks prior to diagnosis of heart failure (Rush et al. 2002). Ketamine was the most common anesthetic administered (89%) in anesthetized cats that developed CHF, which may be explained by the popularity of ketamine in feline practices, the potential for adverse cardiac effects of ketamine in cats with HCM, or a combination of both factors. Typical presenting complaints of cats with heart failure include respiratory difficulty, lethargy, anorexia, vomiting, or weight loss. Often, owners may confuse vomiting with coughing or wheezing, particularly if a coughing fit ends with a terminal retch that produces mucus or a hairball. It is important when a client describes vomiting or hairballs in a cat with pulmonary, airway, pleural, or cardiac disease that the clinician inquire about the connection between coughing and vomiting. If the vomiting/hairball evacuation occurs only at the end of coughing fits, a gastrointestinal disorder may not be the patient's dominant concern, even though it can be the most noticeable, and therefore worrisome, abnormality in the eyes of the owner. Syncope is an uncommon presenting complaint (occurring in 10 of 260 cats, 4%), and it may occur secondary to an arrhythmia, severe CHF, or an intracardiac thrombus (Rush et al. 2002). Lameness, paresis, and pain may be chief complaints in cats affected with arterial thromboembolism (ATE) secondary to HCM, which occurs in 12–17% of cats diagnosed with HCM (Rush et al. 2002; Atkins et al. 1992). Therefore, part of the history should involve specific inquiries regarding prior acute onset of lameness, which may have been transient, or much less commonly acute changes in mentation or gastrointestinal signs in cats suffering from embolization of the brain or gastrointestinal tract, respectively. Age, breed, and sex were not significantly different among cats that were asymptomatic, or had CHF or ATE in the largest study that compared these variables (Rush et al. 2002). Other basic inquiries during the history-taking process should

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evaluate for the potential for concurrent diseases that may potentiate or negatively impact cardiac disease, such as diseases causing dehydration, clinical abnormalities consistent with hyperthyroidism or renal failure, or other systemic diseases that may influence treatment decisions and monitoring for heart disease.

PHYSICAL EXAMINATION

- The most common auscultation abnormality is a systolic murmur (36–72% of cats), followed by a gallop heart sound (33%). Historically, only a small number of HCM cats (5%) were described as having normal heart sounds, although more recent echocardiographic screening studies of overtly healthy cats reported that a majority (up to 69%) of cats with HCM did not have a heart murmur on auscultation.
- Dyspnea is the most common clinical abnormality in cats with heart failure. Dyspnea was present in 36% of cats with HCM in one study.

A systolic murmur is the most common abnormality on physical examination, and is present in 47–72% of cats with HCM examined in a referral hospital setting (Ferasin et al. 2003; Rush et al. 2002). Prevalence of a murmur may be higher in these patients than in the general population of cats screened for HCM, as they were likely referred for evaluation of a murmur. There was a lower occurrence (31%) of a murmur in clinically healthy cats in the general population that were diagnosed with HCM during echocardiographic screening (Paige et al. 2009). Most often the systolic murmur is caused by left ventricular outflow tract obstruction (LVOT), which is typically due to systolic anterior motion (SAM) of the mitral valve and less commonly by a narrowed LVOT due to basilar septal hypertrophy. LVOT obstructions create a dynamic holosystolic left parasternal murmur that typically increases in intensity as the heart rate increases. Cats with SAM of the mitral valve have higher murmur grades than cats without dynamic left ventricular outflow tract obstruction (Rush et al. 2002). In cats with SAM of the mitral valve, the murmur grade does not predict the severity of the disease, including extent of wall thickness or left atrial dilation. Presence of a heart murmur is not diagnostic for HCM and murmurs can be heard as a benign finding in cats with dynamic right ventricular outflow tract obstruction (DRVOTO), which may be present in 25–69% of healthy asymptomatic cats with heart murmurs and echocardiographically normal hearts (see Chapter 1) (Paige et al. 2009; Wagner et al. 2010). Pathologic murmurs may be associated with other heart diseases, although murmurs are more common in cats with HCM compared to other feline cardiomyopathies (Ferasin et al. 2003). Benign murmurs due to DRVOTO are typically soft, with a grade III or less, although there is a significant overlap between benign (innocent) murmurs and murmurs due to SAM of the mitral valve in cats with HCM. Both benign murmurs due to DRVOTO and pathologic murmurs caused by SAM are dynamic and increase in intensity as the heart rate increases, so the dynamic component is not a useful characteristic to distinguish murmur etiology. Presence of a murmur is very insensitive (31–42%) for diagnosis of cardiomyopathy in asymptomatic healthy cats, so auscultation alone is not an adequate screening test (Paige et al. 2009; Wagner et al. 2010). However, the presence of ≥III/VI holosystolic murmur has higher sensitivity (61%) for presence of HCM in healthy cats (Wagner et al. 2010). In conclusion, the presence of a heart murmur justifies diagnostic imaging, ideally with echocardiography but possibly with serial thoracic radiography.

A gallop heart sound is the second most common auscultation abnormality, and is present in approximately 1/3 of cats with HCM. A gallop heart sound is less common (33% of cats) than a murmur in cats with HCM (Ferasin et al. 2003). A gallop consists of an extra heart sound (either S_3 or S_4 heart sounds) due to the reverberation of the ventricular walls during early or late diastolic filling when the ventricle is stiff or enlarged due to cardiac disease or increased preload (see Chapter 1). A gallop is not an abnormal heart rhythm, although popular nomenclature often describes it as a gallop rhythm. An S_3 heart sound occurs when there is rapid passive filling into a stiff, hypertrophied ventricle, which creates the extra heart sound. Other causes of an S_3 gallop include marked increase in volume of blood entering the ventricle in early diastole, which may be present in cats with diseases causing volume overload. An S_4 heart sound occurs during atrial systole when the atrium is ejecting the remaining 20% of stroke volume into a noncompliant left ventricle. A gallop is not specific for HCM and may be heard when there are other heart diseases present, anemia, fluid overload, or hyperthyroidism. In fact, gallop heart sounds are more commonly ausculted in cats with dilated cardiomyopathy (79% of cats) than in cats with other cardiomyopathies including HCM (Sisson et al. 1991). Other "extra" heart sounds that may be confused for gallop heart sounds include a split first or second heart sounds or a systolic click (see Chapter 1).

Tachycardia is variably present in cats with HCM, including only 26% of cats in one study, so it is not likely to be a useful diagnostic parameter (Ferasin et al. 2003). Heart rate is influenced by many factors including environment and stress, so presence of tachycardia is not specific for any heart disease in cats. Heart rate of cats in the hospital setting is often driven by increased

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sympathetic tone and is significantly higher (median HR 150 bpm ± 23 bpm, non-restrained in the veterinary hospital) compared to at home (132 bpm ± 19 bpm, measured by telemetry) in normal cats (Abbott 2005). Furthermore, tachycardia is not useful to distinguish asymptomatic cats with HCM from cats with CHF or arterial thromboembolism (Atkins et al. 1992). Premature beats are occasionally ausculted in cats with HCM, and premature ventricular complexes are more commonly associated with heart disease in cats than in dogs (Côté and Jaeger 2008). Other rhythm abnormalities may include an irregularly irregular rhythm if there is atrial fibrillation or runs of tachycardia if there is supraventricular tachycardia or ventricular tachycardia. Therefore, cats with irregularly irregular rhythms, bursts/runs of tachycardia, or unusually low heart rates (e.g., <150 beats/minute in the exam room) may reasonably be suspected of having heart disease, and both electrocardiography and echocardiography are justified in these patients. As discussed above, many cats (up to 69%) with HCM have no clinical abnormalities or abnormal history (Paige et al. 2009).

Femoral pulses are usually unremarkable unless there is a marked tachyarrhythmia or low output heart failure. Palpation of femoral pulses in cats may be difficult and pulses may feel attenuated or reduced in some normal cats due to certain factors such as obesity or examiner variability. Therefore, assessment of pulse quality should be combined with palpation of the warmth of the extremities, evaluation of the color of the nail beds, and other assessments of peripheral circulation to assess perfusion.

Cats with congestive heart failure may have tachypnea, dyspnea, orthopnea, and increased adventitious lung sounds. Dyspnea was present on physical examination in 36% of cats diagnosed with HCM in a study of 61 cats with HCM, yet only 8% had abnormal respiratory sounds on auscultation (Ferasin et al. 2003). Therefore, absence of abnormal respiratory lung sounds does not rule out heart failure. Cats with pleural effusion may have, depending on the volume of the effusion, muffled lung sounds ventrally, tachypnea, and sometimes increased abdominal effort or orthopnea.

Careful evaluation for other physical abnormalities associated with systemic diseases (i.e., hyperthyroidism, systemic hypertension, acromegaly) that cause "secondary" and compensatory left ventricular hypertrophy is essential in cats suspected of having cardiac disease. The thyroid gland should be palpated and may be enlarged in cats with hyperthyroidism with or without HCM. A palpable thyroid gland is present in 91% of hyperthyroid cats, and this finding warrants measurement of serum thyroxine levels (see Chapter 1) (Feldman and Nelson 2004). Careful palpation that fails to identify an enlarged thyroid gland therefore suggests a <10% likelihood of hyperthyroidism. However, the presence of an enlarged thyroid gland does not automatically equate to hyperthyroidism, because many cats have thyroid gland enlargement and normal serum thyroid hormone levels (and no clinical hyperthyroidism). Clinical complaints such as polyuria, polydyspia, polyphagia in the face of weight loss, and behavioral changes such as hyperactivity or lethargy, should spark the suspicion of hyperthyroidism and prompt measurement of serum thyroxine concentration. Identification of ocular abnormalities such as retinal detachment or hyphema raises suspicion for presence of systemic hypertension, and mandates measurement of systolic blood pressure. Physical signs suggestive of acromegaly, such as a broad forehead and prognathism particularly in an adult cat >10 years old with intractable diabetes mellitus, may suggest an excess of circulating growth hormone (i.e., acromegaly) as a secondary cause of left ventricular hypertrophy and prompts a more specific workup for acromegaly.

DIFFERENTIAL DIAGNOSIS

Key Points

- Systemic hypertension, hyperthyroidism, and acromegaly are secondary causes of concentric ventricular hypertrophy, which reverses several months after effective treatment of the disease.
- SAM of the mitral valve is a hallmark pathologic feature of HCM, and occasionally it can occur in cardiac diseases causing secondary ventricular hypertrophy or in normal cats that are catecholamine-driven (anxiety, stress, fear). Mitral valve dysplasia is the most common differential diagnosis for SAM of the mitral valve.
- Rare causes of infiltrative myocardial diseases include cardiac neoplasia such as rhabdomyosarcoma or lymphoma.

On physical exam, the differential diagnoses for heart murmurs, dyspnea, arterial thromboembolism, and syncope are discussed in Chapters 1, 4, 20, and 2, respectively.

Secondary causes of left ventricular concentric hypertrophy (increased end-diastolic ventricular wall or septal thickness measured by echocardiography) are the main differential diagnoses for HCM. Systemic hypertension and hyperthyroidism are the most common causes of secondary concentric hypertrophy. Systemic hypertension increases left ventricular afterload and systolic wall stress, which trigger the cardiomyocytes to replicate side by side to cause increased wall thickness (i.e., concentric

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hypertrophy). Increased ventricular wall thickness never causes systemic hypertension, but rather is caused *by* systemic hypertension. Aortic stenosis (typically subaortic, rarely valvular or supravalvular) is a congenital heart defect that increases afterload and likewise leads to a secondary concentric left ventricular hypertrophy. Acromegaly causes concentric left ventricular hypertrophy as a result of the direct stimulatory effect of growth hormone on the cardiomyocytes, which increases replication of the sarcomeres (Peterson et al. 1990). Secondary causes of concentric hypertrophy usually lead to only mild left ventricular hypertrophy, with end-diastolic wall thickness usually less than 7 mm. All of these secondary causes of left ventricular hypertrophy have one point in common, which is that they represent an adaptive response to a disturbance (i.e., increased blood pressure or increased thyroxine level). This is in contrast to HCM, which is a spontaneous and maladaptive increase in myocardial mass independent of any concurrent illness or defect. The therapeutic implication is that elimination of the abnormality causing secondary left ventricular hypertrophy may lead to its regression, whereas HCM is an irreversible disorder. Secondary causes of HCM do not usually cause severe concentric hypertrophy or congestive heart failure.

If a secondary cause of left ventricular hypertrophy is identified and successfully treated, the left ventricular hypertrophy should markedly regress or resolve over several months. To illustrate this, left ventricular wall thickness of 91 hyperthyroid cats decreased from a mean of 4.7 mm to 4.2 mm when pretreatment echocardiograms were compared to posttreatment echocardiograms performed 2 to 3 months following radioiodine treatment (Weichselbaum et al. 2005). The maximal end-diastolic septal and free wall thicknesses (from an observed range) decreased from 7.2 and 8.9 mm to 5.5 mm and 5.9 mm, respectively, showing significant regression of hypertrophy in those cats with increased end-diastolic ventricular septal or wall thickness at baseline. Likewise, cardiac troponin-I levels (which may be measured by a benchtop cartridge analyzer (I-Stat; http://www.abbottpointofcare.com) decrease over time in hyperthyroid cats after successful treatment, possibly indicating resolved cardiomyocyte injury once a euthyroid state is achieved (Connolly et al. 2005). In patients with persistent left ventricular hypertrophy despite normalization of blood pressure or thyroid levels, HCM is likely a concurrent disease. Marked dehydration decreases left ventricular chamber size and leads to the appearance of increased wall thickness, which is termed "pseudohypertrophy," and which may be confused with HCM (Campbell and Kittleson 2007). Overt clinical signs of hypoperfusion or dehydration, a low arterial blood pressure, and presence of systemic disease likely to cause dehydration/hypovolemia are clues that should prompt the clinician to consider that a "thick" left ventricle on the echocardiogram may in fact represent only pseudohypertrophy. The pseudohypertrophy normalizes upon restitution of normal circulating blood volume, as does the ventricular size.

Infiltrative neoplastic diseases such as lymphoma or rhabdomyosarcoma can cause asymmetrical concentric hypertrophy (see Chapter 16). Typically the affected myocardium has a different echogenicity than the normal myocardium and is hypokinetic. The infiltration and functional defects may improve with chemotherapeutic treatment, which has been well documented in a few cases including a cat with renal lymphoma and metastatic infiltrative cardiomyopathy (Brummer and Moïse 1989). Infiltrative neoplastic myocardial diseases are uncommon in cats, whereas asymmetrical, segmental HCM is quite common.

Cardiac amyloidosis has been thoroughly described in people, but antemortem evaluation in cats is lacking. In people, concentric left ventricular hypertrophy and severe diastolic heart failure may occur in end-stage amyloidosis. Histologic evidence of amyloid deposition in small vessels within the myocardium was seen in most (86%) Abyssinian cats with amyloidosis, but was classified as mild in a majority of cases and did not cause concentric hypertrophy of the ventricle (DiBartola et al. 1986).

SAM of the mitral valve is a unique abnormality present in some cats with HCM, and may uncommonly occur in secondary causes of left ventricular hypertrophy, or rarely in catecholamine-driven volume underloaded patients (Luckie and Khattar 2008; Sakurai et al. 1985; Yang et al. 2008). Presence of SAM of the mitral valve raises suspicion of HCM, alone or in addition to other secondary causes of left ventricular hypertrophy. Although there has long been the dogma that SAM is a unique feature of HCM, it is now recognized that other forms of heart disease may uncommonly cause SAM in people (Luckie and Khattar 2008). This may be the case in cats, too. SAM is seen in <1% of people with hypertensive heart disease (Luckie and Khattar 2008). The term "pseudo-SAM" is used in people with SAM caused by cardiac disease other than HCM, and there are several distinguishing features compared to "true-SAM" seen in patients with HCM. Pseudo-SAM was identified in 12 of 37 people with hypertensive heart disease, and occurred in those patients with a smaller left ventricular cavity size (Doi et al. 1983). Pseudo-SAM was found to occur at end-systole coincident with the peak contraction of the left ventricular posterior wall, compared to an earlier onset of true-SAM in patients with HCM that

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occurred after two-thirds of systole had been completed (Doi et al. 1983). Given the high heart rates present in cats, it may be very difficult to distinguish these subtle differences noted in human medicine. It is likely that left ventricular geometry—in particular, cavity size and myocardial mass, and the effect of endogenous and exogenous catecholamines can play an important part in the pathogenesis of SAM (Luckie and Khattar 2008). For example, SAM was produced in 9 of 14 (64%) healthy, echocardiographically normal dogs given dobutamine (Sakurai et al. 1995). In 7 of these dogs, the magnitude of SAM and left ventricular outflow tract pressure gradient varied in a dose-dependent manner. Although it occurs rarely, the authors have identified SAM on echocardiography in anxious (catecholamine-driven) cats with structurally normal hearts, and these cats may not necessarily develop HCM over time but require follow-up echocardiograms to monitor for possible emergence of HCM.

The most common differential for SAM of the mitral valve is mitral valve dysplasia (see Chapter 10). The dysplastic mitral valve is malformed, sometimes elongated and thickened, with thick, short chordae tendinae and abnormally positioned or shaped papillary muscles. The mitral valve structure is normal in SAM, but it is pulled anteriorly (ventrally) into the left ventricular outflow tract by hypertrophied papillary muscles. Fixed subaortic stenosis is another differential for SAM of the mitral valve and is a congenital heart defect. SAS is caused by a fibrotic ring, band, or fibromuscular tunnel in the left ventricular outflow tract just below the aortic cusps. With SAS and SAM, the degree of obstruction changes exponentially based on heart rate and contractility, but with SAM, obstruction becomes disproportionately more severe as these parameters increase because the obstruction is dynamic in nature and most severe in mid- or late-systole. In dynamic obstructions such as SAM of the mitral valve and dynamic right ventricular outflow obstructions causing nonpathologic murmurs, the murmur often becomes louder when the cat becomes agitated. The Doppler tracing of fixed obstructions such as SAS shows a peak systolic velocity in mid-systole, with a symmetrical, cone-shaped blood flow velocity pattern. In dynamic obstructions such as SAM, there is a characteristic late systolic peak velocity, creating a dagger shape with a peak velocity at end-systole (see Figure 11.18, later in this chapter).

DIAGNOSTIC TESTING

Overview

Echocardiography is the most useful and sensitive test for diagnosis of HCM in cats. Because the hypertrophy is concentric, overall cardiac size may be normal on thoracic radiographs until moderate left atrial dilation develops. Thoracic radiographic evidence of cardiomegaly in cats may help justify to clients the importance of further evaluation by echocardiography if they were initially reluctant to proceed with an echocardiogram. Thoracic radiographs are essential for diagnosis of congestive heart failure, which may be present in cats with severe HCM or in less severe cases with an inciting trigger such as intravascular fluid administration. Because left ventricular morphologic changes involve increased diastolic wall thickness but not increase in ventricular chamber size, thoracic radiographs are not useful for identifying left ventricular changes, which must be evaluated by echocardiography. Routine biochemical tests are not helpful to diagnose HCM, but they are useful for overall systemic evaluation of the cat and for identification of concurrent disease processes. Electrocardiography is an insensitive test for diagnosis of HCM (see Chapter 18), but is essential for evaluation of an arrhythmia. Systolic blood pressure measurement is necessary to rule out systemic hypertension as a cause of concentric left ventricular hypertrophy.

General Diagnostic Tests

Key Points

- Basic comprehensive blood work including complete blood count, serum chemistry, total thyroxine level, and urinalysis is recommended in cats diagnosed with HCM, especially in middle-aged to older cats, or in cats with heart failure.
- Baseline renal function is important to assess prior to medical treatment of heart failure.
- Significant anemia should be identified, as this may worsen ventricular volume overload (i.e., preload) in cats with HCM.
- Total thyroxine concentration is an essential diagnostic test in middle-aged to older cats with echocardiographic evidence of concentric hypertrophy, because hyperthyroidism is a secondary cause of concentric left ventricular hypertrophy.

Basic comprehensive blood work including complete blood count, serum chemistry, total thyroxine level, and urinalysis is recommended for overall assessment of aged cats or ill cats. It is important to identify other concurrent disease processes in cats with HCM, because they may influence treatment recommendations. A total thyroxine level (and free thyroxine if total thyroxine levels are equivocal) must be measured in all mature cats with concentric hypertrophy of the left ventricle, because hyperthyroidism can cause reversible secondary concen-

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tric left ventricular hypertrophy (see Chapter 26). Mild hepatic enzyme elevations (alanine aminotransferase or aspartate aminotransferase) commonly occurred in approximately 70% of cats with HCM according to a large retrospective study of 260 cats (Rush and Freeman 2002). In this study, serum creatinine or blood urea nitrogen concentration was not different between cats who were asymptomatic versus cats with heart failure or arterial thromboembolism at baseline prior to therapy (Rush and Freeman 2002). However, diuretic treatment is expected to cause some level of prerenal azotemia due to dehydration. The sudden rise in serum BUN or creatinine concentrations in the face of oliguria or anuria in a patient with aortic thromboembolism should raise the suspicion of renal artery embolization. A CBC is important to evaluate for significant anemia (HCT ≤22%), as this may worsen left ventricular volume overload and contribute to heart failure and arrhythmogenesis in cats with severe HCM and diastolic dysfunction.

When renal dysfunction is present, it should be identified prior to treatment with heart failure medications such as furosemide or angiotensin converting enzyme (ACE) inhibitors. Otherwise, abnormalities encountered later (e.g., elevated BUN or creatinine, or inadequately concentrated urine) may not be characterized as being caused by preexisting renal disease, new-onset renal disease, or simply an effect of heart failure medications. Baseline blood chemistry and urinalysis are essential in cats with severe HCM and heart failure. After starting furosemide, the urine specific gravity usually becomes isosthenuric, and renal dysfunction cannot be distinguished from prerenal azotemia. In cats with underlying kidney disease, heart failure therapy may be modified to be slightly more cautious, and recheck renal panels may be done more frequently. Likewise, fluid diuresis for treatment of renal failure may involve lower fluid rates in cats with underlying severe HCM, with careful monitoring of respiratory rate and effort and periodic recheck thoracic radiographs (see Chapter 24). Monitoring is important because the prevalence of azotemia in cats with HCM is 59% compared to 25% prevalence in normal control cats (Gouni et al. 2008). Twenty percent of cats with HCM had congestive heart failure, which was not statistically affected by plasma urea nitrogen and plasma creatinine concentrations. Likewise, there is no effect of plasma urea nitrogen and plasma creatinine concentrations on conventional echocardiographic variables. Therefore, this study documents that cats with HCM also frequently are concurrently affected with kidney disease. In a human study of children undergoing pediatric heart transplant, HCM was an independent risk factor for development of chronic renal insufficiency or end-stage renal disease (Lee et al. 2007). One explanation is that systolic myocardial failure occurs in approximately 10–15% of people with end-stage HCM, which may lead to decreased renal perfusion and renal injury (Lee et al. 2007). In this group of children undergoing pediatric heart transplantation, chronic renal insufficiency postcardiac transplantation increased risk of mortality by ninefold (Lee et al. 2007). Treatment of concurrent renal failure and heart failure secondary to severe HCM can be challenging, with a significantly poorer prognosis than either disease independently. However, it is the authors' clinical impression that asymptomatic cats with IRIS stage 1 or 2 chronic kidney disease (http://www.iris-kidney.com/) and HCM without congestive heart failure tend to do well for many months to years (see Chapter 24).

Routine Cardiovascular Diagnostics

Electrocardiogram (see also Chapter 18)

Key Points

- An ECG has poor accuracy for diagnosis of HCM but is the test of choice to diagnose an arrhythmia in cats with HCM.
- The most common arrhythmias in cats with HCM include ventricular premature complexes (occurring in 41% of cats), ventricular tachycardia (10% of cats), atrial premature complexes (10% of cats), atrial tachycardia (10% of cats), and atrial fibrillation (10% of cats), based on in-hospital ECG evaluation.
- Tachyarrhythmias worsen diastolic dysfunction and lead to higher diastolic filling pressures in HCM, potentially precipitating development of heart failure. Therefore, whether through environmental adjustments, pharmacologic control, or both, high heart rates should be avoided in cats with HCM.
- A left axis deviation suggestive of left ventricular hypertrophy or left anterior fascicular block may be present on the ECG of in cats with HCM (10–33%) but is not specific for HCM. Left axis deviation may be present on the ECG in cats with other heart diseases, particularly hyperthyroidism (6–8% of hyperthyroid cats).

An electrocardiogram is the diagnostic test of choice to evaluate an arrhythmia. If an abnormal heart rhythm is ausculted, an electrocardiogram is essential to define the specific arrhythmia present and aid in the decision of whether antiarrhythmic therapy is necessary. Since cats have small ECG deflections and fast heart rates, the ECG paper speed should be set at 50 mm/s and the amplitude increased to 20 mm/mV to optimize the tracing in most cases. A gallop heart sound, commonly referred to as a gallop rhythm, is not specifically evaluated with an ECG because it does not reflect a change in

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the cardiac electrical rhythm. Rather, it is created by an extra heart sound (S_3 or S_4) that occurs with every heart beat, giving the auscultatory impression of a galloping horse irrespective of the heart's rhythm (see Chapter 1). However, if the clinician is unsure whether there is an arrhythmia versus an extra heart sound, an electrocardiogram is indicated. Arrhythmias are variably present in cats diagnosed with HCM. There is a wide variation in reported incidence of arrhythmias in cats with HCM. Arrhythmias occur in only ~7% of cats in one case series of 61 cats with HCM, whereas another study of 46 cats diagnosed with HCM reported higher incidences of arrhythmias as follows: ventricular premature complexes in 41% of cats, ventricular tachycardia in 10% of cats, atrial premature complexes in 10% of cats, atrial tachycardia or atrial fibrillation in 10% of cats (see Chapter 18) (Ferasin et al. 2003; Fox et al. 1999b). Differences in arrhythmia incidence may be affected by the duration of ECG monitoring, patient selection (whether all cats are evaluated compared to only cats with an auscultable arrhythmia), or severity of disease within the studied population (proportion of asymptomatic versus symptomatic patients evaluated). Ventricular premature complexes appear to be more common in cats with HCM suffering from arterial thromboembolism than in all cats with HCM combined (31% versus 9%, respectively) (Fox and Harpster 1999). Atrial fibrillation occurs when there is significant left atrial dilation, and reflects an advanced stage of disease (Côté et al. 2004). Tachyarrhythmias worsen diastolic dysfunction and lead to higher diastolic filling pressures in HCM (Gwathmey et al. 1991). That is, heart rates sustained above a certain threshold, such as 240–260 beats/min in the cat, may limit diastolic ventricular filling to a substantial degree (see Figure 18.1). This impairment in diastolic filling may trigger development of heart failure in cats otherwise compensated with HCM. Third-degree atrioventricular block is rare in cats with HCM (1/61 cats in one study). In a pathologic study of 13 cats with HCM and third-degree atrioventricular block, all cats had marked degeneration and fibrous replacement of the atrioventricular conduction system, along with endomyocardial and myocardial fibrosis of the basilar interventricular septum (see Chapter 18) (Kaneshige et al. 2006). However, a majority of age-matched control cats (mean age 12.9 years old) also had evidence of slight to moderate fibrosis of the atrioventricular conduction system, but changes were less severe and less extensive. It was hypothesized that abnormal mechanical forces in HCM as well as left ventricular obstruction due to SAM may amplify age-related fibrotic changes to the atrioventricular conduction system. Left axis deviation (0 degrees to minus 90 degrees) suggestive of left anterior fascicular block or left ventricular enlargement is another relatively common finding, occurring in 10–33% of cats with HCM (Figure 18.22) (Fox et al. 1999b; Bright et al. 1992). However, left axis deviation is not specific for HCM, because 6–8% of cats with hyperthyroidism have left axis deviation, and the mean electrical axis may be altered substantially by simple factors such as limb position and electrode clip placement (see Chapter 18) (Fox et al. 1999a).

The electrocardiogram is an insensitive test for detection of cardiac chamber enlargement in cats and should not be used as a screening test for HCM. Only 25% of cats with HCM in one study had a left ventricular

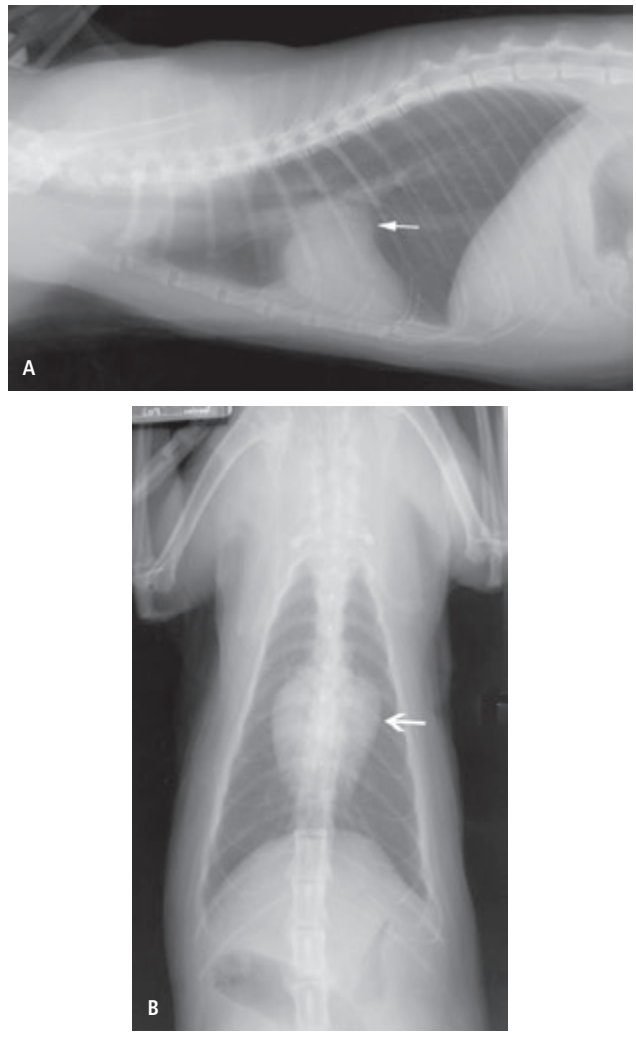


Figure 11.7. Thoracic radiographs of a cat with moderate hypertrophic cardiomyopathy but no congestive heart failure. There is left atrial enlargement (arrow) seen on both lateral **(A)** and dorsoventral **(B)** views in this cat with moderate HCM. The moderate left atrial dilation causes a classic "valentine" heart shape on the dorsoventral view. The pulmonary vasculature is not distended, and the pulmonary parenchyma is unremarkable, with no evidence of heart failure at this time.

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enlargement pattern (QRS amplitude of >0.9 mv ± QRS duration of >0.04 s) on ECG (Ferasin et al. 2003). Increased QRS amplitude is not always specific for left ventricular hypertrophy either, because some cats with hyperthyroidism and normal left ventricular size and wall thickness have tall R waves on ECG (Moïse 1986c). Increased P wave duration is extremely insensitive (ranging from 0–30%) for detection of left atrial dilation in cats (Schober et al. 2007). P wave amplitude and PR intervals are also insensitive for detection of left atrial dilation in cats (12% and 24%, respectively), but are highly specific for left atrial dilation (90–100%) (Schober et al. 2007); therefore, left atrial enlargement rarely alters the ECG in cats, but when a tall P wave or prolonged PR interval does occur, left atrial enlargement is highly likely.

Additional electrocardiographic modalities, such as a 24-hour ambulatory electrocardiogram (i.e., Holter monitor) or an event monitor, may be helpful to identify significant arrhythmias in cats with symptoms of syncope or episodic weakness that have a normal resting electrocardiogram (see Chapter 9). For example, a Holter monitor revealed severe ventricular tachycardia in a cat with syncope, dyspnea, and severe HCM, despite a normal resting electrocardiogram (see Chapter 9) (Goodwin et al. 1992). Diagnosis of episodic but symptomatic arrhythmias is important because these patients may benefit from antiarrhythmic therapy.

Thoracic radiographs (see also Chapters 6 and 19)

Key Points

- Thoracic radiographs may be normal in cats with mild HCM that have concentric hypertrophy but no atrial dilation.
- Cardiomegaly and left atrial dilation may be seen in asymptomatic cats with HCM prior to development of heart failure.
- Thoracic radiographs are essential to evaluate for heart failure in cats with HCM and left atrial dilation, or in cats with presenting complaint of respiratory abnormalities.
- Pulmonary edema and/or pleural effusion may be present in cats with heart failure secondary to severe HCM. Pulmonary edema is more common than pleural effusion in cats with heart failure caused by HCM (22–66% vs 7–34%, respectively).
- Classic radiographic abnormalities of feline heart failure include cardiomegaly, left atrial dilation, pulmonary venous distension, and patchy interstitial to alveolar pulmonary infiltrates that are often variably distributed and not necessarily perihilar to caudodorsal as seen in dogs.

Thoracic radiographs are a readily available, important diagnostic tool to evaluate cats with suspected heart disease. They are essential for evaluation of congestive heart failure, and may play a role in monitoring progression of disease and assessing response to heart failure treatment. However, radiographs are often normal in cats with mild or moderate HCM and normal left atrial size. Normal cardiac size on thoracic radiographs does not rule out HCM as a diagnosis. In two large scale studies of HCM, cardiomegaly was evident on thoracic radiographs in 60–90% of cases (see Figure 11.7) (Ferasin et al. 2003; Rush and Freeman 2002). Left atrial dilation is more difficult to diagnose on lateral thoracic radiographs in cats than in dogs, but is more often identified using the ventrodorsal or dorsoventral views (see Figure 11.7). In a study of 24 normal cats with normal left atrial size measured by echocardiography, 26% of cats were misdiagnosed with left atrial dilation by subjective assessment on thoracic radiographs (Schober et al. 2007). Sometimes presence of intrapericardial fat can lead to a misdiagnosis of cardiomegaly in cats. Seventy-two percent of cats with HCM and left atrial dilation diagnosed by echocardiography have radiographic evidence of left atrial dilation by subjective assessment (Schober et al. 2007). In this study, subjective assessment of left atrial size was moderately sensitive (72%) and specific (74%) for left atrial dilation. Calculation of the vertebral heart size may be useful to quantify cardiac size and confirm presence of cardiomegaly (see Chapter 6). Using the right lateral projection, the long- and short-axis measurements of the heart, expressed in vertebral lengths starting at the fourth thoracic vertebrae, are added to yield vertebral heart size. Normal vertebral heart size is 7.5 ± 0.3 in cats (Litster and Buchanan 2000). Normal VHS cannot be used for ruling out HCM, because concentric hypertrophy causes left ventricular hypertrophy with a normal VHS and normal LV chamber size (Mattoon et al. 2002). It is impossible to predict the specific cardiac disease present in cats with radiographic evidence of cardiomegaly, but identification of cardiomegaly on radiographs warrants further evaluation, first by assessing the radiographs for artifacts that mimic cardiomegaly (expiratory films, improper patient positioning), and if artifacts are ruled out, echocardiography is indicated.

Congestive heart failure may be evidenced by pulmonary edema, pleural effusion, or a combination of both (Figure 11.8). Pulmonary edema is more common (23–66%) than pleural effusion (7–34%) in cats with heart failure secondary to severe HCM (Ferasin et al. 2003; Rush and Freeman 2002). Dyspnea is attributed to pulmonary edema in 80% of cats with HCM, versus only 14% due to severe pleural effusion (Rush and Freeman

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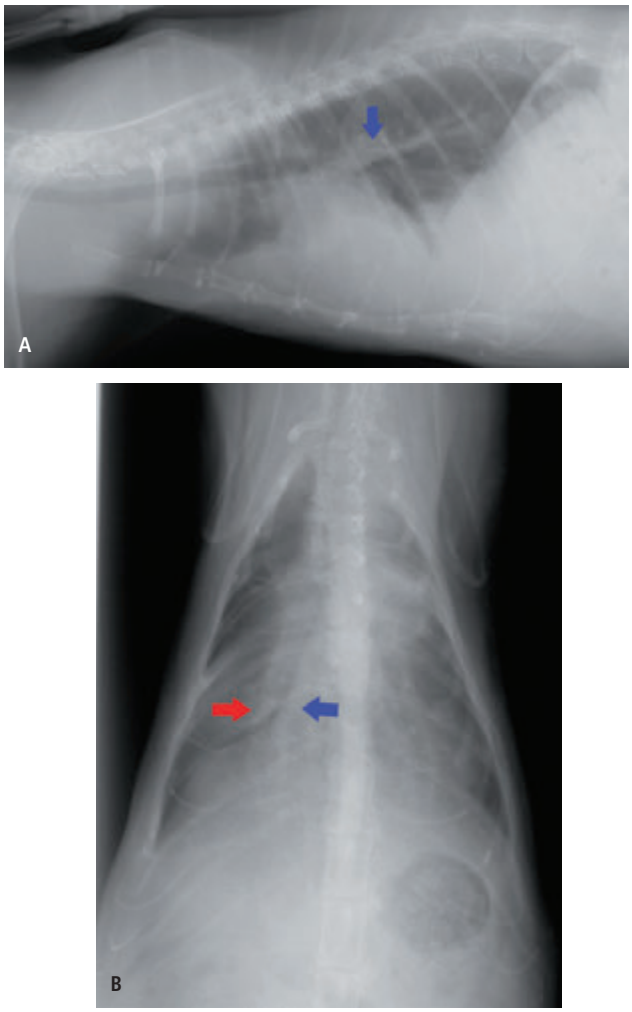


Figure 11.8. Thoracic radiographs of a cat with severe hypertrophic cardiomyopathy and congestive heart failure. This cat has typical radiographic changes indicative of severe pulmonary edema and pleural effusion. Although the cardiac silhouette is partially obscured by the pleural effusion on the lateral view, there is suggestion of cardiomegaly and pulmonary venous distension (blue arrow) at the hilus. The cardiac silhouette is completely obscured by pleural effusion on the dorsoventral view, but pulmonary vascular distension is seen as well as the mixed pattern of pulmonary edema and pleural effusion. Echocardiography is an important tool to confirm that severe heart disease is present, consistent with the pulmonary infiltrates and pleural effusion being caused by congestive heart failure. Red arrow = caudal lobar pulmonary artery; blue arrow = caudal lobar pulmonary vein depicted on the right side of the thorax on the dorsoventral view; the pulmonary vein on the left side of thorax is unaltered.

2002). Pulmonary venous distension is another radiographic abnormality that occurs when there is elevated left atrial pressure and is usually present in heart failure, but absence of pulmonary venous distension does not rule out heart failure. Reasons for absence of pulmonary venous distension on radiographs may include diuretic therapy that has reduced vessel size but not yet resolved pulmonary edema or pleural effusion, interindividual variation in vessel size irrespective of heart failure, patient positioning (DV versus VD views), or pulmonary edema obscuring visualization of the vessels. There is no particular pattern of pulmonary edema distribution in cats with heart failure, unlike dogs that typically have a perihilar to caudodorsal distribution of pulmonary infiltrates. Presence of ascites along with pleural effusion virtually eliminates HCM as a cause of the fluid accumulation and raises suspicion of cardiac diseases involving the right heart such as dilated cardiomyopathy, unclassified cardiomyopathy, tricuspid valve dysplasia, or arrhythmogenic right ventricular cardiomyopathy, or noncardiac disease (feline infectious peritonitis, malignancy, etc.).

Echocardiogram (see also Chapter 7)

Key Points

- Echocardiography is the essential tool to diagnose HCM in cats, and it allows accurate assessment of chamber enlargement, quantification of concentric hypertrophy, evaluation of the source of a murmur, assessment of myocardial systolic and diastolic function, and assessment of whether there is spontaneous echocardiographic contrast or an intracardiac thrombus.
- LV concentric hypertrophy is defined as end-diastolic left ventricular septal or free wall thickness of 6 mm or greater. Measurement of LV wall thickness by the 2-dimensional technique has largely replaced the M-mode technique, because M-mode can underestimate or miss segmental wall thickening, which is common in cats with HCM; unlike M-mode, there is no limitation of cursor placement when measuring wall thickness using the 2-dimensional method. This is important when measuring asymmetric or segmental hypertrophy.
- Left atrial size can be measured by 2-dimensional and M-mode methods, and left atrial enlargement is considered to be present when the left atrial diameter to aortic diameter ratio is ≥1.5.
- Identification of normal left atrial size in cats with HCM that also have pulmonary infiltrates or pleural effusion and no known inciting trigger such as intravenous fluid administration virtually eliminates left-sided congestive heart failure as the diagnosis.
- SAM of the mitral valve can be identified on 2-dimensional echocardiography from the right parasternal long-axis left ventricular outflow tract view. Color-flow Doppler shows the characteristic double turbulent jet of mitral regurgitation and turbulence in the left ventricular outflow tract arising from the common point of the anterior mitral leaflet obstruction.

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Continuous-wave Doppler measurement of the aortic blood flow velocity from the left apical parasternal 5-chamber view is necessary to quantify the severity of the obstruction.

- Diastolic function can be assessed using pulsed-wave (PW) Doppler measurement of the mitral inflow velocity, measurement of pulmonary venous inflow velocity profiles, and by tissue Doppler imaging and measurement of myocardial or mitral annulus velocities.
- A delayed relaxation pattern is commonly seen on PW Doppler measurement of mitral inflow velocities and is defined as prolonged isovolumic relaxation time, decreased early mitral inflow velocity (E), increased late atrial systolic velocity (A), prolonged deceleration of the early diastolic inflow wave, and E:A reversal with E:A ratio <1.
- A restrictive filling pattern is seen when left atrial pressure is significantly increased and is identified as shortened isovolumic relaxation time, increased early diastolic filling (E), shortened early diastolic filling deceleration, decreased late atrial systolic wave (A), and E:A ratio >2.
- Tissue Doppler imaging echocardiography (TDI) is a more sensitive test to evaluate for diastolic dysfunction and is less influenced by preload than is PW Doppler interrogation of mitral inflow velocity. PW TDI and color TDI are two techniques to assess diastolic and systolic myocardial function, which may identify feline heart diseases at earlier stages, but which do not have specific treatment implications at this time.
- Longitudinal left ventricular myocardial function is assessed by measurement of the mitral annulus velocities from the left apical 4-chamber view, and circumferential fiber function is measured from the left ventricular short-axis view from the right parasternal window.
- Diastolic dysfunction is identified on tissue Doppler imaging when there is decreased early diastolic mitral annular velocity (E′), which is inversely proportional to the severity of diastolic dysfunction.
- Using PW TDI of the lateral mitral annulus, E′ > 7.2 cm/sec is highly sensitive (92%) and specific (87%) for discriminating between normal cats and cats with left ventricular concentric hypertrophy due to HCM.

Overview

Echocardiography is the most important diagnostic tool to diagnose HCM. In order for HCM to be confirmed, there must be concentric symmetric or asymmetric left ventricular concentric hypertrophy (i.e., thick left ventricular walls) in the absence of other causes of concentric hypertrophy such as aortic stenosis, systemic hypertension, or hyperthyroidism). Concentric hypertrophy is defined as end-diastolic left ventricular free wall or interventricular septal thickness of ≥6 mm, with an equivocal zone from 5.5–5.9 mm. Although there is not a formalized definition of mild, moderate, and severe concentric hypertrophy, the authors typically classify 6– 6.5 mm as mild, 6.6–7.5 mm as moderate, and >7.5 as severe concentric hypertrophy in euvolemic/hydrated cats. Some cats may have concurrent HCM and other secondary causes of concentric hypertrophy. For example, a hyperthyroid cat that has been treated with antithyroid medications for 2 or more months but whose echocardiogram reveals persistent LV hypertrophy may have poor control of the hyperthyroid state or concurrent HCM. If the total thyroxine concentration is in the low- to midnormal range following several months of hyperthyroid treatment, the cat likely is also affected with HCM. Identification of SAM of the mitral valve supports the diagnosis of HCM, although uncommonly it may be seen in other secondary causes of concentric hypertrophy (Luckie and Khattar 2008). Assessment of left atrial size is crucial for staging of disease severity, because cats with left atrial dilation are at risk for congestive heart failure or arterial thromboembolism. Thoracic radiographs should be taken in cats with significant left atrial dilation to evaluate for presence of heart failure. Assessment of diastolic function is not essential to achieve a diagnosis of HCM but may be informative to follow disease progression or response to therapy.

Left ventricular hypertrophy

Left ventricular concentric hypertrophy is standardly defined as an end-diastolic ventricular wall or septal thickness of 6 mm or greater in cats. Left ventricular wall thickness has historically been determined using M-mode echocardiography, since at that time the 2-dimensional imaging was limited by slower frame rate and resolution (see Chapter 7) (Moïse 1986a,c; Jacobs and Knight 1985). M-mode is still an acceptable method of measurement of left ventricular chamber dimensions during diastole and systole, but it has several limitations that are overcome by using 2-dimensional echocardiography with current machines (see below).

Measurement of interventricular septal and left ventricular free wall thickness is preferably done using 2-dimensional echocardiography in the right parasternal short-axis view at the level of the papillary muscles just below the chordae tendineae (Figure 11.9). This allows global assessment of wall thickness, which is important in cats with regional or asymmetrical hypertrophy (i.e., segmental hypertrophy). Using an ECG, the end-diastolic wall thickness is measured during the R wave, and the thickest regions of the interventricular

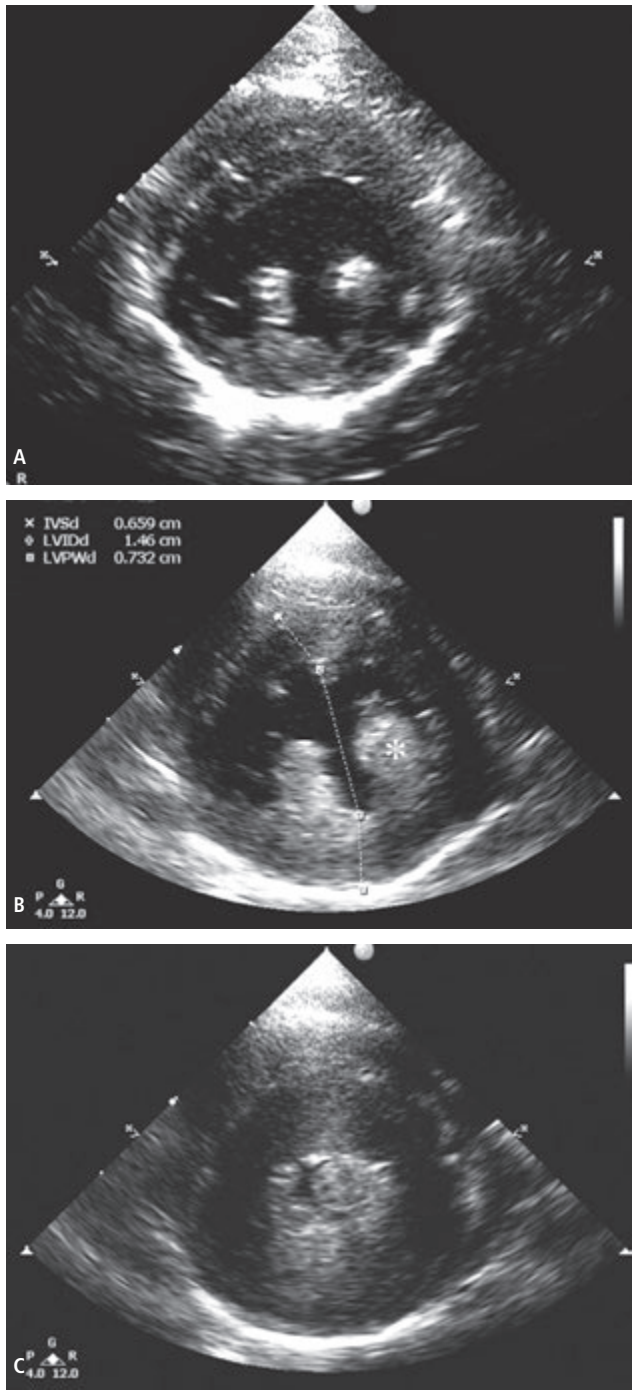


Figure 11.9. Two-dimensional echocardiogram of the left ventricle of a normal cat and a cat with moderate to severe hypertrophic cardiomyopathy. This end-diastolic frame from the right parasternal short-axis view at the level of the papillary muscles of a normal cat depicts normal wall thickness and no papillary muscle hypertrophy **(A)** in comparison to a cat with HCM **(B)**. The cat with HCM has mild to moderate concentric hypertrophy of the left ventricle, with an end-diastolic interventricular septal thickness (IVSd) of 6.6 mm, and a left ventricular free wall thickness at end-diastole of 7.3 mm. There is moderate papillary muscle hypertrophy and hyperechogenicity (*). The end-systolic frame from the same cat as in **(B)** shows end-systolic cavity obliteration **(C)**.

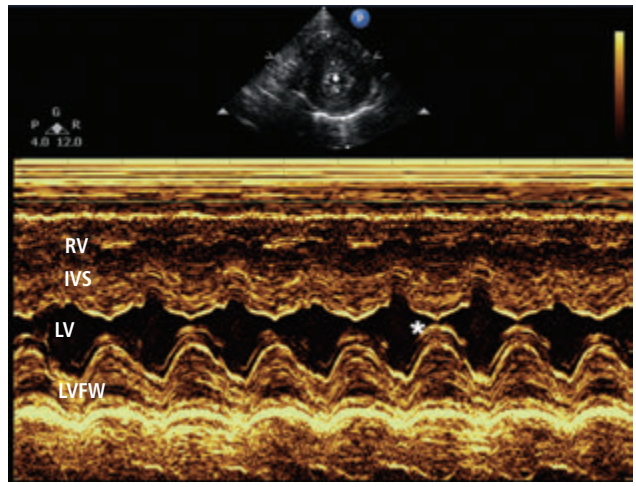


Figure 11.10. M-mode echocardiogram of the left ventricle of a cat with moderate hypertrophic cardiomyopathy. The cursor is positioned at the 12 o'clock position of the interventricular septum and the 6 o'clock position between the papillary muscles at the left ventricular free wall. This M-mode echocardiogram shows increased end-diastolic left ventricular wall thickness of the interventricular septum (IVS) and left ventricular free wall (LVFW), and hyperdynamic wall motion with a fractional shortening of 78%. Papillary muscle interference is indicated with an asterisk.

septum and the left ventricular free wall are measured. If an ECG is not present, subjective assessment of end-diastole is made by scrolling through the cine-loop and looking for the frame with the largest left ventricular internal diameter at end-diastole. By convention, the measurement is made immediately prior to atrial contraction (mechanical atrial systole), meaning that the measurement is made at the end of diastasis (passive ventricular filling) and the final, brief excursion of the ventricular walls caused by atrial contraction is not measured. M-mode can also be used to measure left ventricular wall thickness, but there are limited choices of M-mode cursor positions (Figure 11.10). Often papillary hypertrophy may obscure the ability to carefully define the endocardial surface of the left ventricular free wall to measure. Steerable M-mode has advantages over traditional fixed M-mode because the cursor placement can be adjusted depending on the location of the greatest wall thickness. Some cats with HCM have global symmetrical concentric hypertrophy, whereas most have asymmetrical hypertrophy. For example, some cats have only interventricular septal hypertrophy (Figure 11.11), whereas others have hypertrophy of solely the left ventricular free wall or papillary muscles. The basilar interventricular septum should be measured from the right parasternal long-axis 4-chamber or left ventricular outflow tract view, as it may provide the best visualization and measurement of the thickest part of the basilar

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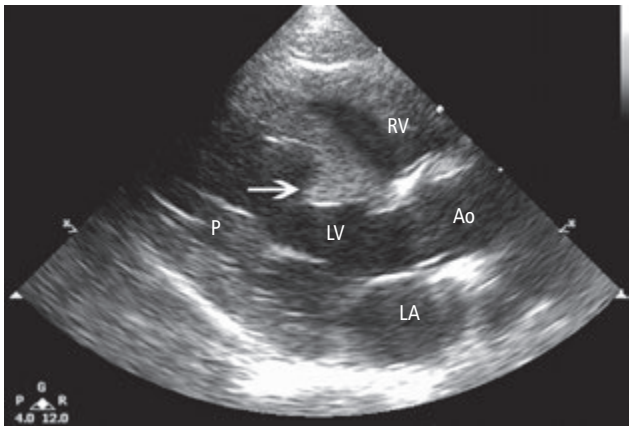


Figure 11.11. Right parasternal long-axis view of concentric hypertrophy of the basilar interventricular septum in a cat with hypertrophic cardiomyopathy. Sometimes there is asymmetrical or segmental hypertrophy of the left ventricle in cats with HCM. This cat has severe basilar interventricular septal hypertrophy (arrow; 9 mm thickness), papillary (P) hypertrophy, and equivocal to mild left ventricular free wall concentric hypertrophy. Sometimes the basilar interventricular septum is best imaged by the right parasternal long-axis left ventricular outflow tract view as shown here, and measurement of this region can be done using this view.

septum compared to the short-axis view (see Figure 11.11).

Focal basilar concentric hypertrophy of the interventricular septum (i.e., "basal or septal bulge") may be seen in some cats with HCM, although there is debate in both human medicine and veterinary medicine over whether normal individuals may also develop this as a benign, age-related variant of normal versus a forme fruste of HCM (i.e., an atypical or attenuated manifestation of the disease) (Belenkie et al. 1988; Spirito et al. 1986; Krasnow 1997; Hecht et al. 1992). Unfortunately, the debate is largely based on conjecture and opinion and lacks substantial data regarding clinical, pathologic, and genetic characterization. Some leading human cardiologists specializing in familial HCM favor the hypothesis that focal septal hypertrophy is a less severe form of HCM caused by less malignant cardiac genetic mutations, and result in a more benign course associated with lack of symptoms and long survival times (Spirito et al. 1989; Shapiro and Zezulka 1883). However, the course of disease may not be as benign in people as initially thought, and this hypothesis was evaluated in a prospective study following a subset of 29 human patients with no symptoms and mild focal left ventricular hypertrophy attributed to HCM. Although 76% (22/29) of these patients never developed symptoms over an average of 8 years of follow-up, 4 (14%) people died suddenly and 3 (10%) had progression of symptoms, indicating that despite a later onset of mild hypertrophy, patients are not devoid of risk of adverse cardiac sequelae. Additional information in cats with focal basilar septal hypertrophy is needed, including genetic analysis, detailed assessment of other concurrent cardiac abnormalities such as diastolic dysfunction, SAM of the mitral valve, clinical course, and pathologic evaluation, which may better characterize this subset of feline patients.

Left ventricular wall thickness obtained by 2-dimensional echocardiography is useful for obtaining the diagnosis, but measurements vary according to region of the left ventricle measured and the time within the cardiac cycle that the image frame was obtained for measurements. There is high inter- and intraobserver variability for measurements of septal and left ventricular free wall end- diastolic thicknesses in awake cats (18% and 20%, respectively) (Chetboul et al. 2004). Therefore, serial quantification of left ventricular hypertrophy and assessment of changes in left ventricular hypertrophy following pharmacologic therapy can be challenging and highly dependent on the sites chosen for wall measurement.

Although left ventricular concentric hypertrophy is typically defined as a maximal end-diastolic wall thickness of 6 mm or greater, there are alternative criteria used by some cardiologists. One proposed method is to divide the interventricular septum into two regions (basilar to middle; middle to apical) measured in both long-axis and short-axis views, and the left ventricular (posterior) free wall measured in both long- and short-axis views on 2D echocardiography (Paige et al. 2009). Presence of concentric hypertrophy is defined as an end-diastolic wall thickness of 6 mm or greater in *more than 50%* of a wall segment, not just the maximal thickness in one part of the wall (Paige et al. 2009). This method yields fewer positive diagnoses of HCM. Another proposed criterion is to define increased end-diastolic left ventricular wall or septal thickness as 5.5 mm or greater, because most normal cats do not have wall thickness of 5.5 mm or greater, which yields greater positive diagnoses and higher prevalence rates of LV hypertrophy in the general feline population (Wagner et al. 2010). For example, when using the criteria of 6 mm or greater wall thickness measured by 2D, 34% of 92 clinically healthy cats were diagnosed with left ventricular hypertrophy, compared to a lower prevalence rate of 23% of cats using a more stringent criteria of >50% of a wall segment having 6 mm or greater thickness (Wagner et al. 2010). Likewise, the lowest prevalence rate (12%) was obtained using the criteria of 6 mm or greater wall thickness measured by M-mode, likely because M-mode missed many cats with segmental ventricular hypertrophy (Wagner et al. 2010). Using a lower value of 5.5 mm or greater for diagnosing left ventricular hypertrophy led to the

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highest prevalence rate of 50% for LV hypertrophy by 2D measurements, and prevalence was lower (28%) when using M-mode measurement of 5.5 mm or greater wall thickness (Wagner et al. 2010). There is no validation of which criterion (5.5 mm or greater, 6 mm or greater, or >50% wall segment 6 mm or greater), is the most appropriate for diagnosing presence of LV hypertrophy and HCM, although standard practice typically utilizes a maximal thickness of 6 mm or greater in any part of the wall segment. Further prospective evaluation of these patients over time, including genotypic data for Maine coon cats and Ragdoll cats, and histopathologic evaluation may help define which criterion is the most appropriate to diagnose HCM.

Left ventricular mass measurements allow the most accurate assessment of extent of left ventricular hypertrophy, but are not typically done for clinical patients. Left ventricular mass may be measured by echocardiography using several methods that require geometric assumption of an elliptical left ventricular shape, and most cardiac ultrasound machines can calculate LV mass from routine left ventricular echocardiographic measurements (Devereux et al. 1986; Stack et al. 1987; Schiller et al. 1983). However, when using routine LV measurements and M-mode–derived calculations for LV mass that include cubing the wall thickness followed by various volume-correcting formulae, these techniques have been shown to overestimate or underestimate left ventricular mass by 6–30% depending on the formula used (Devereux et al. 1986). The truncated ellipse model and the cylinder ellipse area-length model have been validated in dogs and in cats, and reasonably quantify left ventricular mass (Schiller et al. 1983; MacDonald et al. 2004). The modified truncated ellipse model was validated in domestic short hair cats that were normal or had mild left ventricular hypertrophy, and was moderately correlated with actual left ventricular mass measured at necropsy ($R = 0.85$, $P = 0.015$) but consistently underestimated LV mass (actual LV mass = 3.07 + 0.76(echo-derived LV mass) (MacDonald et al. 2004). All formulae described above are still plagued with assuming uniform geometric shape of the left ventricle, which is invalid in HCM. The most accurate method of left ventricular mass quantification is the method of discs (Simpson's rule), where the myocardial volume (volume of the ventricle including walls and lumen, minus the volume of the LV lumen) is summated in a series of parallel discs from the annulus to the apex (Reichek 1994). This method allows measurement of irregular areas and has fewer geometric assumptions. However, echocardiography is often inadequate due to poor visualization of the cardiac apex, inadequate and incomplete delineation of the epicardial surface of the left ventricle, and a limited number of acoustic windows in the cat. In other words, the ability to visualize the entire left ventricular myocardium often limits the use of Simpson's rule by echocardiography to correctly measure LV mass using echocardiography in the cat.

Papillary muscle hypertrophy is sometimes the only abnormality present in cats with early HCM, and concentric hypertrophy often develops 6–12 months later. Papillary muscle hypertrophy is often a subjective assessment. Normal cat papillary muscles are slender, and hypertrophied papillary muscles become wider at the base, larger, and on the short-axis echocardiographic view of the left ventricle may have a more triangular shape (i.e., moundlike) rather than a slender elliptical shape (i.e., like the tip of a pinkie finger) (Figure 11.12). Papillary hypertrophy may occur in just one papillary muscle, creating a disproportionate, distorted shape. This must be differentiated from oblique imaging of a normal papillary muscle due to poor technique, because the left ventricle should appear round (and its lumen should appear mushroom-shaped) in an appropriate short-axis view rather than oblong. Hypertrophied papillary muscles often appear hyperechoic, either patchy or diffusely, which is attributed to myocardial fibrosis. The papillary muscles are the most vulnerable to myocardial ischemia, since they are further removed from the (epicardial) coronary arterial blood supply than the rest of the LV myocardium. Quantitative methods of measuring papillary muscle size have been described in cats with LV hypertrophy and compared to normal cats (Adin and Diley-Poston 2007); such measurements are not yet performed systematically in clinical cases. Papillary muscle size can be quantified on routine 2D studies, using several techniques: the area subtraction method (subtracting the LV myocardial area including the papillary muscles from the LV myocardial area excluding papillary muscles), the direct area trace method (directly tracing the area of the papillary muscle and extrapolating the ventral surface as the continuation of the endocardial surface of the LV free wall), and the papillary diameter method (measuring the vertical and horizontal diameters) (Adin and Diley-Poston 2007). Although there was some overlap in papillary size compared to normal cats, cats with LV hypertrophy had larger papillary size (120–155% greater than normal papillary measurements) quantified by methods described above (Adin and Diley-Poston 2007).

End-systolic cavity obliteration is diagnosed when there is no left ventricular chamber lumen remaining at the end of systole, and it is caused by severe concentric hypertrophy of the papillary muscles and left ventricular walls (see Figure 11.9C). End-systolic cavity obliteration is a common feature of HCM, but may also be present

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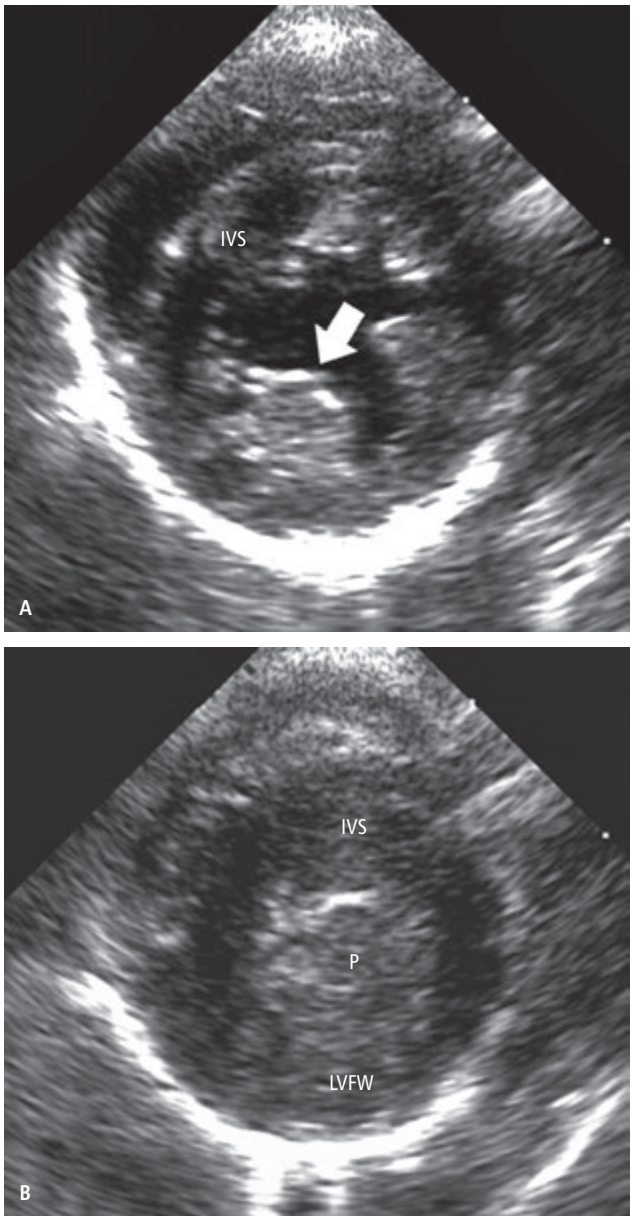


Figure 11.12. Two-dimensional echocardiography of a cat with mild hypertrophic cardiomyopathy showing moderate papillary muscle hypertrophy. Normal left ventricular papillary muscles are slender and upright (see Figure 11.9A). This cat has moderate papillary hypertrophy (arrow), and papillary muscles have a broad base and are hyperechoic. There is mild concentric hypertrophy of the interventricular septum (IVS), measuring 6.5 mm at end-diastole, and normal left ventricular free wall thickness (LVFW) of 3.9 mm. Papillary hypertrophy may be an early abnormality in cats with HCM and is typically assessed by subjective impression. There is end-systolic cavity obliteration (B) due to the moderate papillary hypertrophy (P) and mild septal hypertrophy.

in cats that are severely dehydrated (Campbell and Kittleson 2007).

Cats with HCM often have evidence of replacement or interstitial fibrosis on histopathologic evaluation of the left ventricle. Echocardiographic assessment of replacement fibrosis may include identification of regional hyperechogenicity of the subendocardium and myocardium in hypertrophied regions of the left ventricle. A fibrotic plaque at the basilar interventricular septum often occurs secondary to SAM of the mitral valve, and this may be identified on echocardiography as a thickened hyperechoic region of the endocardium and subendocardium of the basilar interventricular septum in the right parasternal long-axis left ventricular outflow tract view. Sometimes, a hyperechoic oblique band of myocardium may be seen in the interventricular septum of cats with HCM and may represent myocardial fibrosis.

Left atrial size

Assessment of left atrial size is critical in cats with HCM, since left atrial dilation is present in the face of increased diastolic filling pressures and identifies significant risk of development of congestive heart failure and possibly arterial thromboembolism. The left atrium becomes dilated in cats with HCM in response to left ventricular diastolic dysfunction, which increases ventricular diastolic filling pressure. Elevated ventricular diastolic filling pressure is transmitted back to the left atrium and increases left atrial pressure, leading to left atrial enlargement. Mitral regurgitation secondary to SAM of the mitral valve causes a backward leak of blood into the left atrium (i.e., mitral regurgitation) and further increases left atrial volume and pressure. Other factors such as an atrial myopathy or replacement of atrial myocytes with fibrosis may also lead to left atrial dilation and poor left atrial function. Other cats with HCM may have pathologic evidence of a thickened left atrial wall, possibly due to the hypertrophic process extending to the left atrial myocardium, or in response to increased left atrial pressure. Left atrial dilation is a poor prognostic indicator, and cats are at risk of congestive heart failure or arterial thromboembolism. In people with HCM, left atrial enlargement is associated with more adverse cardiac events, greater left ventricular hypertrophy, more severe diastolic dysfunction, and higher filling pressures (Yang et al. 2005). Similarly, left atrial size was an independent negative prognostic factor in 260 cats with HCM (Rush and Freeman 2002).

Using an inner edge to inner edge technique (the inside edge of the atrial wall), the left atrial diameter is measured, typically using 2D echocardiography from the right parasternal short-axis view at the level of the aortic valve, and compared to the aortic diameter (Figure

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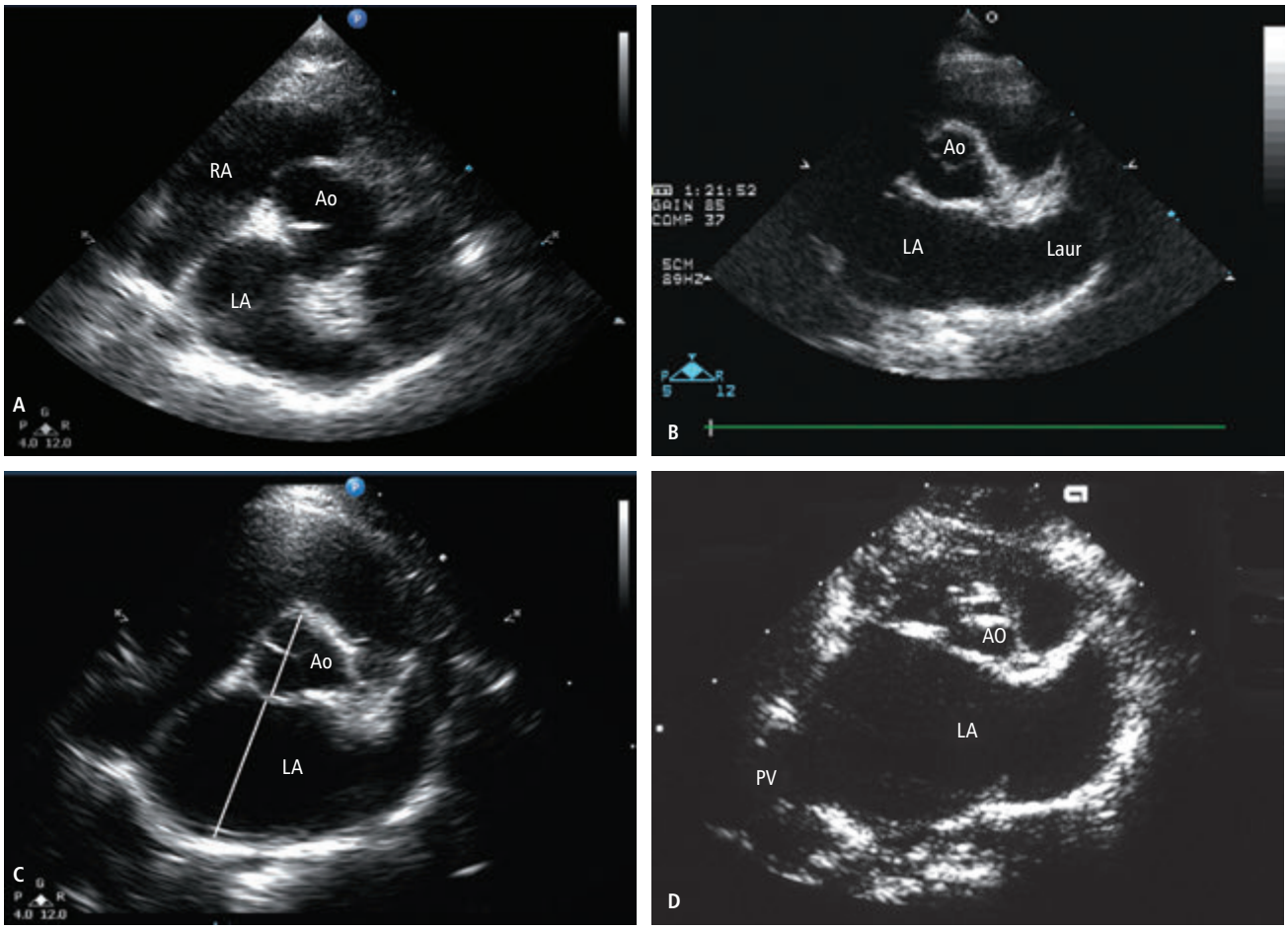


Figure 11.13. Two-dimensional echocardiography of cats with HCM, showing normal, mild, moderate, and severe left atrial dilation.

(A) This right parasternal short-axis view at the level of the aortic cusps of a cat with moderate HCM (same cat as in Figure 11.16A) shows normal left atrial size, with a left atrial diameter to aortic diameter ratio of < 1.5. Image **(B)** shows a cat with moderate HCM and mild left atrial dilation along with a prominent left auricle, and the left atrial to aortic ratio (LA : Ao) = 1.6. Image **(C)** shows moderate left atrial dilation (LA : Ao = 1.8) in a cat with severe HCM. This cat has diastolic dysfunction leading to increased left ventricular diastolic filling pressure and increased left atrial pressure, which causes left atrial dilation. The measurement lines are oriented slightly differently than the description in the text. Image **(D)** shows severe left atrial dilation (LA : Ao = 3), left auricular dilation, and a distended pulmonary vein (PV) in a cat with severe HCM and congestive heart failure. Cats with left atrial enlargement should be evaluated by radiographs as they may have congestive heart failure. LA = left atrium; Laur = left auricle; RA= right atrium; Ao = aorta.

11.13) (Schober et al. 2007; Abbott and MacLean 2006). The ratio of left atrial diameter to aortic diameter (LA:Ao) is used to eliminate the influence of body size on left atrial size and provides a dimensionless index of atrial size, which is especially important when evaluating patients of markedly different body size (i.e., different breeds of dogs). Since cats have less variability in body size and conformation, some cardiologists assess left atrial size by the absolute left atrial diameter (>16 mm) rather than LA:Ao (see Box 11.2).

LA:Ao can be measured by 2-dimensional echocardiography or 2-dimensional guided M-mode echocardiography. These measurements are not interchangeable because measurements taken by 2D tend to be larger than measurements taken by M-mode (Abbott and MacLean 2006). Care must be taken to measure the body of the left atrium and not the left auricle, which would underestimate left atrial size. Other pitfalls that may occur include measurement of the far wall of the left atrium to include the pulmonary vein, which would overexaggerate the left atrial size, or mistaking the pulmonary artery for the left atrium. Given the aforementioned limitations of M-mode, 2-dimensional echocardiography is the recommended technique for measurement of left atrial size, since it is not limited by the location and alignment of a cursor when using M-mode. LA:Ao is measured from the right parasternal short-axis view at the heart base at the level of the aortic

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cusps, and the first diastolic frame of aortic valve closure is selected (see Figure 11.13) (see also Chapter 7). The aortic diameter is measured by a line parallel to the commissures of the right coronary and noncoronary cusps, using the inner edge method. The left atrial diameter is measured by a line parallel to the commissure of the left coronary and noncoronary cusp, with care to avoid the pulmonary vein insertion into the left atrium (which would overestimate left atrial diameter) (see Figure 11.13). In a study of 17 healthy cats, normal 2D-derived LA:Ao was 1.18 ± 0.11 (Abbott and MacLean 2006). LA:Ao ratio of >1.5 is consistent with left atrial dilation (Abbott and MacLean 2006). Using the same right parasternal short-axis view, M-mode echocardiographic measurement of the LA:Ao involves directing the cursor through the body of the left atrium as well as perpendicular to the short axis of the aorta at the level of the aortic cusps. The aortic diameter is measured at end-diastole just before the aortic cusps open, and the left atrial diameter is measured at end-systole just when the aortic cusps close, using a leading edge to leading edge technique (Figure 11.14). Normal M-mode–derived LA:Ao in cats is 1.25 ± .18 with 95% confidence interval of 1.21– 1.29 (Drourr et al. 2005).

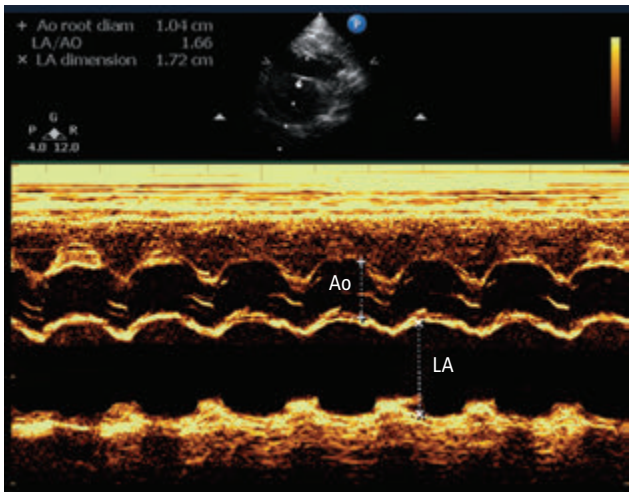


Figure 11.14. M-mode echocardiogram showing left atrial dilation in a cat with severe hypertrophic cardiomyopathy. The M-mode cursor is placed through the aortic root at the level of the aortic cusps and through the body of the left atrium. This image is obtained from the same cat as depicted in Figure 11.13C. The aorta is measured at end-diastole just before the aortic cusps open, and the left atrial diameter is measured at end-systole when the aortic cusps close, using a leading edge to leading edge technique. The left atrial diameter is indexed to the aortic diameter (LA:Ao), and in this cat is moderately increased at 1.7. Care must be taken to avoid measuring the left auricle rather than the body of the left atrium, as this would grossly underestimate left atrial size.

The degree of left atrial dilation is usually a subjective finding. While exact cutoff values for mild, moderate, and severe left atrial dilation have not been formalized, suggested parameters include LA:Ao = 1.51–1.79, 1.8–1.99, 2.1, and ≥2.01, respectively (Box 11.2, see also Figure 11.13).

Identification of left atrial dilation in a cat with HCM confirms that there is significant diastolic dysfunction leading to increased diastolic filling pressures. Mitral regurgitation secondary to SAM of the mitral valve may also contribute to left atrial dilation. In cats with severely elevated left atrial pressure, there is often echocardiographic evidence of pulmonary venous distension seen at the insertion of the anterior and posterior pulmonary veins into the roof of the left atrium (see Figure 11.13). In cats presenting with pulmonary infiltrates or pleural effusion, assessment of left atrial size is crucial for determining whether there is left-sided congestive heart failure versus primary respiratory disease. Identification of normal left atrial size in cats diagnosed with HCM that also have pulmonary infiltrates or pleural effusion and no known inciting trigger such as intravenous fluid administration virtually eliminates left-sided congestive heart failure from the diagnosis.

Spontaneous echocardiographic contrast (i.e., smoke) may be seen throughout a dilated left atrium or only within the left auricle and it occurs when there is red cell aggregation. Spontaneous contrast is viewed as the precursor to a clot and suggests that there is a high risk for development of arterial thromboembolism. In these cases, it is particularly important to carefully evaluate for a thrombus, especially within the stagnant blood of the left auricle in a dilated left atrium, because cats with intracardiac thrombi have higher mortality rates and are at great risk for massive thromboembolic event or sudden death (Figure 11.15). The left auricle has the slowest blood flow velocity within the left atrium and also has small branching pectinate muscles, both favoring thrombus formation in the auricle. Cats with spontaneous contrast or an intracardiac thrombus should be placed on an anticoagulant (see Chapter 20).

BOX 11.2. Echocardiographic Assessment of Left Atrial Size

	Left atrial diameter to aortic diameter (LA:Ao)	Left atrial diameter (mm)
Normal:	<1.5	<16
Mild LAE:	1.51–1.79	16–19.9
Moderate LAE:	1.8–1.99	20–24
Severe LAE:	>2	>24

LAE = left atrial enlargement

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Identification of Systolic Anterior Motion (SAM) of the Mitral Valve

SAM of the mitral valve is a hallmark pathologic feature of HCM. It can be seen on 2-dimensional echocardiography from the right parasternal long-axis left ventricular outflow tract view (Figure 11.16). SAM was previously thought to be caused by the Venturi effect, wherein the rapid blood flow through a narrowed left ventricular outflow tract sucked the anterior mitral leaflet into the rapid flow, much like a shower curtain is drawn toward the rapid flow of the water stream in a shower. Later experiments have proven that this effect is not responsible for SAM, and rather that SAM is caused by alterations in hypertrophied papillary muscle geometry (Sherrid 2006; Levine et al. 1995). In HCM, papillary muscles are almost always hypertrophied and cranioventrally (i.e., anteriorly) displaced within the left ventricle, which pull the chordae tendinae and the anterior mitral leaflet into the left ventricular outflow tract and toward the interventricular septum during systole. During late systole, the anterior mitral leaflet may even contact the basilar interventricular septum. The result is a dual abnormality of blood flow: there is greater resistance for blood flow to be ejected out the left ventricle, and retrograde flow from the ventricle to the left atrium (i.e., mitral regurgitation) occurs due to the gap in coaptation of the mitral valve during systole. A fibrotic plaque is often seen as a hyperechoic region of the endocardium where the mitral leaflet contacts the interventricular septum (i.e., "kissing lesion"). An important differential diagnosis for mitral regurgitation caused by SAM is mitral regurgitation caused by mitral valve dysplasia, and these two disorders have different etiology, pathophysiology, clinical course, treatment, and prognoses. The mitral valve structure is normal in cats with SAM, as opposed to mitral valve dysplasia where the mitral valve is typically thickened, with clubbed leaflets and thickened short chordae tendinae. SAM can also be visualized using 2-dimensional echocardiography in the left apical 5-chamber (left ventricular outflow tract) view (see Figure 11.16).

Color-flow Doppler is a useful tool to readily identify the characteristic double turbulent jets of mitral regurgitation and turbulent systolic ejection blood flow arising from the same spot in the left ventricular outflow tract (see Figure 11.16). The anterior mitral leaflet can be seen at the origin of the turbulent jets. The right parasternal long-axis left ventricular outflow tract view is the most useful view to identify this color-flow disturbance, but it can also be identified from the left

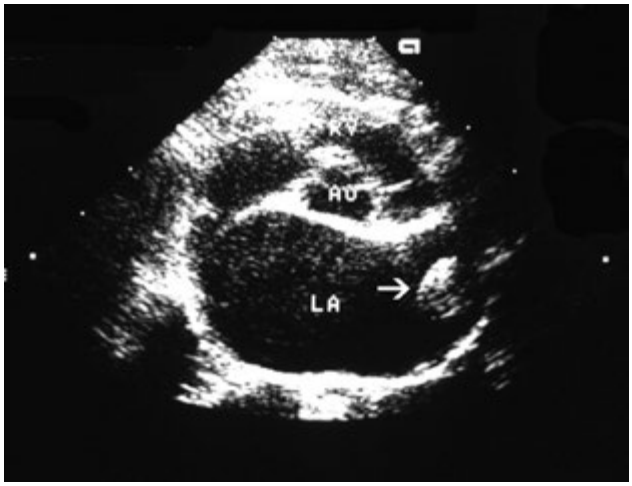
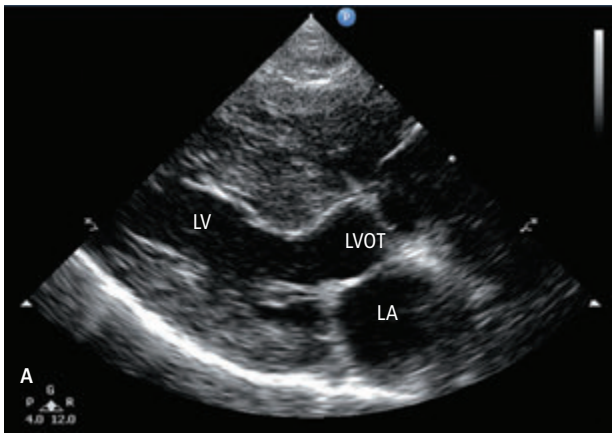
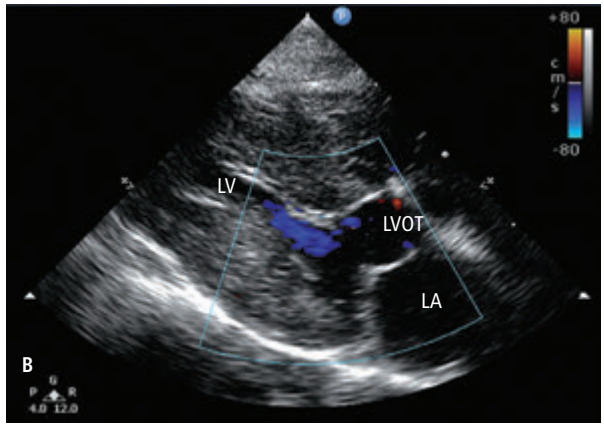
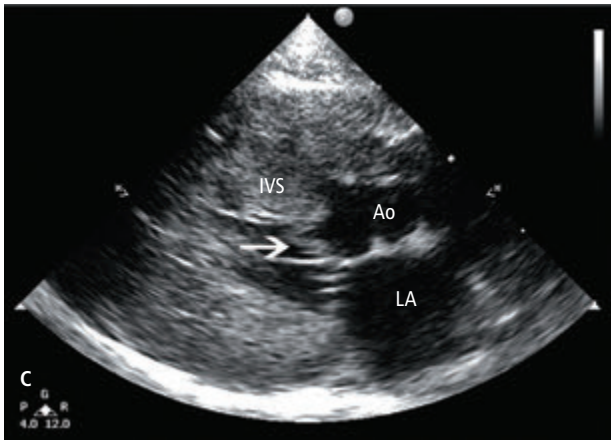


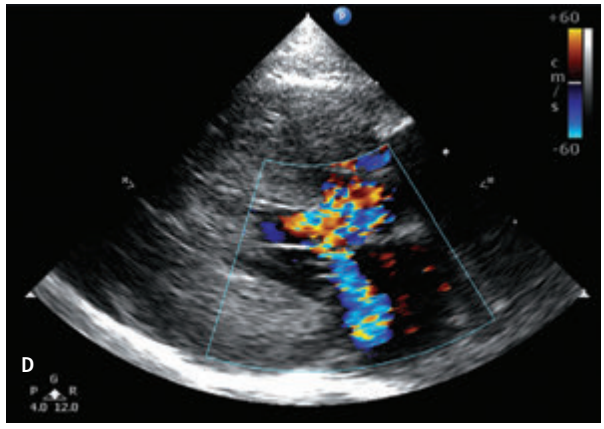
Figure 11.15. Two-dimensional echocardiography showing a left atrial thrombus and left atrial dilation in a cat with severe hypertrophic cardiomyopathy. This right parasternal short-axis view at the level of the heart base shows severe left atrial dilation as well as a hyperechoic, round, soft tissue opacity within the auricle (arrow), which represents a thrombus. There is also spontaneous contrast, seen as a hyperechoic, speckled, swirling pattern within the left atrium, due to red blood cell aggregation. RV = right ventricle; Ao = aorta; LA = left atrium.

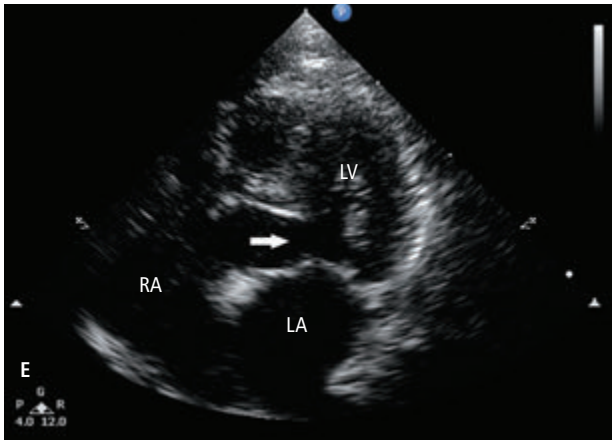
Figure 11.16. Two-dimensional and color-flow Doppler echocardiographic assessment of systolic anterior motion of the mitral valve in a cat with hypertrophic obstructive cardiomyopathy and a cat with hypertrophic cardiomyopathy without systolic anterior motion for comparison. The right parasternal long-axis left ventricular outflow tract view of a cat with hypertrophic cardiomyopathy but no systolic anterior motion (SAM) shows no valvular obstruction of blood flow out the left ventricular outflow tract (LVOT) on 2D and color-flow Doppler **(A and B)**, even though there is evidence of severe basilar septal hypertrophy and papillary hypertrophy. This is in contrast to a cat with HCM and severe systolic anterior motion of the mitral valve **(C and D)**, where the anterior mitral leaflet obstructs the left ventricular outflow tract during systole (arrow). Color-flow Doppler of the left ventricular outflow tract shows a double turbulent jet where the anterior mitral leaflet obstructs the left ventricular outflow tract and also creates mitral regurgitation.
The left apical 5-chamber view of a cat with HCM and no SAM shows an unimpeded left ventricular outflow tract and normal mitral valve coaptation, laminar ejection of blood flow out the LVOT and aorta (blue color), and severe basilar septal concentric hypertrophy **(E and F)**. In contrast, the left apical 5-chamber view of a cat with severe SAM shows an abnormally positioned mitral valve (arrow) that touches the interventricular septum, thus obstructing blood flow out the left ventricular outflow tract and creating mitral regurgitation **(G and H)**. The papillary muscles are hypertrophied, and anteriorly (cranioventrally) positioned, pulling the chordae tendinae and the anterior leaflet toward the severely hypertrophied basilar interventricular septum. Ao = aorta; IVS = interventricular septum; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle

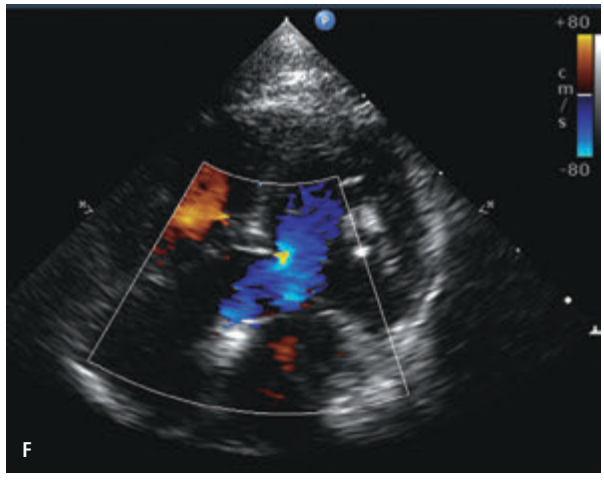

LV
LVOT
LA
A

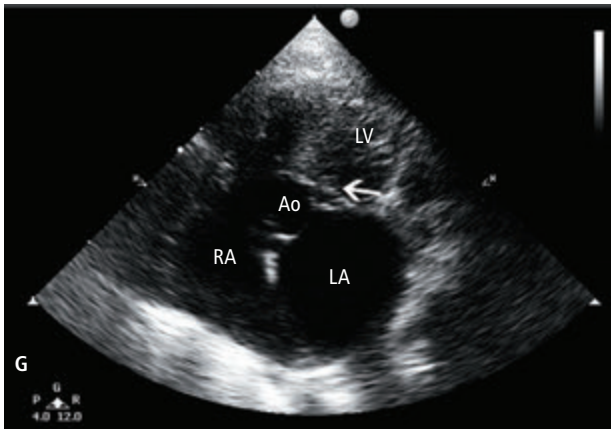

+80
cm/s
-80
LV
LVOT
LA
B

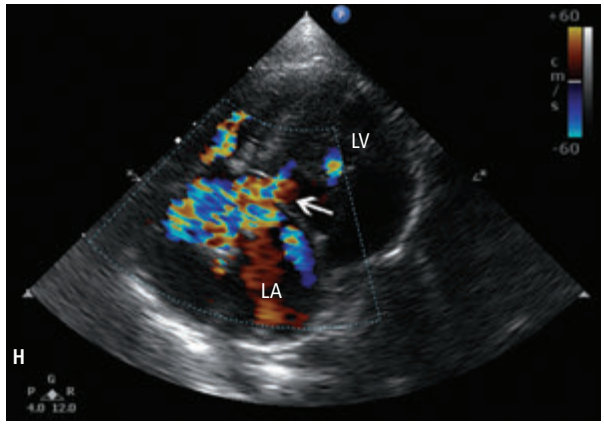

IVS
Ao
LA
C


+60
cm/s
-60
D


LV
RA
LA
E


+80
cm/s
-80
F


LV
Ao
RA
LA
G


+60
cm/s
-60
LV
LA
H

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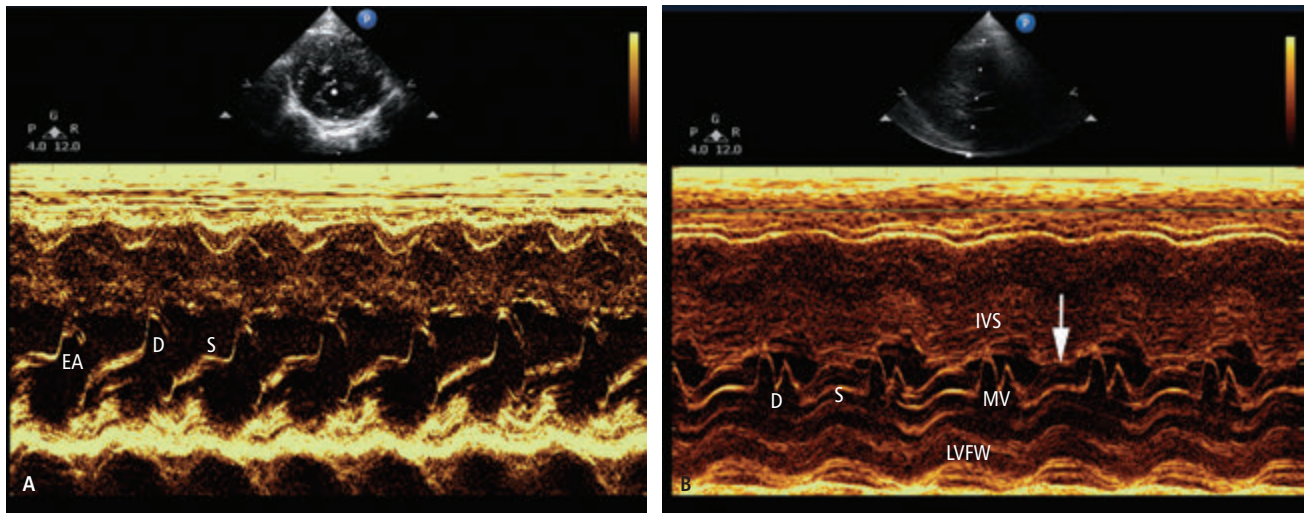


Figure 11.17. M-mode echocardiography showing normal mitral valve motion in a normal cat compared to systolic anterior motion of the mitral valve in a cat with hypertrophic obstructive cardiomyopathy. M-mode echocardiography is done at the level of the mitral valve using either the right parasternal short-axis view or the right parasternal long-axis 4-chamber view. Normally, both mitral leaflets are closed during systole (S) **(A)**. The early (E) and late (A) waves of mitral diastolic movement are summated in this normal cat that has a high heart rate. In contrast, SAM of the mitral valve is seen when the anterior mitral leaflet nearly touches the interventricular septum during systole (arrow) in a cat with hypertrophic obstructive cardiomyopathy **(B)**. D = diastole.

parasternal apical 5-chamber view. The severity of mitral regurgitation secondary to SAM usually ranges from trivial to moderate and is subjectively assessed.

M-mode echocardiography of the mitral leaflet from the right parasternal short-axis view may show the anterior mitral leaflet being anteriorly (ventrally) displaced and touching the interventricular septum during systole, when it should be closed and coapted with the posterior leaflet (Figure 11.17).

Continuous-wave Doppler is necessary to measure the severity of left ventricular outflow tract obstruction. Using the left apical 5-chamber view, the cursor is aligned parallel with blood flow ejected out the left ventricular outflow tract and aorta (Figure 11.18). Using the modified Bernouilli equation, the pressure difference between the left ventricle and the aorta is calculated as pressure gradient = 4 × velocity^2. Mild, moderate, and severe obstructions are defined as pressure gradients <50 mm Hg, 50–80 mm Hg, and >80 mm Hg, respectively. Normal cats may have a slight step up in velocity from the left ventricular outflow tract to the aorta, with a slight pressure gradient. Cats with moderate or severe SAM may benefit from medical therapy to reduce the severity of the obstruction, because it may also significantly reduce the severity of left ventricular concentric hypertrophy. SAM is a dynamic obstruction, which worsens with greater ventricular systolic force and tachycardia, and is decreased by negative inotropic and chronotropic agents (i.e., atenolol). Provoking the cat

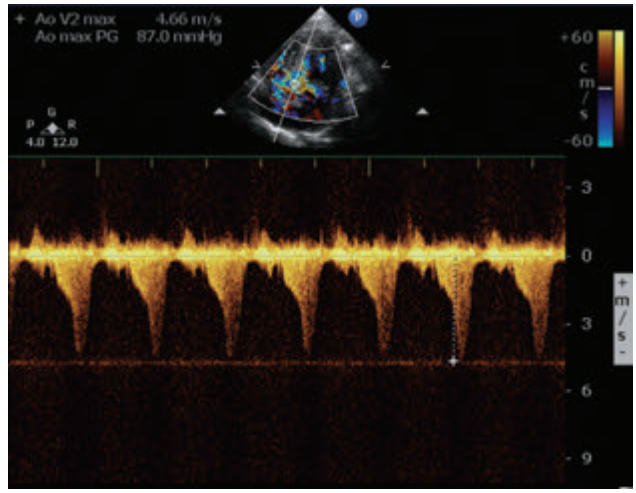


Figure 11.18. Continuous-wave Doppler echocardiography in a cat with severe systolic anterior motion of the mitral valve and hypertrophic cardiomyopathy. The severity of SAM is assessed by continuous-wave Doppler measurement of the aortic blood flow velocity, using the left apical 5-chamber view. This cat has severe SAM as evidenced by an aortic blood flow velocity of 4.7 m/s (normal <1.8 m/s; 4.7 m/s corresponds to a left ventricular to aortic pressure gradient of 87 mm). SAM causes a dynamic obstruction, which worsens later in systole and creates this characteristic concave, late-peaking, dagger-shaped appearance (rather than a symmetrical cone shape) to the Doppler velocity profile.

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with mild agitation (i.e., mildly startling the cat) allows measurement of the maximal aortic blood flow velocity and greatest severity of SAM. Cats are typically anxious and catecholamine driven in the veterinary hospital while restrained for echocardiography, and this portrays the most severe spectrum of SAM severity, which may also be present in other stressful home events such as being chased by a dog. In contrast, the average (sedentary) household cat that is resting comfortably at home has low sympathetic tone and severity of SAM may be quite mild in this setting. Therefore, the echocardiographic severity of SAM should be placed in its individual context for each cat based on the cat's character, daily routine, medications, and similar variables.

Assessment of diastolic function

Pulsed-wave Doppler echocardiography

Noninvasive methods have been devised to characterize the filling phases of diastole (Figure 11.19). PW Doppler of mitral inflow has been used to identify a pattern of progressive diastolic dysfunction in people and animals with a variety of cardiac diseases (see Figure 11.19)

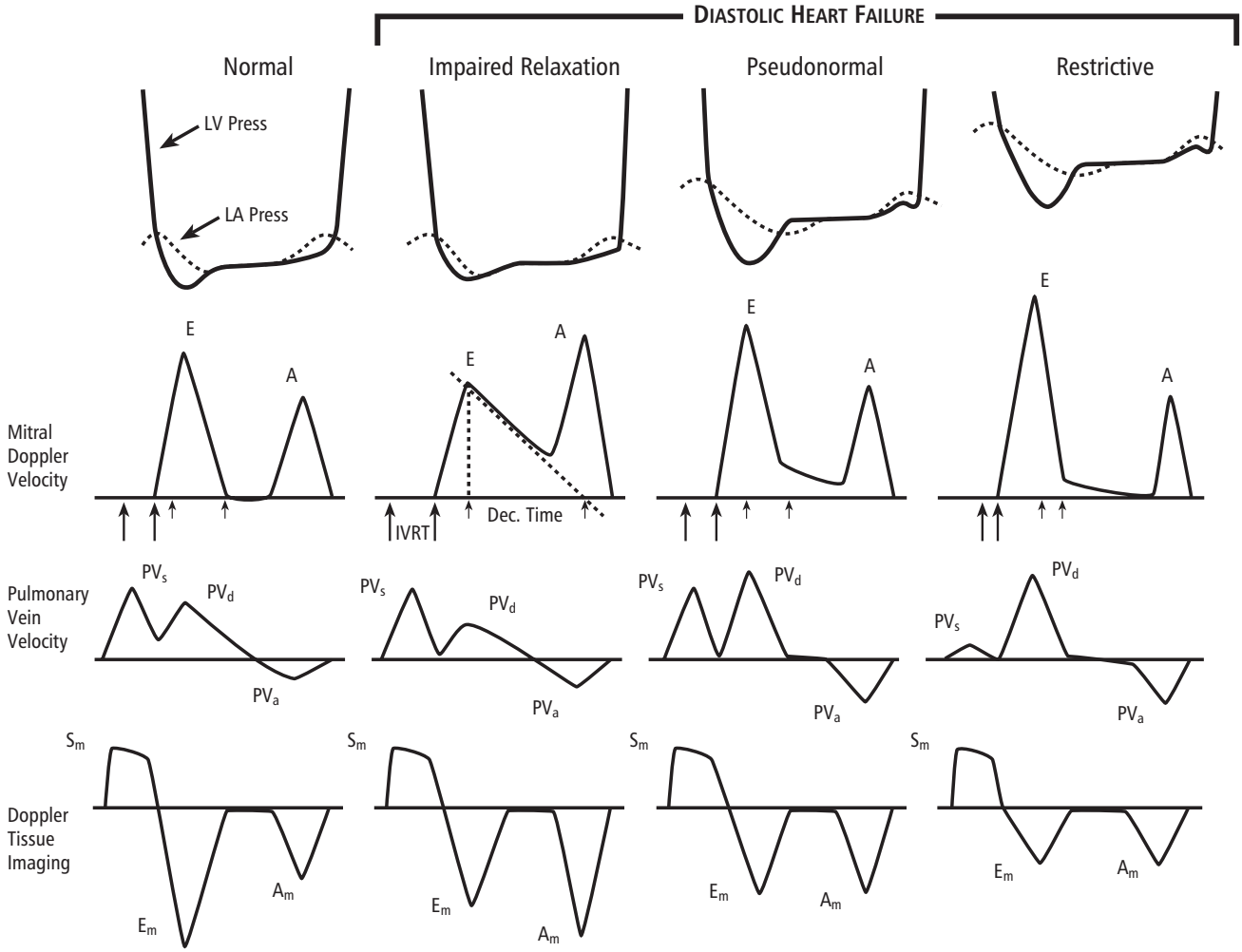


Figure 11.19. Doppler echocardiographic assessment of diastolic dysfunction. The top panel shows left ventricular (LV) and left atrial (LA) pressures measured during diastole at worsening degrees of diastolic dysfunction. Transmitral pulsed-wave Doppler LV inflow velocity distinguishes delayed relaxation and restrictive patterns from the normal pattern, but there is an ambiguous intermediate stage where velocity profiles "pseudonormalize." Pulmonary vein blood flow velocities are measured to identify increased atrial reversal velocity (PV_a) during more severe diastolic impairment and sometimes in the pseudonormal phase. Tissue Doppler imaging of the lateral mitral annulus shows reduced early diastolic velocity (E_m) in all levels of diastolic dysfunction, which becomes progressively lower as the diastolic dysfunction worsens. E, early LV filling velocity; A, velocity of LV filling during atrial systole; IVRT, isovolumic relaxation time; PV_s, systolic pulmonary vein velocity; PV_d, diastolic pulmonary vein velocity; PV_a, pulmonary vein velocity during atrial systole; S_m, ventricular systolic mitral annular velocity (synonym, S'); E_m, early diastolic mitral annular velocity (synonym: E'); A_m, late diastolic mitral annular velocity during atrial systole (synonym: A'). Obtained and modified with permission from Zile MR, et al. Circulation 2002, 105:1387, p 1392.

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(Bright et al. 1999; Schober et al. 2003). A normal diastolic filling pattern consists of a relatively short isovolumic relaxation time (IVRT), a predominant early filling wave (E), and an early to late (A) diastolic filling wave, creating a ratio (E : A) >1 (Zile and Brutsaert 2002). In normal anesthetized cats, echocardiographically measured IVRT was found to be highly correlated with invasive measurements of isovolumic relaxation (tau, r = 0.78), with a mean IVRT of 71 ± 17 ms (Schober et al. 2003). Delayed relaxation causes prolongation of IVRT, reduced E wave velocity, prolonged E wave deceleration time, and decreased E:A ratio (<1). Cats with HCM commonly have evidence of delayed relaxation by PW Doppler (Figure 11.20). In cats with HCM, IVRT is prolonged to 76 ± 3.1 ms versus 46 ± 3.3 ms in normal anesthetized cats (Bright et al. 1999). Early mitral inflow is also reduced (0.54 ± 0.04 m/s versus 0.7 ± 0.04 m/s), deceleration rate is slower, and atrial systolic flow velocities are increased (0.48 m/s versus 0.29 ± 0.04 m/s) in cats with HCM compared to normal cats (Bright et al. 1999). These abnormalities are consistent with the pattern of delayed relaxation. As diastolic dysfunction worsens, the LA pressure rises and results in an increased E wave amplitude and E : A >1 similar to the normal mitral inflow waveforms. This is termed the "pseudonormal" phase, and causes ambiguity in diagnosis of diastolic dysfunction using PW Doppler of the mitral inflow. Measurement of pulmonary venous flow by PW Doppler is useful to identify an increased retrograde pulmonary venous flow during atrial systole (termed either pulmonary vein in atrial systole [PVa] or atrial reversal [Ar] wave) in the pseudonormal phase (see Figure 11.19). In the most extreme form of diastolic dysfunction, the left atrial pressure and LV stiffness are greatly increased, resulting in rapid early diastolic ventricular filling with an abrupt decrease in filling due to the stiff ventricle and a restrictive filling pattern. This pattern is summarized as reduced IVRT, decreased deceleration time, E : A ratio >2, and possibly a decreased A wave duration compared to the pulmonary venous PVa (Ar) wave.

Although widely used as a simple, noninvasive method to assess diastolic function, PW Doppler mitral inflow characteristics are greatly impacted by filling pressures and the LA : LV pressure gradient. For example, peak early mitral inflow velocity was found to be moderately correlated with LV filling pressure in normal anesthetized cats (r = 0.48) (Peterson et al. 1993). Increased left atrial pressure may mask a delayed relaxation pattern. Oppositely, increased heart rate, decreased preload, and increased afterload accentuate a delayed relaxation pattern (Movsowitz et al. 1993). Consequently, there has been a search for noninvasive methods to assess diastolic

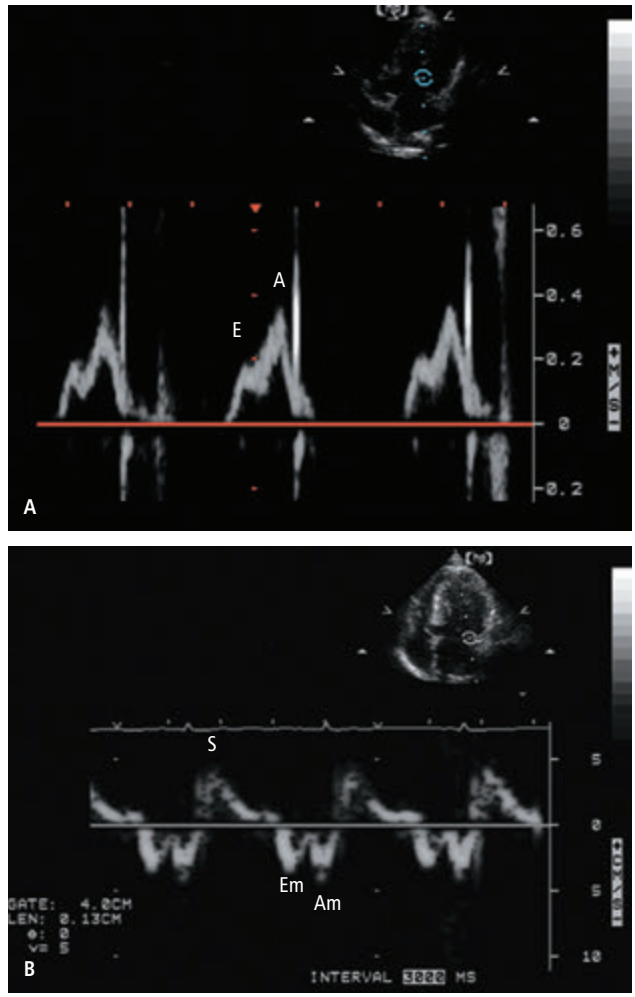


Figure 11.20. Diagnosis of diastolic dysfunction using pulsed-wave Doppler and tissue Doppler imaging echocardiography in a cat with severe hypertrophic cardiomyopathy. **(A)** Pulsed-wave Doppler echocardiography of the mitral inflow showing delayed relaxation pattern indicative of early diastolic dysfunction. **(B)** Pulsed-wave tissue Doppler imaging echocardiography of the lateral mitral annulus showing diastolic dysfunction.
A delayed relaxation pattern is commonly seen in cats with HCM, and is identified by pulsed-wave Doppler interrogation of the mitral inflow (see Figure 11.19), which shows reduced E wave velocity, reduced E:A ratio (<1), and prolonged deceleration time. Pulsed-wave tissue Doppler imaging can be done at the mitral annulus using the left apical 4-chamber view (B), with the gate placed in alignment with the myocardial motion. The velocity of the longitudinal myocardial fibers is measured in this way. This pulsed-wave TDI tracing of the same cat in (A) shows severely impaired diastolic function with a markedly reduced early mitral annular diastolic velocity (Em or E′), and Em:Am velocity. E = early mitral inflow; A = mitral inflow during atrial systole; Em = early diastolic mitral annular velocity; Am = late diastolic mitral annular velocity during atrial systole; S = mitral annular velocity during systole.

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function that are less influenced by alterations in load. At the present time, cardiologists generally do not use spectral Doppler information on diastolic function to make specific treatment decisions, but it may contribute to the overall clinical picture along with other abnormalities identified clinically, radiographically, and echocardiographically. Abnormal spectral Doppler measurements of diastolic function may thus help differentiate normal cats from abnormal cats when the diagnosis is equivocal. Serial characterization of diastolic inflow patterns (normal, delayed relaxation, pseudonormal, or restrictive) in an individual patient may also clinically parallel the overall impact of HCM and progressive elevation in left atrial pressure that may be present in cats as HCM worsens.

Tissue Doppler imaging

Assessment of diastolic function can be an intimidating topic to many veterinarians and often involves use of specific techniques different from those used for traditional echocardiography (2D, color flow, M-mode, and spectral Doppler). However, assessment of diastolic function can be as basic as assessment of the left atrial size in cats with HCM, since in this disease left atrial dilation occurs when there is clinically relevant diastolic dysfunction (excluding influence of anemia, fluid administration, etc.). However, there are more specific technical methods to evaluate diastolic dysfunction that may aid in early diagnosis of HCM, possibly prior to development of left ventricular hypertrophy, which may be important for breeding population screening or monitoring at risk breeds (MacDonald et al. 2007; Chetboul et al. 2006; Carlos et al. 2009).

Tissue Doppler imaging (TDI) is the preferred echocardiographic method to specifically evaluate diastolic dysfunction in cats with various heart diseases, particularly HCM (Koffas et al. 2002; Gavaghan et al. 1999). It is not essential for making a diagnosis of HCM, but it may contribute additional information in patients that are equivocal for HCM and breeds at risk for HCM, or for following progression of disease. TDI accurately diagnoses diastolic dysfunction in a variety of cardiac diseases in people (HCM, endomyocardial fibrosis, hypertensive heart disease, restrictive cardiomyopathy, and Duchenne's muscular dystrophy) as well as in cats with HCM (Chetboul et al. 2004; MacDonald et al. 2007; Carlos et al. 2009; Koffas et al. 2002, 2006; Gavaghan et al. 1999; Oki et al. 2000; Garcia et al. 1996; Rodriguez et al. 1996). TDI has been used to distinguish HCM from other secondary causes of left ventricular hypertrophy in people (Vinereanu et al. 2001). This principle was tested in cats with HCM and with hyperthyroidism, and the early diastolic myocardial velocity (E', also called Em) was reduced in aged cats with HCM, but was normal in cats with hyperthyroidism, who had increased S' velocities (Simpson et al. 2009). However, TDI measurements of diastolic function were abnormal in both cats with HCM and cats with systemic hypertension and occurred independently from presence of concentric hypertrophy, so they may be less useful in discriminating HCM and systemic hypertension in cats (Carlos et al. 2006).

TDI has been shown to be an excellent method for noninvasive assessment of diastolic function because it is less sensitive to preload and therefore to alterations due to hydration status, heart rate, or other variables than traditional PW Doppler measurement of mitral inflow (Schober et al. 2003; Sohn et al. 1997; Nagueh et al. 1997). TDI uses the same principle that assesses the movement of blood flow, but it amplifies the lower velocity, higher amplitude movement of the myocardium. TDI has both spectral and color-flow modalities, and the pattern of velocity of the ventricular walls during diastole helps to identify the earliest abnormalities of ventricular relaxation. TDI measurements may be obtained from several sites within the left and right ventricles, notably the mitral annulus. There are several techniques of TDI including PW Doppler, color M-mode of the myocardium, and 2-dimensional color TDI. PW TDI is the most readily applicable technique that does not require offline analysis, and it allows measurement of peak myocardial velocity during systole (S), early diastole (E' or Em), and atrial systole during late diastole (A' or Am). Color TDI allows measurement of myocardial velocity gradient (MVG) and calculation of mean myocardial velocity. MVG is the transmyocardial velocity gradient from the endocardium to the epicardium throughout the cardiac cycle. The fastest myocardial velocities are in the endocardial region, and they decrementally decrease toward the epicardium (Chetboul et al. 2004). Myocardial velocities measured by PW Doppler are higher than by color M-mode because PW Doppler TDI measures peak velocities, whereas color Doppler measures mean myocardial velocities (Nikitin and Witte 2004). Ideally, TDI measurements of diastolic and systolic function would be load-independent, and not confounded by changes in hydration status, presence of valvular insufficiency, or increased afterload. No technique is totally devoid of these influences. The effect of preload on TDI measurements has been assessed in dogs, people, and healthy cats. In an experimental canine model of abnormal LV relaxation, early diastolic mitral annular velocity (E') dependence on preload was more prominent in the normal physiologic state, but dependence was markedly diminished with diastolic dysfunction (Firstenberg et al. 2001). TDI is a highly reproducible and accurate method to assess diastolic and systolic

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function in cats, with low error (within-day coefficient of variation 6.5%, between-day 13.6%) (Chetboul et al. 2004; Schuster et al. 2004).

In PW Doppler TDI, the wave that occurs during ventricular systole is called Sm or S' (see Figure 11.19). E' (or Em) is the wave that occurs during LV relaxation and elastic recoil in early diastole, and A' (or Am) is the wave that occurs during atrial contraction at end-diastole atrial systole (see Figure 11.19). Mitral annular motion is determined by the summation of the longitudinal motion of myocardial fibers and allows assessment of global diastolic and systolic function (Nikitin and Witte 2004; De Boeck et al. 2003). Impairment in diastolic function results in reduced amplitude of E', and systolic dysfunction results in reduced S' velocity (see Figure 11.19). In the normal heart, there is a progressive increase in E' from apex to mitral annulus, and the lateral LV free wall has a higher E' than the septum (Nikitin and Witte 2002, 2004). E' measured by PW TDI, color M-mode, and peak negative MVG correlates closely with invasive indices of diastolic function including tau, dP/dT, and LV end-diastolic pressure in normal people and people with HCM (Oki et al. 2000; Ohte et al. 1998; Bruch et al. 1999; Kato et al. 2003; Border et al. 2003). E' is also positively correlated with heart rate in cats, such that tachycardia-associated elevations in E' velocities may potentially falsely normalize the E' of cats with HCM with mild diastolic dysfunction (Chetboul et al. 2004; Gavaghan et al. 1999). Although E' and A' waves may become summated (EA') with heart rates >160–180 BPM, there are discordant results in several studies regarding whether the velocity of summated EA' is higher compared to nonsummated E' (Chetboul et al. 2004; Gavaghan et al. 1999; MacDonald et al. 2008).

One advantage of PW TDI over color TDI is that specialized postprocessing software is not necessary for measurement of diastolic and systolic velocities, and peak velocities can be immediately measured at the time of examination. Limitations include the inability to simultaneously assess velocities at more than one region of the myocardium and inability to obtain endocardial to epicardial velocity gradients. Given the translational movement of the heart within the chest due to breathing and intrinsic cardiac forces, stable consecutive PW Doppler tracings are often difficult to obtain.

TDI has been used to diagnose diastolic dysfunction in humans and in animals with various types of cardiac diseases including HCM, endomyocardial fibrosis, hypertensive heart disease, restrictive cardiomyopathy, and Duchenne's muscular dystrophy (Chetboul et al. 2004; Gavaghan et al. 1999; Oki et al. 2000; Garcia et al. 1996; Rodriguez et al.1996). E' accurately discriminates between people with HCM and from athletes with physiologic hypertrophy or from patients with hypertensive heart disease with a high sensitivity of 87% and specificity of 97% (Vinereanu et al. 2001). Reduced E' velocity occurs in cardiac diseases with myocardial fibrosis, and is negatively correlated ($R = -0.7$) with percent interstitial fibrosis in people with coronary artery disease and LV dysfunction (Shan et al. 2000).

TDI is useful to detect diastolic dysfunction in cats with HCM (see Figure 11.20) (Chetboul et al. 2004; Gavaghan et al. 1999; Koffas et al. 2003). E' is often reduced in cats with HCM when compared to normal cats (Carlos et al. 2009; Gavaghan et al. 1999; Koffas et al. 2006). There are only a few studies that have evaluated PW TDI in normal cats and cats with HCM. Normal E' in cats was 12.1 ± 2.3 cm/sec in one study, and 8.39 ± 2.58 in another study (Gavaghan et al. 1999; Koffas et al. 2006). E' of cats with HCM generally is lower than E' of normal cats, and was 7.9 ± 1.7 cm/sec in one study and 5.24 ± 1.22 cm/sec in another study (Gavaghan et al. 1999; Koffas et al. 2006). A cutoff of >7.2 cm/sec is highly sensitive (92%) and specific (87%) for discriminating normal cats from cats with HCM (Koffas et al. 2006). Other TDI measurements of diastolic function have been shown to be abnormal in cats with HCM including prolonged acceleration and deceleration times of E' and prolonged isovolumic relaxation time (Koffas et al. 2006).

TDI has been useful to detect diastolic dysfunction in people and in animal models of HCM prior to development of concentric hypertrophy. E' is reduced in humans with familial HCM and in transgenic β-MHC mutation-bearing rabbits with HCM before myocardial hypertrophy develops (Nagueh et al. 2000, 2003; Ho et al. 2002; Oki et al. 2000; Li et al. 2004; Severino et al. 1998). This early diastolic dysfunction likely reflects mechanical impairment in familial HCM prior to development of the final phenotype of LV hypertrophy (Marian and Roberts 1995). E' is further reduced as diastolic dysfunction progresses, and is strongly negatively correlated with amount of increase in LV mass (Nagueh et al. 2003). In people with HCM, the greatest impairment of diastolic function (lowest E') occurs in the regions with the greatest amount of hypertrophy, but other nonhypertrophied regions also have impaired diastolic function (Oki et al. 2000). PW TDI identifies diastolic dysfunction in 50% of adult Maine coon cats that are genotypically affected with the MYBPC3 mutation, despite no echocardiographic phenotypic evidence of left ventricular concentric hypertrophy or SAM of the mitral valve (MacDonald et al. 2007). E' is decreased

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in genotypically affected Maine coon cats compared to normal domestic shorthaired cats, and is further decreased in genotypically affected Maine coon cats that have the abnormal phenotype of concentric left ventricular hypertrophy (MacDonald et al. 2007). Therefore, it appears that diastolic dysfunction is an early pathophysiologic abnormality in Maine coon cats with familial HCM, and is independent of left ventricular concentric hypertrophy. Similarly, TDI was able to detect diastolic dysfunction in all carrier cats and affected cats prior to development of concentric hypertrophy in a family of cats affected by dystrophin-deficient hypertrophic muscular dystrophy (Chetboul et al. 2006). Thus, evidence exists to support TDI as a diagnostic modality that detects HCM earliest, even before measurable ventricular hypertrophy in some cats.

Future applications of TDI may include improvement in accuracy of prognosis for patients with heart disease. For example, peak early diastolic mitral annular velocity (E') is a powerful predictor of outcome in a variety of cardiovascular conditions including HCM (Wang et al. 2003; Sanderson et al. 2004; McMahon et al. 2004). E' was the strongest predictor of cardiac mortality of all the TDI variables in people with various cardiac diseases in one study: E' <3 cm/s was associated with over a fivefold increased risk of cardiac death (Wang et al. 2003). In another study, unlike traditional mitral inflow Doppler indices, E' also correlated with severity of heart failure (New York Heart Association functional class) and exercise capacity in adults with HCM (Matsumura et al. 2002). In children with HCM, transmitral E/septal E' predicted risk of death, cardiac arrest, ventricular tachycardia, and significant cardiac symptoms (McMahon et al. 2004). The index of transmitral E/E' is a useful, noninvasive method to estimate LV filling pressure in normal people ($r = 0.87$) and people with HCM ($r = 0.8$) (Nagueh et al. 1997, 1999). Changes in pulmonary capillary wedge pressure (PCWP) in patients with HCM are also tracked by changes in E/E' (Nagueh et al. 1999). E/E' ≥10 predicts LV filling pressure (just before atrial systole) of >15 mm Hg, and yields the best sensitivity (92%) and specificity (85%). In dogs with acute experimentally induced mitral regurgitation, E/E' is highly correlated ($r = 0.83$) with mean left atrial pressure (Oyama et al. 2004). An LA pressure >20 mm Hg is highly probable when mean E/E' is >9.1 (Oyama et al. 2004). Color M-mode measurement of the early diastolic mitral inflow of blood can be used to calculate the velocity of flow propagation (Vp). The slope of the first aliasing inflow velocity is the velocity of propogation (Vp) along the left ventricle during early diastole. Vp progressively decreases as the diastolic function worsens. Mitral inflow E/Vp by TDI was moderately correlated in LV end-diastolic pressure in anesthetized normal cats ($R = 0.64$) (Schober et al. 2003). No studies have evaluated the ability of E/E' to predict PCWP pressure in cats with HCM.

Although diastolic dysfunction is the main pathophysiologic abnormality in HCM, there is evidence of reduced longitudinal systolic function on TDI in humans, transgenic rabbits, and cats with HCM (Nagueh et al. 2001; Meurs et al. 2000; Koffas et al. 2006; Vinereanu et al. 2001; Tabata et al. 2000; Yip et al. 2002). Decreased systolic function in HCM is counterintuitive, since the ventricular wall motion often appears hyperdynamic. However, if the systolic myocardial function is more carefully assessed using TDI echocardiography, regional or global systolic dysfunction may be identified in patients with HCM, even prior to an end-stage remodeling with overt systolic failure. This is likely due to the pathophysiology of HCM, where sarcomeric systolic and diastolic dysfunction is the earliest myocardial defect. S' (but not fractional shortening), is lower in cats with HCM without left ventricular outflow tract obstructions compared to normal cats (Koffas et al. 2006). Cats with reduced S' velocity in this study had normal fractional shortening, which illustrates that fractional shortening is an insensitive test for systolic myocardial function and may be confounded by many other factors such as preload. Systolic dysfunction appears to be more common in cats with severe HCM and heart failure than asymptomatic cats because all cats with heart failure secondary to HCM had decreased S' velocities in one study (Koffas et al. 2006). Similar findings of systolic impairment detected by TDI have been described in human medicine and in genetic models of HCM. S' velocities were reduced by 12–31%, and time to peak systolic velocity was increased in people with HCM (Vinereanu et al. 2001; Tabata et al. 2000). S' velocities are even reduced in humans or rabbits with β-MHC mutations prior to development of LV hypertrophy (Nagueh et al. 2000, 2001). In normal humans, the radial systolic velocity is lower than the longitudinal velocity at the mitral annulus, but this relationship is reversed in people with HCM, indicating that longitudinal fibers may be more affected than circumferential fibers (Tabata et al. 2000). S' velocities are reduced in hypertrophied as well as nonhypertrophied regions (Tabata et al. 2000). There is no difference in systolic and diastolic TDI velocities in obstructive versus nonobstructive HCM. Postsystolic thickening is another indication of systolic impairment, which occurs when part of the left ventricular wall contracts after the end of the T wave while other parts of the ventricle undergo isovolumic

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relaxation in the beginning of diastole. Postsystolic thickening occurred in 6 of 23 cats with HCM in one study, providing additional evidence of systolic dysfunction in cats with HCM (Kaffas et al. 2006). Traditional estimates of systolic function such as ejection fraction or fractional shortening reflect global LV chamber function, which is altered by heart rate, hydration, and other preload-associated factors, rather than intrinsic myocardial contractility. Possible factors involved in reduced systolic myocardial velocity in HCM include subendocardial ischemia, myocyte disarray, heterogeneity of regional wall stress, and myocardial fibrosis (Tabata et al. 2000). It has been hypothesized that reduced myocardial systolic function may be an early abnormality in HCM, but the compensatory concentric LV hypertrophy overcomes the reduced contractile ability of the mutated cardiomyocytes (Marian et al. 1995). However, other studies have shown a hypercontractile state or normal contractility in certain sarcomeric mutations of familial HCM (Witt et al. 2001; Palmiter et al. 2000; Saito et al. 1987). Strain and strain rate imaging are new echocardiographic imaging methods based on color TDI ultrasound, devised to overcome pitfalls of overall heart motion, cardiac rotation, and contraction in adjacent segments encountered when using TDI measurement of tissue velocity. The rate of systolic ventricular wall deformation (strain) is another way to assess systolic myocardial function and can be done using color TDI and offline postprocessing programs. Systolic strain rate is decreased, indicating systolic myocardial failure, in people with HCM (Runqing et al. 2006; Ganame et al. 2007, 2008). Systolic function is impaired in hypertrophied and nonhypertrophied segments, as well as in regions of myocardial fibrosis evidenced as delayed enhancement on cardiac MRI, and it is correlated with reduced exercise capacity in people with HCM (Runqing et al. 2006; Ganame et al. 2007). Strain rate has been evaluated in normal cats (Wess et al. 2006). In summary, the findings of systolic dysfunction on TDI of cats with HCM, while provocative, remain preliminary, and are not sufficiently tested or validated in cats to justifiably influence treatment decisions or prognostication, nor imply or justify the use of positive inotropic agents for standard therapy of HCM in cats.

Advanced Cardiovascular Diagnostic Testing

Overview

Although not necessary to achieve a diagnosis, advanced imaging with cardiac magnetic resonance imaging has been done to quantify the severity of left ventricular hypertrophy and assess response to therapy for clinical trials.

A genetic screening test for cardiac myosin binding protein C is commercially available through the North Carolina State University College of Veterinary Medicine's Veterinary Cardiac Genetics Laboratory and may be used to screen Maine coon cats and Ragdoll cats in breeding programs. Cats may develop HCM despite negative tests, and cats with positive tests should be evaluated by echocardiography to assess whether there is phenotypic evidence of disease.

Neurohormones such as natriuretic peptides serve as useful circulating biomarkers for diagnosis of heart failure and may help justify whether further workup is needed, including echocardiography in asymptomatic cats to evaluate for cardiac disease. There are disparate findings regarding the utility of NT-proBNP as a screening test for asymptomatic cats with HCM (Hsu et al 2009; Fox et al. 2008). Hormonal assays including insulinlike growth factor-1 and growth hormone may be done in cats with left ventricular hypertrophy and clinical abnormalities consistent with acromegaly, but they are not recommended for routine use in cats with echocardiographic evidence of concentric hypertrophy of the left ventricle.

Markers of hemostasis, including thrombin-antithrombin complex, D-dimer, and FDP are invariably abnormal in cats with HCM and are not routinely necessary for clinical patients.

Cardiac magnetic resonance imaging (cMRI)

Key Points

- Cardiac MRI is the most accurate test to measure left ventricular mass in cats with HCM, making it the gold standard for quantification of severity of left ventricular hypertrophy, but it is limited to a research basis at this time.
- Limitations of cardiac MRI include an expensive imaging system with a 1.5 Tesla (or greater) magnet, a highly skilled operator with the ability to appropriately interpret images, expensive postprocessing software for quantification of left ventricular mass and function, and a requirement of a light plane of general anesthesia.
- Delayed enhancement may be identified in regions of myocardial fibrosis. Although 80% of people with HCM have evidence of delayed enhancement secondary to myocardial fibrosis, cats with HCM rarely have evidence of delayed enhancement on cardiac MRI and do not have different myocardial contrast enhancement than normal cats. Cardiac MRI does not appear to be useful to quantify myocardial fibrosis in asymptomatic cats with HCM.

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In human cardiology, cardiac MRI (cMRI) is frequently used to evaluate cardiac function, calculate LV mass, and assess regional wall motion abnormalities in various cardiomyopathies (Devlin et al. 1999; Soler et al. 2003; Rathi et al. 2004). Delayed gadolinium contrast enhancement is seen in regions of myocardial fibrosis in patients with diseases such as HCM (Moon et al. 2003, 2004; Choudhury et al. 2002). Advantages of cMRI over echocardiography include independence from an acoustic window, limitless imaging planes, no translational artifacts, more accurate 3-dimensional data acquired for determination of intracardiac volumes and myocardial mass, ability to detect myocardial fibrosis or infarction via contrast enhanced imaging, information on myocardial perfusion, and more comprehensive visualization of cardiac and vascular structures (Devlin et al. 1999; Grothues et al. 2002; Bogaert et al. 2003). Major limitations of cMRI in veterinary medicine are the requirement for general anesthesia for image acquisition, the high cost, a lack of experience in obtaining and analyzing cMRI, and lack of efficient semiautomated image analysis. Currently, cMRI in animals is limited to cardiovascular research settings.

Technique of cardiac MRI in cats

In order to perform cMRI with high spatial and temporal resolution, a state-of-the-art MRI machine is necessary. Cardiac MRI requires a strong magnetic field of at least 1–1.5 Tesla, which allows for high temporal resolution at fast heart rates. Strong and fast gradient coils (15 mT/m) are necessary. Surface phased array receiver coils may be useful to define a smaller field of view (FOV), improve signal to noise ratio (SNR), and improve spatial resolution in small animals.

Electrocardiographic (ECG) gating is mandatory for adequate image acquisition. With ECG gating, image acquisition is synchronized to occur during the same instant of the cardiac cycle for several hundreds of consecutive heartbeats. This "snapshot" approach delivers hundreds of static images throughout the cardiac cycle of the beating heart. Without ECG gating, the cardiac motion would render an MRI image uninterpretable, in contrast to an MRI image of a static structure (e.g., brain) wherein gating is not needed. Obtaining a quality ECG tracing for proper ECG gating on the R wave is a common initial obstacle in cats because of their small QRS complexes. In people, 2–5% of cases have an unreliable ECG signal, and triggering must be based on peripheral pulse gating. The ventral surface of veterinary patients must be shaved before MRI compatible specialized ECG electrode pads (Quatrode®, In Vivo Research, Inc.) are placed. Electrode position may vary between patients, but generally the optimal placement in cats is in a rectangular arrangement on the ventral surface of the cat with 2 leads placed cranially at the level of the heart just to the left and right of the sternum, and 2 caudal leads placed in the left and right ventral caudal abdomen, with maximal space between the cranial and caudal leads. The lead with the highest amplitude R wave is chosen for gating. If S waves have greater amplitude than R waves, that lead may be selected and inverted. The pulsed gradient fields may distort the ECG once the patient has been placed inside the MRI machine, and respiration often induces significant ECG artifact. ECG gating compensates for cardiac motion and synchronizes image acquisition to the cardiac cycle. Prospective ECG gating is routinely used with fast gradient echo sequences, but it may not acquire the first 10% and the last 20% of the cardiac cycle. For diastolic function studies, a retrospective ECG gating technique using cine pulse sequence should be utilized that acquires data regardless of the ECG and then retrospectively calculates the appropriate cardiac phases based on the stored ECG and imaging data. If ECG gating is impossible, peripheral pulse gating from the lingual artery may be used, where gating should occur on the sharp upstroke of the arterial flow tracing.

Spin echo and gradient echo techniques are the two main pulse sequences used in cMRI. The spin echo technique is often used for examining cardiac anatomy, where the blood pool is black and the myocardium is white (hyperintense). Spin echo is often utilized to evaluate for arrhythmogenic right ventricular cardiomyopathy, where fatty infiltration of the myocardium is better identified (Tandri et al. 2003). Gradient echo and cine MRI are often used for cardiac function analysis, where the blood pool is white and the myocardium is dark gray. The three major sources of artifact with cMRI are respiratory motion, blood flow artifact from rapid or slow flowing blood, and cardiac motion. Turbulent blood flow creates a signal void (black) when using gradient echo sequencing. ECG gating and a fast acquisition rate reduce cardiac motion artifact. Breath-hold imaging (at end-expiration) negates respiratory artifact.

During image acquisition, three-plane spatial localizing images are first obtained, depicting the heart in sagittal, transverse, and frontal views. With the patient in dorsal recumbency, the long-axis of the heart is oriented obliquely to the localizing imaging planes. The sagittal view often resembles the lateral view of a thoracic radiograph, where the LV apex and left atrium are visualized. Initially a long-axis view is acquired primarily from the sagittal view where a line is placed connecting the LV apex and the center of the mitral valve, and slices are adjusted to bisect the midleft ventricular level at the 2–3 o'clock position of the heart on the frontal or cross-sectional view. Appropriate 4-chamber long-axis views depict a symmetrical LV with adequate visualization of

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the basilar interventricular septum and the maximal length of the LV (Figure 11.21). Short-axis slices are then acquired perpendicular to the long-axis, from just above the mitral annulus to below the apex (see Figure 11.21). Short-axis views are used for endocardial and epicardial tracings to quantify LV intracardiac volume and LV mass. LV mass is calculated using Simpson's rule. The endocardial and epicardial borders are traced on slices from base to apex at a defined phase of the cardiac cycle (Figure 11.22). LV myocardial volumes are summated, and multiplied by myocardial density (1.05 g/cm^3) to obtain LV mass. There is semiautomated edge detection software that enables faster quantification of LV mass or ventricular volumes, but this feature comes at a significant financial expense.

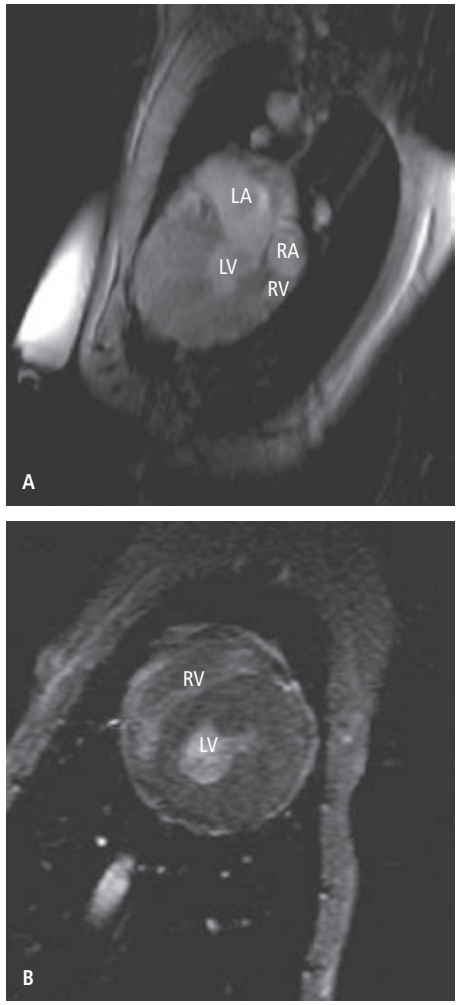


Figure 11.21. Four-chamber long-axis view and short-axis view of the heart of a cat with hypertrophic cardiomyopathy using cardiac magnetic resonance imaging. A 4-chamber long-axis view **(A)** of the heart in this cat with severe HCM is acquired by prescribing an imaging axis from the sagittal and coronal localizer views. Slices are placed perpendicular to the long-axis to obtain the short-axis view **(B)**. There is massive concentric hypertrophy of the anterior free wall of the left ventricle, and papillary hypertrophy. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Cardiac MRI for left ventricular mass quantification

Cardiac MRI (cMRI) has been shown to be the most accurate method of noninvasive LV mass quantification in normal people and people with HCM, as well as in animals as small as mice (see Figure 11.22) (Soler et al. 2003; Franco et al. 1998). There is good agreement between cMRI calculated LV mass and actual LV mass in dogs and people, with a mean difference of 4.4 and 10 grams for mean LV masses of 87 g and 190 g, respectively (Myerson et al. 2002; Katz et al. 1988). cMRI using Simpson's rule more accurately quantifies LV mass in normal people and people with HCM than using 3-dimensional echocardiography (with Simpson's rule), biplane MRI, or biplane echocardiography (Devlin et al. 1999). Whether using cMRI or echocardiography, Simpson's rule more accurately quantifies LV mass in people than geometric models, especially in people with HCM. cMRI allows better complete visualization of the LV and better morphologic assessment of degree and extension of LV hypertrophy in humans with HCM. For example, one study found that LV wall thickness could be measured in only 67% of myocardial segments using echocardiography, versus 97% of LV segments using cMRI (Pons-Llado et al. 1997). cMRI also has been shown

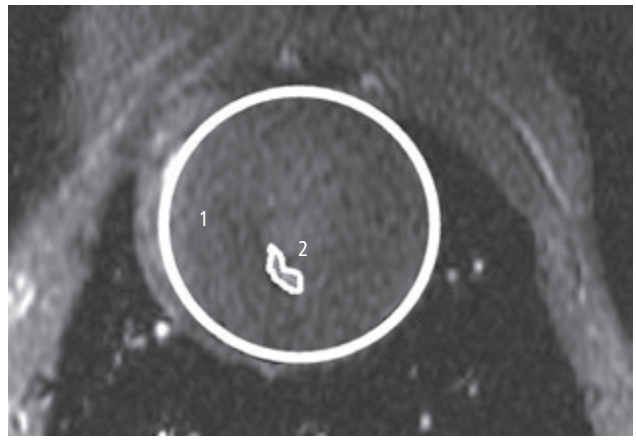


Figure 11.22. Endocardial and epicardial tracing to quantify myocardial mass in a cat with hypertrophic cardiomyopathy using cardiac magnetic resonance imaging. Endocardial (2) and epicardial (1) borders are manually traced at end-systole for all slices extending from the mitral annulus to the apex. Myocardial area is the difference between epicardial and endocardial area and is multiplied by slice thickness to determine myocardial volume. Total myocardial volume is the sum of myocardial volumes of each slice, and is then multiplied by the density of muscle (1.05 g/cm^3) to determine LV mass.

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to accurately quantify LV mass in animal models of LV hypertrophy including experimental canine aortic stenosis and a transgenic mouse model of LV hypertrophy (Franco et al. 1998; Wang et al. 1990). Results of cMRI are also highly reproducible, with much lower inter- and intraobserver variability than echocardiography (7.8 grams vs 19.2 grams mean weighted interstudy standard deviation) in normal people and patients with LV hypertrophy (Grothues et al. 2002). Studies that quantified LV mass in dogs and normal people have found similar low intraobserver error (0.4% and 4%, respectively) and interobserver error (5.8% and 4%, respectively) (Fieno et al. 2002). Similarly, there was extremely low intraobserver and interobserver variability of 2% for cMRI quantification of left ventricular mass in cats (MacDonald et al. 2004). With the higher accuracy and reproducibility of cMRI, the number of subjects needed to obtain meaningful data is dramatically reduced. For example, in one study the sample size necessary to demonstrate a 10 gram change in LV mass in people with LV hypertrophy was 15 patients with cMRI versus 152 patients with echocardiography (Grothues et al. 2002).

An unexplored area of research is the use of cMRI to evaluate LV variables over time to assess whether pharmaceutical interventions cause significant changes in patients with cardiomyopathy (Hoffmann et al. 2001). cMRI has been proposed as the gold standard for measuring regression of LV mass in people (Hoffmann et al. 2001; Rajappan et al. 2003). Regression of LV mass following aortic valve replacement in patients with aortic stenosis was evaluated in one study by cMRI and by echocardiography using M-mode measurements. cMRI identified a regression of LV mass in all patients 1 year after valve replacement, while M-mode echocardiography failed to accurately identify the regression in these individuals. Using cMRI for LV mass quantification, there was no regression in concentric hypertrophy in 26 asymptomatic Maine coon cats with familial HCM that were treated with ramipril for 12 months (MacDonald et al. 2006b). The use of cMRI provides more accurate assessment of LV mass with less variability in measurements than echocardiography and allows for fewer patients needed while maintaining a powerful study.

Assessment of myocardial fibrosis with cardiac MRI

Contrast enhancement cMRI is a noninvasive technique used to identify myocardial fibrosis or necrosis in various cardiac diseases. A low molecular weight paramagnetic contrast agent is administered intravenously, distributes to the myocardium, and is reabsorbed by the capillary bed to be excreted by the kidneys. In regions of abnormal myocardium, the contrast agent accumulates in the extracellular (interstitial) space and has a slow washout period (6–20 minutes). In cardiac fibrosis, the extracellular space is expanded due to the loss of myocytes and the presence of collagen. The expanded extracellular space results in pooling of the gadolinium and slow washout in this region. Using T1-weighted images, delayed enhancement (DE) is a hyperintense (bright) appearance of the myocardium where contrast medium has accumulated.

DE-cMRI has been used in human patients as well as cats with HCM to noninvasively assess the presence of myocardial fibrosis (Figure 11.23) (Moon et al. 2004; Choudhury et al. 2002; Wilson et al. 2002). A majority of asymptomatic to mildly symptomatic human patients (80%) have evidence of DE of the hypertrophied regions of the LV, with a patchy to multifocal distribution, predominantly involving the middle third of the LV wall (Choudhury et al. 2002). Histologic studies have confirmed that regions of DE correspond to regions of myocardial fibrosis in people with HCM (Moon et al. 2004). Given the spatial resolution of contrast cMRI, replacement fibrosis is the most likely type of fibrosis detected. Detection of diffuse interstitial fibrosis by DE is more limited since the technique is sensitive to regional differences in gadolinium accumulation. DE is seen in fewer than 50% of patients with dilated cardiomyopathy where there is diffuse interstitial fibrosis (McCrohon et al. 2003). DE-MRI has also been performed in Bio 14.6 cardiomyopathic hamsters, which have regions of

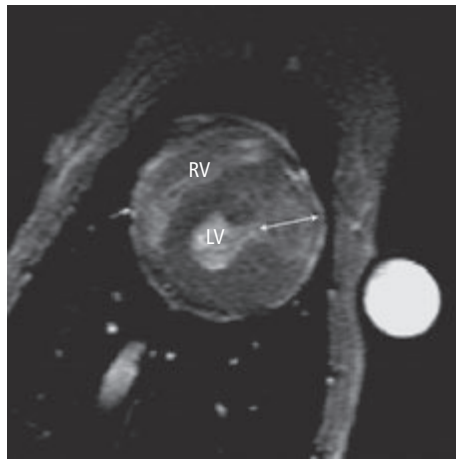


Figure 11.23. Delayed enhancement seen on cardiac magnetic resonance imaging in a cat with severe hypertrophic cardiomyopathy.

Approximately 7–10 minutes after administering intravenous gadolinium, postcontrast cross-sectional images are obtained of the left ventricle to evaluate for delayed enhancement (DE). There is a large region of DE (i.e., a bright, hyperintense region) of the anterior left ventricular free wall, indicating myocardial fibrosis (arrow). The DE occurred at the most severely hypertrophied region of the left ventricle (LV) in this cat with severe HCM. The hyperintense circle to the right is a reference marker. RV = right ventricle.

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DE that correspond to histopathologic regions of replacement and interstitial fibrosis, and inflammation (Nanjo et al. 2002). Assessment of myocardial fibrosis may yield important clinical information such as risk of development of CHF or sudden cardiac death in patients with HCM. Regional heterogeneity of diastolic function has been diagnosed by cMRI, and occurs in regions of extensive fibrosis. The extent of DE is highly correlated with extent of diastolic dysfunction in people with HCM.

Delayed enhancement cardiac MRI in cats with HCM

Currently, there are no noninvasive methods to assess the extent of myocardial fibrosis in cats. Circulating biomarkers of collagen synthesis and degradation (collagen type I terminus (ICTP), procollagen type I (PINP), and procollagen type III) were measured using a radioimmunoassay (Orion Diagnostica, Finland), and were not significantly elevated in asymptomatic Maine coon cats with mild to severe HCM compared to normal cats (author's unpublished data). Assessment of myocardial fibrosis using DE-MRI and calculation of myocardial contrast enhancement has been performed in 26 Maine coon cats with mild to severe HCM without heart failure and 10 normal control cats (MacDonald et al. 2005). Only one cat with HCM had obvious evidence of DE (see Figure 11.23), and there was no difference in myocardial contrast enhancement between normal cats and cats with HCM. Therefore, contrast cMRI appears to be minimally useful to evaluate for evidence of myocardial fibrosis in asymptomatic Maine coon cats with familial HCM, since presence of delayed enhancement is rarely seen in these cats.

Assessment of diastolic function by cardiac MRI

cMRI is an accurate noninvasive tool for quantifying LV mass and assessing left and right ventricular function in normal people and people with cardiac diseases including dilated cardiomyopathy, HCM, hypertensive cardiac disease, and aortic stenosis (Kudelka et al. 1997). Diastolic function may be assessed using cine or gradient echo cMRI (Figure 11.24), velocity encoded cine cMRI, and myocardial tagging techniques. For the cine or gradient echo assessment of cardiac function, short-axis images are acquired extending from the mitral annulus to the apex over multiple phases of the cardiac cycle (18–25 phases, depending on heart rate). The endocardial border is manually or semiautomatically traced using a specialized program (MASSPlus®, Netherlands). Papillary muscles are included within the tracing. LV volume is the sum of the endocardial volumes of all slices. LV volume versus time in cardiac cycle is plotted, interpolated, and smoothed between measurement points (see Figure 11.24). End-systolic and end-diastolic volume (ESV and EDV) are defined by the smallest and largest volumes on the plot, respectively. Stroke volume (SV) is calculated by subtracting ESV from EDV, and cardiac output (CO) is the product of SV and heart rate. Cardiac index equals CO/body surface area (m^2). The first derivative of vol/time is then calculated, which produces the graph dV/dt (see Figure 11.24). From this plot, cMRI indices of diastolic function are obtained and include peak early filling rate within the first half of diastole (ml/s), peak late filling rate within the last half of diastole, peak filling rate, average filling rate, early filling percentage (volume increase from end-systole to midpoint of diastole/SV × 100), time to peak early filling, and early to late filling rate ratio.

Gradient echo cMRI was insensitive to detect diastolic dysfunction in 7 Maine coon cats with moderate to severe HCM without heart failure (MacDonald et al. 2006a). PW TDI identified diastolic dysfunction in all cats with HCM, but there was no difference in the cardiac MRI indices of diastolic function in normal and HCM cats. It is possible that other techniques of diastolic function quantification by cardiac MRI such as velocity encoded cine would be able to identify diastolic dysfunction in cats with HCM, but no studies have evaluated other cMRI techniques in cats. There are few cMRI studies assessing diastolic function in humans with HCM (Jarvinen et al. 1996). One study examined 24 patients and 10 normal volunteers and identified that there was regional early diastolic dysfunction in people with HCM, with greater diastolic impairment in patients with greater LV mass (Yamanari et al. 1996). Left atrial volume was increased in mildly symptomatic patients with HCM, and both left and right atrial filling and emptying rates were reduced (Jarvinen et al. 1996). Increased LV stiffness may reduce atrial emptying rates, and increased atrial stiffness may reduce atrial filling rates.

One disadvantage of the gradient echo sequence, which is often used for cMRI, is that it employs prospective ECG gating, where no images are acquired during the brief trigger delay at the R wave and a short trigger window preceding the R wave. Prospective gating may result in a loss of early systolic and late diastolic images, which may impact functional analysis. Velocity encoded cine cMRI is an attractive alternative to gradient echo cMRI for cardiac function studies, since it employs retrospective gating throughout the cardiac cycle. Velocity encoded cine is a novel technique that encodes the velocity of moving blood cells to the phase of the MR signal. Red blood cells undergo a shift in magnetic spin as they move along the magnetic field gradient relative to the myocardium. Black and white correspond to the directionality of the flow. Flow is summated throughout the cardiac cycle. The amount of time required for image analysis is reduced compared to cine MRI since images

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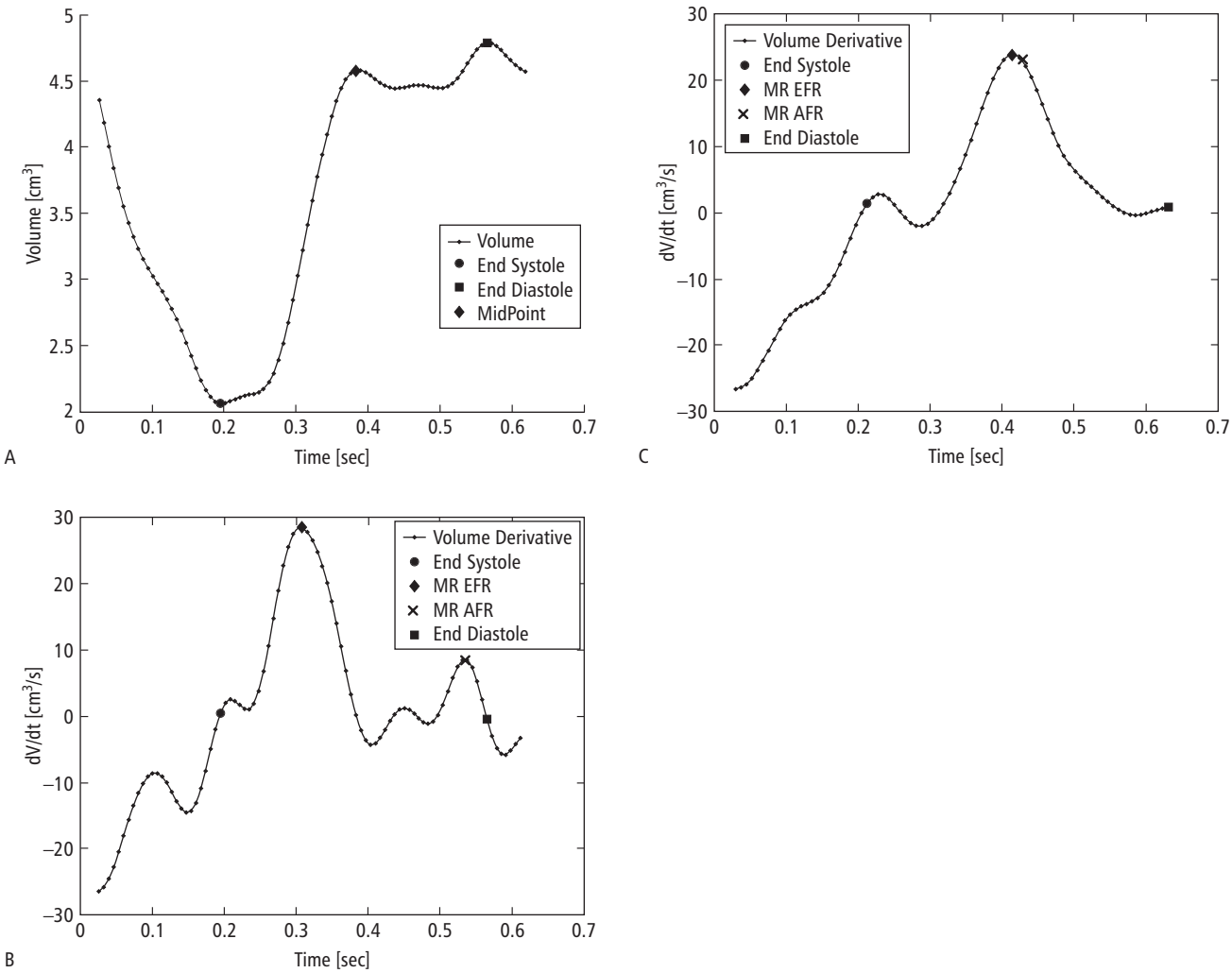


Figure 11.24. Assessment of diastolic left ventricular function by cardiac magnetic resonance imaging and Simpson's rule. Left ventricular volume is summated throughout the cardiac cycle and plotted versus time **(A)**. End-systolic and end-diastolic volumes, stroke volume, cardiac output, cardiac index, and early filling percentage are then calculated. The first derivative is obtained and plotted as dV/dT **(B)** to determine peak diastolic filling rate, mean diastolic filling rate, early diastolic filling rate (EFR), and late diastolic filling rate (AFR). Normally, the peak diastolic filling rate occurs in early diastole. Both **(B)** and **(C)** are obtained from cats with HCM. The cat in (B) has a normal diastolic filling profile where the peak diastolic filling rate is greatest in early diastole, but the cat in (C) has abnormal diastolic function, with equal early and late diastolic filling rates.

are acquired from only one slice placed below and parallel to the mitral annulus. Velocity encoded cine may also be applied to quantify myocardial velocities over the cardiac cycle, and myocardial strain rates may be calculated. There are no velocity encoded cine studies evaluating diastolic function in people with HCM. The majority of the velocity encoded cine studies have involved aortic stenosis or aortic insufficiency. In patients with aortic stenosis and compensatory concentric LV hypertrophy, velocity encoded cine has been used to detect an increased atrial contribution to LV filling, indicating a restrictive pattern of diastolic dysfunction (Hartiala et al. 1994).

Other advanced cMRI techniques for quantification of diastolic function include regional wall thinning rate and myocardial tagging to assess regional myocardial function and quantify myocardial strain and torsion (Rathi et al. 2004). Early diastolic impairment (i.e., a reduced early diastolic strain rate) was identified in humans with familial HCM using cMRI tagging (Ennis et al. 2003). Impaired regional LV contractility and systolic LV wall asynchrony has also been identified in people with HCM using cMRI tagging (Ennis et al. 2003; Mishiro et al. 1999). Overall, there are limited potential clinical applications for the use of cMRI to assess diastolic function at present, both because of the general limitations of cardiac MRI in veterinary patients and because of effects of general anesthesia on cardiac function.

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Genetic Screening Test (see Chapter 28)

Key Points

- Cardiac myosin binding protein C mutations (MYBPC3) have been found to cause HCM in some families of Maine coon cats and Ragdoll cats
- A genetic screening test for MYBPC3 mutation is commercially available for Maine coon cats and Ragdoll cats and may be useful for breeding programs. No other breeds have yet to be identified with a causative mutation.
- An echocardiogram is necessary in cats positive for the mutation, to evaluate whether there are phenotypic abnormalities or whether the cat is a carrier.
- Purebred cats may develop HCM without possessing the MYBPC3 mutation, so a negative test does not exclude the possibility that cat may have HCM.

Two sarcomeric mutations of the myosin binding protein C gene (MYBPC3) have been discovered to cause familial HCM in some Maine coon cats and Ragdoll cats. Each breed has an exclusive mutation, not found in other breeds of cats tested. The mutations result in a change in conserved amino acids and altered computed structure of myosin binding protein C (Meurs et al. 2005). There is an incomplete penetrance of the gene, so some positive cats may be carriers that do not develop the abnormal phenotype of concentric left ventricular hypertrophy. Likewise, some Maine coon cats or Ragdoll cats have phenotypic evidence of HCM without a positive genetic screening test, indicating that there are likely other mutations or factors that cause HCM. The MYBPC3 mutation screening is recommended for Maine coon cats and Ragdoll cats intended for breeding (see Chapter 28). There is a prevalence of 34% of genetically affected asymptomatic Maine coon cats in the general breeding population (Fries et al. 2008). Given this high prevalence, rapid removal of all genotypic positive cats could result in a bottleneck effect with concentration of other abnormalities, so geneticists have recommended a slower removal through breeding only negative progeny if possible, or for exceptional cats that are heterozygous positive and echocardiographically normal, breeding those cats to negative cats and over a few generations gradually selecting negative kittens for replacement (see Chapter 28). Any cat testing positive for the mutation should be examined by a cardiologist and an echocardiogram done to assess the clinical status of the cat. Repeat echocardiograms are recommended every 6–12 months in asymptomatic genotype positive cats to identify whether phenotypic evidence of HCM is present and whether treatment is indicated. The MYBPC3 mutation analysis is performed at the North Carolina State University College of Veterinary Medicine's Veterinary Cardiac Genetics Laboratory (www.cvm.ncsu.edu/vhc/csds/vcgl/index.html). A buccal mucosal swab using a special test kit provided by the laboratory or preferably whole blood (1–1.5 ml) collected into an EDTA tube can be submitted for mutation analysis. Genetic screening of Maine coon or Ragdoll cats related to a cat with confirmed HCM is also recommended, and they may also benefit from further evaluation with an echocardiogram.

Circulating Biomarkers (see Chapter 8)

Key Points

- Amino-terminal pro-brain natriuretic peptide (NT-proBNP) is a sensitive and accurate screening test for detection of heart failure in cats with cardiomyopathy, and may be used to help distinguish whether the dyspnea is caused by heart failure or primary respiratory disease.
- NT-ProBNP appears to be useful as a screening test to detect cardiomyopathy in asymptomatic cats, but there may be false negatives and false positives.
- There are mixed results on the usefulness of cardiac troponin I and endothelin-1 for detection of heart disease or heart failure in cats with HCM.

Natriuretic peptides

The natriuretic peptide family includes atrial, brain (B-type), and C-type, D-type, and V-type natriuretic peptides. Natriuretic peptides are considered beneficial neurohormones that counterregulate the renin-angiotensin-aldosterone system (RAAS) and endothelin-1. Independent of their biological activity, they are produced specifically by cardiac chambers that are stretched or overfilled, and as such, they have emerged as useful biomarkers to identify heart disease in people and animals (Maisel et al. 2003; Oyama et al. 2009; Chetboul et al. 2009; Fine et al. 2008; Fox et al. 2009; Connolly et al. 2009). In human medicine, they also serve as negative prognostic indicators for early cardiovascular mortality and levels are often monitored to help tailor heart failure treatment (Porapakkham et al. 2010; Troughton 2000; Koglin et al. 2001). Likewise, brain natriuretic peptide elevations are an independent predictor of cardiovascular mortality in dogs with symptomatic mitral valve degeneration (Moonarmart et al. 2010; Serres et al. 2009). Brain natriuretic peptide (BNP or B-type) is normally synthesized in the atria in cats, and there is a novel ventricular synthe-

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sis in response to increased ventricular wall stress or other neurohormonal stimulation such as endothelin 1 (Yasue et al. 1994; Biondo et al. 2003). Atrial natriuretic peptide (ANP or A-type) is synthesized in the atria in response to volume overload and increased wall stretch, but BNP appears to have a greater diagnostic potential than ANP given its greater degree of elevation in cardiac disease and congestive heart failure in cats (Sisson 2004). In people with HCM, there is increased ventricular BNP and ANP content in regions of myocardial fibrosis, hypertrophy, and myocyte disarray (Hasegawa et al. 1993). Amino terminal pro-brain natriuretic peptide (NT-ProBNP) offers the most promise of all neurohormonal biomarkers for detection of heart failure in cats, and likely for detection of heart disease in cats (see Chapter 8).

Atrial and brain natriuretic peptides have similar biologic effects of diuresis, natriuresis, selective dilation of the afferent renal arterioles with subsequent increased glomerular filtration rate, and vasodilation leading to reduction in pulmonary capillary pressure, mean right atrial pressure, systemic and pulmonary vascular resistance, pulmonary artery pressure, and increased cardiac index and coronary blood flow (Mills et al. 1999). Natriuretic peptides also inhibit release of renin and endothelin I, causing secondary decreases in angiotensin II and aldosterone (Nakao et al. 1992). Ancillary properties of ANP and BNP include antifibrotic and antihypertrophic effects in the renal mesangial cells, cardiac fibroblasts, cardiomyocytes, and endothelial cells.

Plasma brain natriuretic peptide concentration ([BNP]) is a sensitive biomarker for cardiac disease and heart failure in people and in animals. [BNP] is elevated in both systolic and diastolic dysfunction, and it is further elevated proportional to the severity of heart failure in people. Plasma [ANP] is moderately elevated and [BNP] is markedly elevated in people with HCM (Mizuno et al. 2000; Briguori et al. 2001). Although initially thought to be released only from atrial stretch, it is now known that ANP is synthesized in the ventricles of people with heart failure and asymptomatic people with HCM (Ogino et al. 2004). Increased plasma [ANP] and [BNP] are due to increased LV synthesis in people with HCM and are correlated with diastolic dysfunction but not with left atrial dimension (Ogino et al. 2004). Although higher than normal, plasma [BNP] in patients with HCM was fourfold less than patients with idiopathic dilated cardiomyopathy (DCM) (94 pg/ml versus 418 pg/ml, respectively) in one study (Mizuno et al. 2000). A possible explanation for the much greater degree of BNP elevation in DCM is that there is greater wall stress in DCM when compared to HCM. [ANP] and [BNP] were minimally correlated to LV mass in one study ($r = 0.36$ and $r = 0.32$, respectively), and were not correlated to left ventricular mass index in another study (Mizuno et al. 2000). It is likely that stimuli such as neurohormones (angiotensin II and ET-1), in addition to hypertrophy, induce BNP synthesis in patients with HCM. [BNP], but not [ANP], is highly correlated with degree of LV ventricular outflow tract obstruction, which is understandable given that BNP secretion is partially load dependent (Hasegawa et al. 1993). To no surprise, plasma concentrations of both natriuretic peptides are higher in people with HCM and evidence of diastolic dysfunction on Doppler echocardiography compared to normal individuals (Ogino et al. 2004). Similarly, [BNP] and [ANP] are moderately correlated with LV end-diastolic pressure in patients with HCM ($r = 0.69$ and $r = 0.51$, respectively), which is a reflection of the severity of diastolic dysfunction (Mizuno et al. 2000). In patients with asymptomatic HCM but without SAM, measurement of [BNP] but not [ANP] is predictive of exercise-induced myocardial ischemia (Nakamura et al. 2002).

The undeniable appeal of cardiac biomarkers is the potential to assess the heart using a blood sample and detect various degrees of heart disease and heart failure. The only commercially available (Cardiocare by IDEXX Laboratories) and clinically applicable assay in cats is a rapid sandwich ELISA to measure the inactive fragment amino-terminal ProBNP (NT-ProBNP). The principal application of NT-proBNP testing is the differentiation of congestive heart failure from noncardiogenic disorders (i.e., primary respiratory disease) in cats with acute dyspnea. Initial data appear very promising for screening for heart failure, but its use for screening asymptomatic cats with cardiac disease is less clear because there are variable results and lower sensitivity. NT-proBNP has a longer circulating half-life than BNP, which may increase its sensitivity for detection of heart disease or failure. NT-proBNP is useful to discriminate between heart failure and primary respiratory disease in cats, with a high sensitivity of 90% and a specificity of 86–88%. It also may be useful to screen for cardiac disease in asymptomatic cats, but the sensitivity is likely less than when screening for heart failure. In a small pilot study of 23 asymptomatic cats with various cardiomyopathies (mostly HCM), NT-proBNP was highly sensitive (88%) and specific (100%) for detection of heart disease (Fox et al. 2008). Oppositely, NT-proBNP was not elevated, using the same assay as the study aforementioned, in any asymptomatic Maine coon cat with mild to moderate HCM ($n = 21$) compared to normal cats ($n = 9$), but was elevated in asymptomatic cats with severe HCM ($n = 10$) compared to normal cats, mildly affected cats, or moderately affected cats, with a high sensitivity and specificity for diagnosis of HCM (90%

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and 83%, respectively) (Hsu et al. 2009). Elevated plasma [BNP] does not define the type of heart disease present, nor the presence or absence of secondary cardiac changes such as atrial enlargement or SAM of the mitral valve. Elevated plasma [BNP] is also not specific for heart disease, since some normal cats have an elevated plasma NT-proBNP, but raises the suspicion that heart disease may be present. A substantial degree of overlap in plasma levels exists between normal and mildly abnormal cats, and a plasma NT-proBNP measurement cannot be considered a substitute for a complete cardiac evaluation, nor as a stand-alone screening test for HCM in the cat.

Other pertinent areas of future research need to explore the utility of NT-proBNP for monitoring disease progression, guidance of pharmacologic therapy, and potential use as a prognostic indicator as it is in humans. NT-proANP appears to be less useful than NT-proBNP for detection of HCM in asymptomatic cats, as plasma levels are not elevated in cats with HCM compared to control cats (MacLean et al. 2006).

Cardiac troponin I

Cardiac troponin I (cTnI) is released from cardiomyocytes when they are damaged. Unlike ANP and BNP, cardiac troponins are not species-specific; the molecular structure is the same across mammalian species. Cardiac troponins are entirely distinct from skeletal troponins, and therefore skeletal muscle injury or inflammation does not cross-react with cTnI tests. Cardiac troponin-I appears to be the more sensitive test (providing greater accuracy), compared to the cTn-T test that preceded its development. Serum cardiac troponin I (cTnI) has been studied in cats with cardiomyopathy and heart failure, and it has been shown to be a sensitive biomarker for heart disease in cats (sensitivity 87%, specificity 84%) but did not distinguish cats that were symptomatic from asymptomatic cats (Connolly et al. 2003). Another study found contradictory results, with increased cTnI in asymptomatic cats with cardiomyopathy, and that was further increased in symptomatic cats with heart failure (Herndon et al. 2002). Normal reference ranges are not interchangeable between the different cTnI sandwich assays, because the five commercially available cTnI assays evaluate five different areas of the molecule using proprietary technology. Therefore, when interpreting a cTn-I result in any species, the reference range for the instrument used in the analysis must be provided. A positive cTnI value obligates the clinician to identify potential cardiac disease by reviewing the history for potential trauma or illness leading to myocarditis and the history of heart disease in the individual or family, and typically by also performing an echocardiogram and an electrocardiogram.

Endothelin I

Endothelin 1 (ET-1) is a potent vasoconstrictor that also exerts other deleterious effects including cardiomyocyte hypertrophy and activation of cardiac fibroblasts. ET-1 levels are increased in people with heart failure, and they increase with severity of heart failure. Increased ET-1 was associated with a higher 1-year mortality in people with chronic heart failure. Only one study has evaluated plasma ET-1 levels in cats with various cardiomyopathies; most had HCM (Prosek et al. 2004). ET-1 was increased in asymptomatic cats with cardiomyopathy (11/12 cats had HCM) compared to normal cats, and in cats with heart failure compared to normal cats, but was not different between asymptomatic cats and symptomatic cats. No cut-off values or sensitivity and specificity calculations were made. There appeared to be considerable overlap in ET-1 concentrations between individual cats in the normal group and the asymptomatic cardiomyopathy group. Given the lack of ability to distinguish asymptomatic cardiomyopathic cats from cats with heart failure or arterial thromboembolism, it is likely that other biomarkers such as NT-proBNP are more clinically useful than ET-1 in cats.

Other Laboratory Tests

Serum growth hormone

Key Points

- Serum growth hormone levels may be mildly increased in cats with HCM, but they are much higher in cats with acromegaly. The increase in growth hormone in HCM is not likely a primary factor in development of concentric ventricular hypertrophy.
- Serum insulin like growth factor-1 ± growth hormone levels should be measured in cats with concentric hypertrophy of the left ventricle and clinical abnormalities suggestive of acromegaly.

Growth hormone exerts an endocrine effect on the heart by inducing cardiomyocyte growth, which leads to concentric ventricular hypertrophy in people and cats with acromegaly. Growth hormone also increases calcium sensitivity of the cardiac myofilaments and increases calcium content within cardiomyocytes, which increases contractility. Given the known relationship of growth hormone and insulinlike growth factor-I to hypertrophic cardiac remodeling, serum growth hormone was mea-

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sured in 31 cats with HCM, 38 normal cats, and 35 cats with other cardiac disease. Sixty percent of cats with HCM and 18% of normal cats had increased serum growth hormone concentrations (Kittleson et al. 1992). Serum growth hormone levels were higher in cats with HCM compared to normal cats or cats with other cardiac diseases. The increase in growth hormone in cats with HCM was considered mild compared to markedly elevated growth hormone levels in cats with acromegaly. No cats with HCM had evidence of pituitary tumors on necropsy, and none had clinical evidence of acromegaly. Other factors are likely present in cats with HCM that stimulate release of growth hormone. In contrast to the previous study, another study found that although cats with HCM often have larger body size (i.e., larger somatotype) than normal cats, IGF-1 levels in these cats were not increased compared to normal cats (Yang et al. 2008).

Insulinlike growth factor-1 and growth hormone should be measured in any cat with concentric left ventricular hypertrophy and clinical suspicion of acromegaly. Typical clinical signs of acromegaly include insulin-resistant diabetes mellitus; increased soft tissue growth of the viscera, tongue, cartilage and nasal tissue; and increased bony formation often of the calvarium, mandible, and vertebrae (Peterson et al. 1990). Cats with elevated IGF-1 and GH should be further evaluated with by cranial imaging by computed tomography or magnetic resonance imaging to assess presence of a pituitary mass. Echocardiography reveals concentric hypertrophy of the left ventricle in a majority of cats diagnosed with acromegaly. Concentric hypertrophy of the left ventricle may regress in acromegalic cats treated with pituitary irradiation or medical therapy to suppress growth hormone secretion. Overall, the significance of elevated serum growth hormone levels in feline HCM remains a matter of speculation, and elevated levels do not necessarily imply that they are causative of HCM, but may represent a secondary change.

Hemostatic markers

Key Points

- A thrombus may form secondary to vascular stasis, endothelial disruption, or hypercoagulability (i.e., Virchow's triad).
- Asymptomatic cats with HCM do not have strong evidence of a hypercoagulable state.
- Half of cats with spontaneous contrast, left atrial thrombus, or arterial thromboembolism are hypercoagulable.

Cats diagnosed with HCM may be at increased risk of developing arterial thromboembolism (ATE), especially if there is significant left atrial dilation (see Chapter 20). Twelve to seventeen percent of cats diagnosed with HCM have a chief complaint of ATE, but no studies have evaluated the incidence of ATE in HCM cats over their lifetimes (Rush et al. 2002; Atkins et al. 1992). In one study of ATE in cats, the left atrium was severely enlarged in 57%, moderately enlarged in 14%, and mildly enlarged in 22%, with only 5% having a normal left atrial size (Laste and Harpster 1995). Thrombus formation may develop when there is an abnormality in one or more of the components of Virchow's triad, which consists of hypercoagulability, endothelial disruption, and blood stasis. Hypercoagulability may occur when there is an imbalance or excess of coagulation factors (Factor VII and fibrinogen) and/or a deficiency of coagulation inhibitors, and is characterized by increased products formed during thrombin generation (prothrombin fragment 1 and 2), increased products generated by increased thrombin activity (fibrinopeptide A, thrombin-antithrombin complex (TAT)), or products generated by fibrinolysis (D-dimer and fibrin degradation products [FDP]). Abnormalities of two or more coagulation parameters are typically necessary to classify a hypercoagulable state, and elevation in only one parameter is suggestive. Forty-five percent of asymptomatic cats with HCM had suspected evidence (but not strong evidence) of hypercoagulability based on elevated TAT or D-dimer (Bedard et al. 2007). In contrast, another study reported no evidence of hypercoagulability in 11 asymptomatic cats with cardiomyopathy and left atrial dilation (Stokol et al. 2008). The same study reported that half of cats with spontaneous contrast or a thrombus within the left atrium or with overt arterial thromboembolism were hypercoagulable. However, only 50% of cats with overt ATE had increased D-dimer, making it an insensitive test to detect presence of thromboembolism in these cats. Coagulation parameters (TAT, D-dimer, FDP) were evaluated and no correlation was observed with left atrial size in either study.

Conclusive Diagnosis of HCM

Echocardiography is necessary to establish the diagnosis of HCM in cats. Presence of clinical signs, a murmur or gallop, radiographic evidence of cardiomegaly, or electrocardiographic abnormalities are variable and often absent. Left ventricular concentric hypertrophy is the main abnormality identified by echocardiography in cats with HCM, but it may also be seen in cats with hyperthyroidism, systemic hypertension, or aortic stenosis. Left ventricular concentric hypertrophy is defined as a left ventricular free wall or interventricular septal end-diastolic thickness of 6 mm or greater. Identification

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of systolic anterior motion of the mitral valve is consistent but not entirely specific for HCM. Systolic blood pressure and thyroid level should be measured in all cats with evidence of left ventricular hypertrophy to identify possible secondary causes of hypertrophy. A gray zone exists for diagnosis of HCM, where there may be papillary hypertrophy that is subjectively apparent, or intermediate wall thickness of 5.5–5.9 mm, and these cats are typically classified as equivocal for HCM. The cardiac myosin binding protein C (MYBPC3) genetic screening test may be useful to evaluate Maine coon or Ragdoll cats as a preliminary test, but false negatives exist since there may be other causative genes yet to be identified (see Chapter 28). A positive test indicates that the cat has the genotypic abnormality that may lead to phenotypic development of HCM, but some cats may be have the mutation and may not develop concentric hypertrophy. The main uses of the test at this time are for breeding programs to identify breeding animals that may have the mutation and for pet animals of these two breeds that may be at risk for developing the disease, which justifies further, more comprehensive evaluations with an echocardiogram. The MYBPC3 test is not useful at this time in other breeds of cats, but over time additional mutations are likely to be discovered in different breeds of cats with familial HCM.

Diastolic dysfunction is often identified using tissue Doppler imaging in cats with HCM, but it is not necessary to make the diagnosis. Diastolic dysfunction is not specific to HCM, and cats with other cardiac diseases may also have diastolic dysfunction.

HCM is definitively diagnosed by postmortem examination and histopathologic evidence of myofiber disarray of the left ventricular cardiomyocytes, as well as gross evidence of concentric left ventricular hypertrophy and increased cardiac mass. However, myofiber disarray may be patchy with regional distribution, so it may be missed in some cases. The reader is referred to the Pathology subsection of the Etiology section for more detailed information on pathologic abnormalities seen in cats with HCM.

TREATMENT

Treatment of Asymptomatic Cats

Key Points

- There is significant controversy regarding when to initiate treatment, and what is the most appropriate medical therapy in asymptomatic cats with HCM and no heart failure.
- Beta blockers (i.e., atenolol) or calcium channel blockers (i.e., diltiazem) are the most commonly used drugs in asymptomatic cats with HCM, and they may reduce severity of hypertrophy.
- Beta blockers are more effective than calcium channel blockers to reduce severity of systolic anterior motion of the mitral valve and control heart rate to prevent tachycardia.
- Clinical evidence from placebo controlled, blinded clinical studies indicate that early use of angiotensin converting enzyme inhibitors or aldosterone antagonists in cats with asymptomatic HCM and no heart failure is not warranted.
- Prophylactic anticoagulant therapy is indicated if there is echocardiographic evidence of spontaneous contrast (i.e., red blood cell aggregation) or an intracardiac thrombus. It is controversial whether cats without these findings but with significant left atrial dilation should be placed on prophylactic anticoagulation. Prophylactic anticoagulant therapy is not necessary in cats with mild HCM and normal left atrial size, except in the rare incidence where such a cat has a history of confirmed ATE.

Decision processes in treatment of asymptomatic cats with HCM

Treatment of asymptomatic cats with HCM and without heart failure, thromboembolism, or significant arrhythmia is controversial and clinical data are limited. There are many factors involved in deciding whether treatment is appropriate for individual asymptomatic cats (Table 11.1), and objective data are insufficient to make a definitive treatment recommendation for all asymptomatic cats with HCM. In addition, cats with mild nonprogressive HCM may live many years without deterioration and may not require medical treatment. Finally, long-term clinical benefit has not been evaluated, so at this time there is a void in information regarding potential prolongation in symptom free interval or survival benefit.

The decision of whether to treat asymptomatic cats with HCM is typically based on the degree of concentric hypertrophy, the severity of left ventricular outflow tract obstruction in cats with systolic anterior motion of the mitral valve, left atrial size, presence of tachyarrhythmias, and the temperament of the cat and the client's wishes for giving lifelong oral medications. Most often, the choice of medications for asymptomatic cats is whether to consider a beta blocker or a calcium channel blocker. According to the American College of Cardiology Expert Consensus on HCM in people, there is debate over whether treatment of asymptomatic patients actually prevents or delays development of symptoms and

Table 11.1. Decision process for treatment of asymptomatic cats with HCM using beta blockers*

Medication Considerations	Argument for the Use	Argument against the Use
↓Systolic anterior motion (SAM) of the mitral valve	Dramatic reduction in the left ventricular to aortic pressure gradient is possible in cats with moderate or severe SAM, which may ↓ severity of concentric LV hypertrophy By decreasing SAM, mitral regurgitation (MR) is decreased, which may ↓ left atrial volume overload and left atrial pressure in cats with moderate MR due to SAM Some cats with moderate to severe SAM have unrecognized symptoms until they are treated, and then the owner observes symptomatic benefit including increased energy and playfulness	Indoor cats are sedentary animals that may not have high sympathetic tone until a stressor such as a trip to the veterinary office, which magnifies the severity of the SAM far beyond what is seen at home No information is available to confirm whether reduction of SAM leads to improved quality of life, survival, or delays onset of clinical signs
↓ LV concentric hypertrophy	Some cats receiving atenolol may experience reduction in severity of LV concentric hypertrophy ↓ LV hypertrophy may improve diastolic filling properties of the myocardium (i.e., ↓ stiffness), ↓ diastolic filling pressures and lessen risk of congestive heart failure	No information regarding effect on morbidity, mortality, or time to onset of clinical signs The reduction in LV hypertrophy appears to be relatively small in a placebo-controlled prospective study Some cats have improvement in LV hypertrophy without treatment or their hypertrophy never worsens over many years, making the role of medication questionable
Suppression of tachycardia	Acute stressful events may cause sinus tachycardia, ↑ diastolic filling pressure, and acute development of congestive heart failure in cats, so blunting this acute tachycardic response may be protective	Indoor cats may not have many acute stressful events that could cause this phenomenon, aside from visits to the veterinary hospital, which likely would be increased during initial monitoring of the cat receiving medications Potentially similar effect can be achieved without medication, by instructing owners to avoid situations causing vigorous activity for the cat (e.g., play with laser pointer, feather toys; minimizing or avoiding outdoor roaming, etc.)
Effects on diastolic function	↓ Heart rate will ↑ diastolic filling time, which may be beneficial in cats with stiff hypertrophied ventricles by lessening diastolic filling pressures occurring during tachycardia ↑ Myocardial stiffness is likely a more important determinant of ↑ diastolic filling pressure in cats than early diastolic relaxation because cats have high heart rates compared to other species, which minimizes the overall negative impact of beta blockers effects on slowing diastolic relaxation	Beta blockers prolong early diastolic relaxation (negative lusitrope), which impairs early diastolic function

(*Continued*)

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Table 11.1. (*Continued*)

Medication Considerations	Argument for the Use	Argument against the Use
Owner considerations	Inexpensive Widely available	Lifelong therapy commits owner to q 12h dosing; cannot abruptly stop the medication after chronic use
	Proactive owners may want to feel that they are giving their cat every opportunity for positive response and/or improvement	Lack of perceived benefit (although no symptomatic benefit expected in asymptomatic cats) may cause discouragement and discontinuation of the medication
		Because cat is receiving medication, owner may be reluctant to continue important follow-up diagnostic testing such as echocardiograms or radiographs if they may perceive there is nothing else to be done
		Intermittent "on and off" use may be dangerous due to beta receptor up-regulation and possibility for adverse cardiac effects with acute cessation
		Sacrifice of other necessary medications for treatment of noncardiac systemic diseases due to inability to administer several concurrent medications or prioritization of the cardiac medication over other medications
Cat considerations	Well tolerated, side effects are rare	May exacerbate bronchoconstriction, especially at high doses, in cats with concurrent lower airway disease
	Most cats will tolerate medication administration if the tablet is concealed in a treat/food or the medication is compounded in a meat-flavored suspension	Pilling may be difficult and emotionally traumatic to the cat and owner, and transdermal preparations are ineffective
		Development of medication aversion causing discontinuation of the medication, may make it challenging to medicate if/when life-saving medications are needed later for heart failure or thromboembolism
		Difficulty medicating the cat may lead to antagonistic experience with owner
Morbidity and mortality	No information available for asymptomatic cats	No information available, although no clinical evidence of hastened deterioration in asymptomatic cats with HCM

*Many variables influence whether an asymptomatic cat with HCM should receive medications (atenolol), which is aimed at delaying the progression of hypertrophy and associated complications. The advantages and drawbacks of treatment help the clinician and owner to decide whether to pursue such treatment in each individual case.

improves prognosis and is on an "empiric basis without controlled data to either support or contradict its potential efficacy" (Maron et al. 2003). The same situation is true in cats. Asymptomatic human patients with massive LV hypertrophy are usually treated, with expectations that pharmacologic therapy will improve diastolic filling, reduce myocardial ischemia, and prolong time to development of symptoms (Spirito et al. 1997). Likewise, negative inotropic therapy with either a beta blocker or calcium channel blocker is often recommended in cats with moderate or severe left ventricular hypertrophy (wall thickness >6.8–7–7.5 mm) or significant left ven-

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tricular outflow tract obstruction (LV:Ao pressure gradient >40 mm Hg). This decision must include the impact of chronic oral medications for the client and cat; patient temperament; the owner's motivation for administering lifelong oral therapy; and whether clinical signs are present (associated with moderate to severe SAM, such as reluctance to play or exercise, exercise-induced tachypnea or weakness, lethargy) (Table 11.1).

Exertional dyspnea, chest pain, dizziness, presyncope or syncope, and reduced exercise capacity occur in some people with HCM and diastolic dysfunction, often with concurrent significant left ventricular outflow tract obstruction (Maron et al. 2003). These symptoms are caused by increased left ventricular pressure during exertion (since the left ventricular outflow tract obstruction worsens with increased contractility), leading to myocardial ischemia, and elevated diastolic filling pressure and left atrial pressure with exertion (Maron et al. 2003). These patients are aggressively treated with various medications (beta blockers, calcium channel blockers, disopyramide) or medical interventions (ethanol septal ablation, septal myectomy) to dramatically reduce the severity of left ventricular outflow tract obstruction and relieve symptoms (Maron et al. 2003). It is challenging to identify cats with intermittent symptoms that occur with moderate to severe hypertrophic obstructive cardiomyopathy with moderate to severe SAM, because cats, unlike people, are sedentary and tend to mask intermittent or mild symptoms. Among veterinary cardiologists, there is great controversy regarding whether the benefits of medicating an asymptomatic cat outweigh the potential negative impact of lifelong oral medication administration cats.

Presence of left atrial dilation is considered to indicate a more severe disease state with an elevated diastolic filling pressure, which may prompt more serious consideration for treatment. Still, there are many cats in a "gray zone" of mild or moderate left atrial dilation wherein some deteriorate more rapidly and others remain well compensated for extended periods of time. Conversely, cats with mild left ventricular hypertrophy (6– 6.5 mm), normal left atrial size, and mild or no SAM of the mitral valve do not require therapy, but should be monitored for echocardiographic evidence of disease progression.

Suspected but unconfirmed HCM: Whether to treat asymptomatic cats with a murmur but no echocardiogram

Empirical treatment of an asymptomatic cat that has an incidental murmur with beta blockers, calcium channel blockers, or ACE inhibitors is not warranted (see Chapter 1). Often veterinarians are challenged by the inability to further define the cardiac disease by echocardiography due to an owner's financial constraint or lack of perceived need for further workup, which makes it difficult to appropriately assess whether treatment is justified. Without further assessment with an echocardiogram, many asymptomatic cats with murmurs and possible radiographic evidence of cardiomegaly may not actually require any therapy and may be overtreated by empirical therapy.

A common misconception based on the wide margin of safety of beta blockers and aspirin is the concept that neither will do any harm. Such a belief fails to take into account the logistics of medication administration and lack of conclusive studies demonstrating benefit to disease progression or survival. Adverse responses of chronic oral therapy in cats are not necessary based on deleterious effects of the actual medication, but effects of administering any medication chronically to cats that may be notoriously resistant to this procedure (see Table 11.1).

It is critical to remember that not all heart murmurs are caused by HCM, and there are many other causes of heart murmurs that do not require treatment. A common cause of murmurs in cats is dynamic right ventricular outflow tract obstruction, which is not associated with any structural cardiac abnormality, yet cannot be distinguished from pathologic murmurs based on auscultation alone (Rishniw et al. 2002). In fact, 69% of cats (11/16) with murmurs have no echocardiographic evidence of cardiac disease (Paige et al. 2009). Misdiagnosis can logically lead to mistreatment. For these reasons, treatment of a heart murmur alone, without documentation of underlying structural heart disease, is not warranted and may be detrimental. An exception is the cat with a heart murmur that also has a tachyarrhythmia (specifically ventricular tachycardia, atrial tachycardia, or atrial fibrillation) demonstrated on ECG, in which case beta blockade may be indicated for treatment of the arrhythmia. Similarly, a cat with a conclusive physical diagnosis of aortic thromboembolism in its past medical history should be given an anticoagulant, even if an echocardiogram is not possible.

Drug selection for treating asymptomatic HCM in cats

HCM does not represent a single, uniform disease, but it has wide clinical variations, likely due to different causative mutations and potential predisposing or exacerbating factors. Due to the void in data on clinical effects on disease progression, an intense debate exists over whether calcium channel blockers or beta blockers are superior for treatment of patients with HCM. Although beta blockers worsen early ventricular relaxation, there is symptomatic benefit in people with HCM

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that beta-blockade confers by slowing the heart rate and prolonging diastole to increase passive LV filling (Maron et al. 2003). Negative inotropic effects and reduction of myocardial oxygen demand may reduce microvascular myocardial ischemia. Troponin I is a cardiac isoenzyme that increases when there is cardiomyocyte damage or ischemia, and was shown to decrease over 1 to 4 weeks of atenolol therapy in five asymptomatic cats with HCM (Côté 2007). These results indicate that atenolol may reduce myocardial damage or ischemia in this small number of asymptomatic cats with HCM and warrant continued investigation. Beta blockers are also effective in reducing LVOT obstruction from SAM of the mitral valve, and, in cats, are superior to calcium channel blockers for doing so (Wey and Kittleson 2000). Preliminary results from a prospective, blinded, placebo controlled study evaluating the effects of atenolol versus diltiazem in asymptomatic cats with HCM revealed that atenolol had modest effects (improved one variable of diastolic function and slightly reduced septal wall thickness), and diltiazem had no effects on diastolic function, left atrial size, LV hypertrophy, or SAM of the mitral valve. In contrast, a small, open-label, randomized, prospective clinical trial found that diltiazem reduced LV free wall and interventricular septal thickness from 9 mm ± 0.5 mm to 6 mm ± 0.6 mm after 6 months of therapy, improved symptoms, and shortened LV relaxation time index after 3 and 6 months of treatment in 12 cats with HCM (Bright et al. 1991). In summary, treatment of asyptomatic cats with HCM using atenolol or diltiazem has produced conflicting results with regard to myocardial effects, and no information is available with regard to effects on disease progression or survival.

Beta Blocker Therapy

Beta-blocking drugs have undergone a resurgence in popularity for treating feline cardiovascular disease since the 1970s and 1980s. Originally, propranolol (beta blocker) and diltiazem (calcium-channel blocker) were used, but both require every-8-hour dosing, which is very challenging for lifelong therapy in cats. Subsequently, atenolol, a beta blocker, which is administered q 12–24 h in the cat, was demonstrated to be safe through repeated anecdotal use in cats and is now the beta blocker of choice in this species. Conversely diltiazem, administered once daily as a sustained-release preparation made for the human, but not feline, gastrointestinal and hepatobiliary systems, is associated with a 10–20% rate of systemic complications and is now used infrequently in cats.

The potential targets of beta blocker therapy are to decrease severity of SAM of the mitral valve (if moderate or severe), to decrease severity of left ventricular concentric hypertrophy, or to treat concurrent supraventricular or ventricular tachyarrhythmias. The most common, affordable, well-tolerated beta blocker used in feline medicine is atenolol, which is a selective B-1 receptor antagonist. Atenolol is highly bioavailable (90%), has a half-life of 3.5 hours in the cat, and beta blocking effects last for at least 12 hours but less than 24 hours, so many cardiologists feel that it should ideally be given every 12 hours (Quinones et al. 1996). The lowest strength tablet size of atenolol available is 25 mg. Doses range from 6.25 mg PO 24 hr to 12.5 mg PO q 12 h, starting typically at 6.25 mg PO q 12 h and then up-titrated to achieve a heart rate in the exam room of <160–180 bpm (cardiologists' opinions vary regarding optimal target heart rate; ideally, a limit of ~140 bpm could be achieved, without inducing any clinical signs of lethargy, decreased appetite, or behavioral changes). In one approach, atenolol is started at 6.25 mg PO q 12 h, because pharmacologic studies in cats have demonstrated that q 12 h dosing is optimal for sustained beta blockade, and the cat is rechecked a week later (Quinones et al. 1996). The sympathetic stimulation of a visit to the veterinary hospital serves as a stress test for assessing beta blocker efficacy and duration of effect. If the heart rate at recheck remains >160–180 bpm, there is not adequate beta blockade, so the dose may be increased to 12.5 mg PO q 12 h and the heart rate rechecked a week later. Alternatively, clinical experience suggests that in some cats, duration of the beta blocker effect of atenolol approaches 24 hours and once-daily dosing may be appropriate in these cats. In this approach, atenolol is administered q 24h in the evening, and a daytime recheck is done after 7–14 days of ongoing treatment, corresponding to >12 hours postpill. A pretreatment baseline heart rate of 180 beats/minute that is <160–180 beats/minute after treatment suggests ongoing adequate beta blockade, whereas persistent tachycardia suggests inadequate beta blockade warranting an increase in dosing to q 12h. The increase from q 24h to q 12h dosing in this manner has been associated with further reductions in circulating cTnI concentrations in asymptomatic feline HCM (Côté 2007). Assessment of murmur intensity is also important, as often the beta blocker is used for treatment of significant SAM of the mitral valve. Murmur intensity and heart rate should decrease on beta blocker therapy. Follow-up echocardiographic quantification of the severity of SAM may be done, especially in cats with moderate to severe SAM, to help guide therapy and determine whether the current dose of the beta blocker effectively reduced the pressure gradient or whether a higher dose is needed. The selectivity of atenolol for blocking β-1 receptors diminishes at higher doses,

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where there may be blockade of β-1 and β-2 (bronchial smooth muscle) receptors. Since β-2 receptors stimulate bronchodilation, blockade of β-2 receptors with nonspecific β-blockers (e.g., propranolol) may trigger or exacerbate an asthmatic crisis in cats with asthma. Therefore, nonselective (concurrent β-1 and β-2 receptor) beta blockers are contraindicated in cats with asthma, and cats with bronchial disease should be monitored for signs of exacerbated bronchoconstriction even on selective beta blockers (e.g., atenolol), especially at higher doses. The every-8-hour dosing requirement of propranolol precludes its use as chronic therapy in cats with HCM, given the availability of atenolol as a q 12 h or q 24 h drug. Subjectively, propranolol is responsible for a greater number of adverse drug reactions in cats than is atenolol. Atenolol has a high margin of safety in the cat, including inadvertent overdoses.

In addition to negative inotropic effects, beta blockers are also negative chronotropic drugs, which may effectively reduce tachycardia and lessen the influence of tachycardia on elevated diastolic filling pressure. This may be important in cats with sustained sinus tachycardia (HR >220 bpm) or in cats with other more malignant tachyarrhythmias. There is a potential for periods of marked tachycardia that may contribute to development of congestive heart failure in cats with diastolic dysfunction from HCM. These periods may occur in situations of extreme stress or physical exertion, such as being chased by another animal, so beta blockers may blunt the extreme sinus tachycardia during these stressful situations. Beta blockers address the sympathetic potentiation of both supraventricular and ventricular tachyarrhythmias, either of which may be present in asymptomatic cats with HCM.

Short-term administration of atenolol for planned stressful events such as a plane trip may be considered in cats that otherwise would not be given chronic lifelong therapy. The theory is to lessen the magnitude of stress-induced tachycardia, which can be a trigger to worsen diastolic function and precipitate heart failure in some cats with HCM. Atenolol (6.25 mg) may be administered q 12 h–24 h for 5–7 days prior to the event, continued for 2–3 days after the end of the stressor, and then weaned off. Ideally the atenolol is dosed 1–3 hours prior to the stressful event. This technique is recommended by some cardiologists, but there is no proven benefit.

Beta blockers may be safely used concurrently with other medications including methimazole or amlodipine in cats with hyperthyroidism or systemic hypertension, respectively. However, beta blocker therapy should not be used in substitution for methimazole or amlodipine in cats, as direct treatment of any underlying systemic disease that can contribute to cardiac hypertrophy is imperative. Side effects of atenolol are relatively infrequent, and may include lethargy, weakness, and exacerbation of cough or wheeze in asthmatic cats; gastrointestinal side effects are extremely rare. Selective beta blockers are not contraindicated for patients with diabetes mellitus, contrary to unfounded statements made in drug formularies regarding their effect on insulin resistance or prolonged physiologic response to a hypoglycemic crisis (Majumdar 1999).

Calcium Channel Blocker Therapy

Diltiazem is a nondihydropyridine (i.e., not vascular selective) calcium channel blocker used in HCM. It has mild negative inotropic effects (less than verapamil) and is used as an antihypertrophic agent in HCM, as well as for treatment of supraventricular arrhythmias. Calcium channel blockers improve early diastolic relaxation by reducing isovolumic relaxation time (Lorell et al. 1982). Calcium channel blockers also may reduce LV end-diastolic pressure and cause a downward shift of the LV diastolic pressure volume relation, suggesting improved LV distensibility (Lorell et al. 1982). In apparent contradiction, a study measured LV pressure- volume relations in human patients with LV hypertrophy before and after intravenous esmolol (beta blocker) and/or verapamil (calcium channel blocker) and found unaltered late diastolic compliance with both drugs (Kass et al. 1993). This study helps illustrate that chamber compliance is determined by passive structural elements (i.e., hypertrophy and fibrosis) rather than active processes. Even if early diastolic relaxation is improved, increased chamber stiffness has a large impact on overall diastolic dysfunction. Early diastolic relaxation was found to be improved in a small study of 40 people with HCM treated with verapamil. At baseline, 70% of patients had evidence of diastolic dysfunction based on reduced peak filling rate and time to peak filling rate from gated radionuclide angiograms (Bonow et al. 1981). After 1 week of oral verapamil, only 30% had evidence of diastolic dysfunction. Verapamil increased peak filling rate and reduced time to peak filling rate (Bonow et al. 1981). Improvement of diastolic function by verapamil was associated with improved exercise capacity (Bonow et al. 1985). Another acute study of intravenous diltiazem in people with HCM showed that it reduced asynchronous LV filling and improved global diastolic parameters (Ito et al. 2004). Like beta blockers, calcium channel blockers may also relieve myocardial ischemia.

There are four different forms of diltiazem: standard oral formulation (30 mg), two sustained release formulations, and an intravenous preparation. Whether

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regular or sustained release preparation is prescribed, the drug name remains diltiazem hydrochloride, so the clinician must be careful not to confuse the preparations when writing prescriptions. The nonsustained release standard formulation (Diltiazem HCl, Cardizem) is typically dosed at 7.5 mg PO q 8 h and can be slightly up-titrated if needed. Owner compliance of administering q 8 h dosing frequency for the life of the cat is of concern. There is much higher bioavailability of standard diltiazem in cats (71%) compared to dogs (17%). Time to peak concentration postpill is 45 minutes, with a terminal half-life of 113 minutes (Johnson et al. 1996). Cardizem CD is a sustained release formulation which is available as a 180 mg capsule that is filled with hundreds of microspheres, and can be divided by a compounding pharmacy to 45 mg doses placed in smaller gelatin capsules, to be administered as 45 mg PO q 24 hr or 10 mg/kg PO q 24 hr (Johnson et al. 1996). Cardizem CD has half the bioavailability of the conventional preparation. The time to peak concentration is 340 minutes and terminal half-life is 410 minutes. Pharmacodynamic effects on heart rate and PR interval were studied in healthy cats, and neither conventional nor CD formulation reduced heart rate or prolonged PR interval, despite blood concentrations within the therapeutic range defined in people. Dilacor XR is another sustained-release form of diltiazem, and it is supplied as 120 mg, 180 mg, and 240 mg capsules, containing 2, 3, or 4 60 mg sustained release tablets, respectively, which are removed from the gelatin capsule and then broken in half and given at 30 mg PO q 24 hr. A pharmacologic study of Dilacor XR in normal cats and cats with HCM showed that 30 or 60 mg PO q 24 hr produced erratic blood levels of diltiazem; many cats had higher than the recommended range of blood concentration for 12 hours, and less than recommended range at 18 and 24 hours postpill (Wall et al. 2005). Thirty-six percent of cats with HCM had adverse reactions, consisting of decreased appetite, vomiting, lethargy, weight loss, and diarrhea. Therefore, sustained-release diltiazem is no longer recommended (and may even be considered as relatively contraindicated due to these limitations) in cats.

There are only two small but important studies evaluating diltiazem in asymptomatic cats with HCM, with disparate results as described above (see Drug selection for treating asymptomatic HCM in cats, above). Therefore, given the possibility of adverse effects (sustained-release diltiazem) versus q 8h dosing schedule (regular diltiazem), and lack of demonstrated superiority over atenolol, calcium channel blockers have largely been replaced by atenolol in feline cardiology.

Neurohormonal Antagonists in Asymptomatic HCM

There is a logical rationale for early use of an ACE inhibitor (e.g., enalapril, benazepril, ramipril), angiotensin receptor blocker (e.g., losartan, irbesartan), or aldosterone antagonist (e.g., spironolactone) for reduction of left ventricular hypertrophy and fibrosis in HCM, since these pharmacologic agents have been shown to exert antihypertrophic and antifibrotic effects in other cardiac diseases and in transgenic rodent models of HCM (Lim et al. 2001; Linz et al. 2004; Zhu et al. 1997; Schmieder et al. 1996; Tsybouleva et al. 2004). Unfortunately, in veterinary medicine, we are limited by a lack of clinical studies that confirm or deny benefit of treatment in many diseases such as HCM, so often clinicians are faced with the remaining choice of theoretical rationale, extrapolations from other species, and clinical experience. Cardiac effects of pharmacologic therapy may be different in cats with spontaneously occurring HCM compared to transgenic models of HCM in mice and rabbits, so data cannot be directly extrapolated from laboratory studies to clinical feline medicine. Four studies have evaluated RAAS antagonists for treatment of asymptomatic cats with HCM (MacDonald et al. 2006b; MacDonald et al. 2008; Rush et al. 1998; Amberger et al. 1999). The first study was a randomized, placebo controlled, double blinded, prospective design, which evaluated the effect of ramipril on LV mass quantified by cardiac MRI, diastolic function quantified by pulsed-wave tissue Doppler imaging, neurohormones (plasma aldosterone and BNP concentrations), and blood pressure in 26 asymptomatic Maine coon cats with mild to severe familial HCM (MacDonald et al. 2006b). There was no difference in LV mass, diastolic function, delayed contrast enhancement assessment of myocardial fibrosis, blood pressure, or neurohormones between the placebo and ramipril treatment groups over 12 months of therapy. Approximately 60–70% of cats treated with ramipril had elevated plasma aldosterone concentration, demonstrating the phenomenon of ACE escape that is also seen in people and dogs treated with ACE inhibitors. It is likely that persistent elevations of plasma aldosterone in the face of low plasma ACE activity may have been due to alternative tissue-dependent pathways of ATI conversion to ATII, mainly chymase. In contradiction to the first study, two small, uncontrolled or retrospective studies reported that ACE inhibitors reduced LV hypertrophy assessed by echocardiography (Rush et al. 1998; Amberger et al. 1999). The first of the two studies was a randomized, open-label prospective clinical study of benazepril in 28 cats with HCM (Amberger et al. 1999). All cats were treated with a background (stan-

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dard) therapy of sustained release diltiazem and other medications if needed such as diuretics or antiarrhythmics. One group received standard therapy (n = 9) and the other group received benazepril (n = 19) orally once a day for a year. Only 7 cats (26%; 4 benazepril, 3 standard therapy) reached the end point evaluation at 1 year, and the remaining either died, developed arterial thromboembolism, or were lost to follow-up. There was no difference between groups on death or rate of dropout. The authors report a reduction of LV free wall thickness in the benazepril group of 0.1 mm/month, but median values and standard errors were not published. The ability to measure actual changes in LV thickness of 0.1 mm by echocardiography is doubtful due to the high variability of the method, even though the results were reported to be statistically significant. The second study was a retrospective, unblinded study evaluating the effects of enalapril in 19 cats with HCM over 3–6 months of treatment (Rush et al. 1998). Mean interventricular septal thickness decreased from 7 mm ± 2 mm to 6 mm ± 1 mm, and mean LV free wall thickness decreased from 8 mm ± 2 mm to 7 mm ± 2 mm. Mean left atrial diameter also decreased. Neither study quantified LV mass as an end point, and both relied upon 2-D or M-mode echocardiographic measurement of LV free wall and interventricular septal thickness, which is fraught with tremendous variability and interday or interobserver error of 18–20% (Chetboul et al. 2004). Since hypertrophy is most often asymmetrical, the LV thickness measurements are extremely site-dependent. In the absence of convincing evidence to the contrary, it is the authors' viewpoint that treatment of asymptomatic cats with HCM using an ACE inhibitor is unwarranted.

Another pharmacologic target for reduction of myocardial fibrosis and hypertrophy is to block aldosterone receptors. In a cardiac troponin T transgenic rat model of HCM, spironolactone reversed interstitial fibrosis, decreased myocyte disarray by 50%, and improved diastolic function assessed by mitral inflow velocity measurements (Tsybouleva et al. 2004). The effects of spironolactone in asymptomatic cats with HCM has been studied in a prospective, blinded, placebo controlled study of asymptomatic Maine coon cats with mild to severe familial HCM with diastolic dysfunction identified on tissue Doppler imaging echocardiography (MacDonald et al. 2008). The study evaluated the effect of spironolactone (2 mg/kg PO q 12 h for 4 months) on diastolic function assessed by pulsed-wave tissue Doppler imaging, cardiac mass quantified by the truncated ellipse formula using echocardiography, left atrial size, and plasma aldosterone concentration. There was no difference in diastolic function or systolic function assessed by tissue Doppler imaging, LV mass, or left atrial size. Plasma aldosterone concentration was markedly elevated in cats treated with spironolactone (baseline 235 pmol/l; posttreatment 1000 pmol/l), indicating that aldosterone receptor antagonism was achieved. Approximately one-third of cats treated with spironolactone developed severe ulcerative facial dermatitis, which resolved 4–6 weeks after discontinuing the medication. The histopathologic diagnosis of necrotizing and ulcerative dermatitis with superficial to deep eosinophilic and neutrophilic perivascular dermatitis and the resolution of the lesions after discontinuation of the drug are consistent with an adverse drug reaction. Therefore, there is a lack of evidence of benefit (i.e., no change in echocardiographic measurements of left ventricular hypertrophy, left atrial size, or diastolic function), in asymptomatic cats with HCM given spironolactone, yet there is a significant risk of adverse drug reaction.

Specific antifibrotic drugs are theoretically plausible for further investigation in cats with HCM. An unpublished study investigating the effects of pirfenidone, an antifibrotic agent used to treat pulmonary fibrosis in humans, was conducted in Maine coon cats with familial HCM, but the study was discontinued due to the intense impalatability in cats (K. MacDonald, unpublished observations). No studies have evaluated the effect of colchicine, a microtubule depolymerase with possible antifibrotic, immunomodulator effects, in cats with HCM.

Treatment of Symptomatic Cats with HCM

Key points

- Furosemide is the most effective and life-saving treatment of cats in congestive heart failure and can be given at a dose range of 1–4 mg/kg PO q 8–24 hr to for outpatient therapy depending on the severity of heart failure. The minimal effective dose should be used. An initial moderate to high dose may be started and then rapidly tapered based on respiratory rate, effort, and evaluation of severity of heart failure by thoracic radiographs.
- Treatment of acute heart failure includes parenteral furosemide (2–4 mg/kg q 1–8 hr). The dose and frequency should be rapidly tapered once the respiratory rate decreases to 50 breaths/minute or less and the effort is decreased. Oxygen therapy with 60–70% FiO_2 can be provided initially and then decreased to 50% or less within 12 hours to avoid barotrauma secondary to high inspiratory oxygen concentration.
- Transdermal nitroglycerin causes venodilation in people, but it has not been evaluated in cats. Its use

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is debatable in cats and it can be given short-term to hospitalized cats for no longer than 2 days; the main drawback appears to be a lack of efficacy rather than adverse effects.
- Negative inotropic therapy including beta blockers and calcium channel blockers may be used in some cats with chronic heart failure but are not given in acute heart failure unless there is a hemodynamically significant tachyarrhythmia.
- ACE inhibitors such as enalapril or benazepril may help provide adjunctive treatment in cats with heart failure. Rather than starting as an emergency in-hospital treatment, the ACE inhibitor may be started at home once the cat is stabilized, eating and drinking, and hydrated.
- Prophylactic anticoagulant may be started in cats with high risk of arterial thromboembolism (ATE), including those with spontaneous echocardiographic contrast, left atrial thrombus, history of prior ATE, or severe left atrial dilation.

Outpatient treatment of symptomatic cats with HCM

Cats with severe HCM may develop symptoms of dyspnea, tachypnea, exercise intolerance and lethargy, anorexia, or syncope once heart failure develops. Furosemide is the most efficacious and life-saving treatment to reduce pulmonary edema and slow accumulation of pleural effusion in cats with heart failure. Diuretics (furosemide) and ACE inhibitors are indicated for treatment of CHF due to almost any etiology except pericardial effusion and cardiac tamponade, so they should not be withheld in animals that cannot be examined by echocardiography. Treatment of symptomatic cats with CHF due to diastolic heart failure caused by HCM or other causes of increased myocardial stiffness is aimed at reducing fluid accumulation (i.e., pulmonary edema and/or pleural effusion) with furosemide and additional chronic therapy with an ACE inhibitor.

Cats in active heart failure rely on elevated sympathetic tone for maintaining, albeit decreased, cardiac output and blood pressure to remain alive. When beta blockers are given in the setting of acute heart failure, loss of the beta receptor stimulation may lead to further deterioration and worsened cardiac output and arterial hypotension. Therefore, treatment of cats with active heart failure with a beta blocker is contraindicated unless there is a significant tachyarrhythmia such as ventricular tachycardia or supraventricular tachycardia with high heart rates (over 250 bpm). Massive tachycardic events (>250 bpm) adversely impact diastolic and systolic function in the failing heart, exacerbate congestive heart failure, or cause low-output (forward) heart failure that is evidenced by arterial hypotension. Cats that are chronically treated with beta blockers for asymptomatic HCM and then subsequently develop congestive heart failure can be continued on atenolol, although the dose is often reduced by 30–50%. Beta blockers should be stopped, either temporarily or indefinitely, in the following situations: the cat has bradycardia (HR ≤140) and is hypotensive, the degree of dyspnea precludes oral administration, or the cat is not able to tolerate oral medications. In the chronic setting, the use of beta blockers or calcium channel blockers in cats with HCM and heart failure is debatable since the largest multicenter study to date in cats did not identify an improved survival in cats with cardiomyopathy and CHF or arterial thromboembolism treated with beta blockers, calcium channel blockers, or ACE inhibitors, and a trend toward decreased survival in cats treated with atenolol (Fox 2003b). One hundred and eighteen cats were enrolled in this study, including 57 cats with HCM and 37 cats with HOCM. Although no treatment improved survival, there was a trend toward improved survival in the enalapril group ($p = 0.06$) (Fox 2003b). The opinion of many cardiologists is that some cats with CHF clinically improve when treated with an ACE inhibitor, and it should be used as adjunctive therapy along with furosemide in all cats with heart failure.

Thoracic radiographs are essential to confirm the presence of, and evaluate the severity of, heart failure in cats that have clinical signs of tachypnea or dyspnea. In cats with moderate or severe pleural effusion, thoracocentesis should be done to immediately stabilize the cat prior to further diagnostic workup. Often a brief thoracic ultrasound can be done to rapidly assess whether there is significant enough pleural effusion to require thoracocentesis. The cat is placed in sternal recumbency with minimal manipulation or stress during the scan. Assessment of significant atrial dilation may also be made during this initial brief ultrasound, which helps establish the likelihood of a cardiogenic cause of the pleural effusion. Thoracocentesis is done with the cat typically in sternal recumbency. Ultrasound helps guide the optimal site for thoracocentesis, where there is the most pleural effusion and furthest away from vital structures such as a severely dilated left atrium. Thoracocentesis is needed to physically remove substantial pleural effusion, since diuretic therapy is not expected to mobilize the fluid quickly but is expected to lessen further fluid buildup. Often the best site for thoracocentesis is caudal to the heart, at the level of the costochondral junction, on the right side of the thorax. Unless the cat has life-threatening dyspnea, the site is clipped and sterile prepa-

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ration done. Sedation may be needed in anxious or fractious cats. Typical sedation "cocktails" may include midazolam and an opioid, or low-dose acepromazine (0.01 mg/kg) and an opioid. The opioid chosen depends on the clinician's personal preference; options include hydromorphone (0.05–0.1 mg/kg parenterally) or butorphanol (0.1–0.4 mg/kg preferably IV using gentle restraint). Many cats with an even temperament or with significant dyspnea do not require sedation. A butterfly catheter (19 gauge is preferred by the authors), 3-way stop cock, extension set, and a 30–60 ml syringe are attached. A sample of the pleural effusion should be submitted for fluid analysis and cytology (see Chapter 3).

In cats stable enough to be treated at home, oral furosemide is started at doses as low as 1 mg/kg PO q 24 hr for mild heart failure, to higher doses of 2–3 mg/kg PO q 8–12 h for moderate heart failure, and 3–4 mg/kg PO q 8 h for severe or refractory heart failure (see Chapter 10). Cats with significant heart failure that do not require hospitalization can be given an injection of furosemide (2–3 mg/kg) prior to discharge. Cats tend to be more prone to dehydration, anorexia, and prerenal azotemia on furosemide therapy than dogs. Assessment of basal renal function prior to furosemide and an ACE inhibitor is necessary, including chemistry and urinalysis. The initial furosemide dose may be higher to clear the fluid, and then tapered to the minimal effective dose depending on respiratory rate and character at home. Ideal respiratory rate is <40 breaths/min at rest in the home environment, with normal respiratory effort. Owners should be trained on monitoring resting respiratory rate and subjectively assess the respiratory effort twice a day initially and then at least once a day, and a log should be kept and reviewed by the doctor during phone follow-ups and recheck evaluations. Cats with resting respiratory rates of >40 at home often have ongoing congestive heart failure and may require a higher dose of furosemide. A recheck is planned in 1–2 weeks for cats with mild heart failure that respond well to treatment (normalization of respiratory effort and rate and return of good appetite, in 24 hours or less), and in 3–7 days for cats with more severe heart failure depending on clinical response. If a 7-day recheck is unavailable or unacceptable to the owner, a phone consultation and review of the respiratory log and overall clinical status of the cat is very helpful to identify whether the response to diuretic therapy is adequate. The main criteria of a good clinical response to diuretic therapy is the normalization of resting respiratory rate and respiratory effort, return of appetite, and return of normal or near-normal behavior. Thoracic radiographs are essential to monitor for presence of pulmonary edema or pleural effusion that would dictate increasing the furosemide dose. Once in heart failure, cats require lifelong furosemide therapy, the only exception being congestive heart failure that was triggered by a transient precipitating factor such as intravenous fluid administration.

Often cats with HCM and heart failure are given a multitude of medications, including furosemide, an ACE inhibitor, an anticoagulant, and possibly a negative chronotrope. Since cats are often sensitive to side effects (i.e., lethargy, anorexia, vomiting) of multipharmacy treatment, starting the two most important drugs and then staggering the remainder over the next 7–10 days is recommended. An ACE inhibitor may be started concurrently with furosemide in outpatient treatment of heart failure. In cats that have been hospitalized and given high doses of furosemide, the ACE inhibitor can be postponed until they are home, eating and drinking, to lessen likelihood of significant azotemia. ACE inhibitors may be given to cats with mild prerenal azotemia secondary to diuretic therapy, but initially should be postponed in cats with moderate to severe azotemia (acute change from normal values to BUN >80 mg/dl (28 mmol/l), creatinine >3 mg/dl (264 mmol/l)). A low dose of the ACE inhibitor (preferentially benazepril to avoid problems with sole renal elimination of the drug) may be initially started in azotemic cats, and up-titrated depending on the cat's clinical status and whether azotemia has significantly worsened (i.e., 50% increase in azotemia in already azotemic animals) on a follow-up renal panel. In cases of worsened azotemia as described above, the dose of the ACE inhibitor may need to be decreased or the drug discontinued.

When choosing the specific ACE inhibitor, cost of the medication, frequency of dosing, and route of elimination of the drug affect the decision. Enalapril is the most commonly used ACE inhibitor in the United States and is entirely eliminated by the kidneys. The recommended dose is 0.5 mg/kg PO q 12–24 h, and the smallest size tablet available is 2.5 mg. Benazepril is mainly metabolized through the liver (85%), and pharmacokinetics are not altered in the face of renal dysfunction. The recommended dose of benazepril is 0.5 mg/kg PO q 24 hr, and the smallest size available is 5 mg tablets (King et al. 1999, 2003). Likewise, ramipril is mostly eliminated through the liver (87%) and is also a good choice for cats with known renal insufficiency. The recommended dose of ramipril is 0.5 mg/kg PO q 24 hr, and it is supplied as 2.5 mg tablets (Coulet and Burgaud 2002).

All ACE inhibitors exhibit a class effect of reducing glomerular efferent arteriolar tone through reducing angiotensin II. In some patients, there is excessive efferent arteriolar vasodilation, leading to a moderate decrease in glomerular filtration rate and development of significant azotemia (i.e., functional azotemia). This

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functional azotemia is usually temporary and resolves after discontinuation of the ACE inhibitor along with supportive care (see Chapter 19).

Treatment of Acute Congestive Heart Failure in Cats with HCM (Inpatients)

In cats with severe dyspnea, aggressive diuretic therapy with high furosemide doses repeatedly is needed for immediate stabilization. These cases are best suited for referral to a cardiologist, criticalist, or 24-hour care facility. However, the cat needs to be stabilized first. Initial workup is aimed at establishing whether the dyspnea is from heart failure or other causes. An in-depth diagnosis of the specific cardiac disease is not necessary in the emergency setting, and often patients are referred to a cardiologist or specialist adept at performing echocardiograms later once stabilized. The first step of triage is to determine whether there is significant pleural effusion that can be rapidly removed to immediately stabilize the cat. With minimal manipulation and the cat in sternal recumbency, a thoracic ultrasound can be quickly done to scan for significant pleural effusion, and the left atrial size can also be assessed for significant dilation. Thoracocentesis can be done with the cat in sternal recumbency, please refer to chronic heart failure section and Chapter 3. If there is no significant pleural effusion and depending on the stability of the patient, a thoracic radiograph can be quickly obtained without overrestraining and manipulating the cat (i.e., no aggressive positioning techniques or placing weights that could interfere with the cat's ability to breathe) to assess for significant pulmonary edema and cardiomegaly. For example, a dorsoventral radiograph (cat in sternal recumbency) is optimal for identifying pleural effusion in the least distressing manner with the least manipulation and restraint when ultrasound is unavailable. Initial workup of a dyspneic cat should be cautiously done as they are extremely fragile. If the cat is too unstable for a radiograph, oxygen administration and a parenteral dose of furosemide (3–4 mg/kg) can be given.

Emergency oxygen support using 60–70% FiO_2 may be necessary and the need is determined based on severity of dyspnea. The optimal method of oxygen support is with a specialized oxygen cage that controls inspired oxygen concentration, carbon dioxide, temperature, and humidity. If one is not available, an incubator tank can be used with ice packs to cool the environment and high oxygen flow rates to help flush out excess carbon dioxide. An oxygen mask may give temporary assistance, but also may further stress the cat and exacerbate dyspnea. A makeshift option for oxygen administration in a crisis without an oxygen cage is to wrap the cage door with cellophane wrap, allowing a space for air (carbon dioxide) to exit, and use of high oxygen flow rates and cooling measures with cool packs. Placement of Saran Wrap over the front of an e-collar also may serve to administer oxygen to a cat that won't allow placement of a face mask.

Furosemide is rapidly life-saving in a dyspneic cat with pulmonary edema and can be given parenterally at doses ranging from 2–4 mg/kg every 1–8 hours depending on the severity of heart failure. The intravenous route is preferable over other routes because it achieves a rapid onset of action in 5 minutes, but it may not be possible in the severely dyspneic cat that will not tolerate restraint. Intramuscular (IM) furosemide injection has a relatively fast onset of action of 30 minutes, although skeletal perfusion may be dramatically reduced in fulminant congestive heart failure, which would limit the efficacy. If there is no improvement in the dyspnea after 1 hour of intravenous injection or 2 hours of IM injection of furosemide, another dose (3–4 mg/kg) should be given. Ideally an intravenous catheter is carefully placed if the cat can withstand the procedure. Water should be always available or offered every hour, since withholding water will exacerbate profound dehydration during the aggressive diuretic stage of treatment. Once the respiratory rate decreases to 50 breaths/minute or less and the effort improves, the dose and frequency of administration of furosemide can be promptly decreased to minimize overzealous diuretic therapy and severe dehydration.

Transdermal nitroglycerin is a venodilator that effectively reduces pulmonary capillary wedge pressure and pulmonary edema accumulation in people with heart failure. Although no studies have evaluated the effect of nitroglycerin in cats, it appears safe and well tolerated. One-eighth to one-quarter inch (2–5 mm) of 2% nitroglycerin paste may be applied to the inside of the pinna every 4–6 hours for 1–2 days in cats. Nitrate tolerance develops rapidly within 2 days, so its use is during the first 2 days of hospital treatment, and it should not be dispensed for chronic home therapy. An alternative protocol is administration of the paste as described on the pinna, removal of the paste 12 hours later, and repeat the 12 hours on/12 hours off cycle for 3 days. The main drawback of transdermal nitroglycerin is the lack of efficacy, rather than adverse effects, although precautions are needed for people handling the cat to minimize their own transdermal absorption (i.e., gloves should be worn).

In cats that are not responding to aggressive diuretic treatments, nitroprusside may be a last-ditch attempt to reduce pulmonary venous pressures and left ventricular filling pressures. Nitroprusside is a rapidly acting mixed vasodilator (arteriolar and venous), so careful and frequent monitoring of the blood pressure with a Doppler blood pressure machine is needed. Initial dose of

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2–4 mcg/kg/min is started, and rapid up-titration can be done. Effects may occur within 5 minutes of starting the nitroprusside. Because pulmonary capillary wedge pressure is not measurable by noninvasive methods, a target is to decrease systolic blood pressure by 10–20 mm Hg, depending on the baseline blood pressure. Nitroprusside should not be used in cats with low-normal to low blood pressure (systolic BP <110 mm Hg) because it would exacerbate low output heart failure and create a more severe complication than the congestive heart failure.

Positive inotropic therapy with dobutamine (3–6 mcg/kg/min IV CRI) or pimobendan (0.25 mg/kg PO q 12 h) can be used for cats with "burnt-out" HCM that have significant concentric hypertrophy and also systolic myocardial failure, which is identified by echocardiography as thick ventricular walls and moderate to severely decreased myocardial contractility. This phenomenon is rare and usually represents a terminal stage of the disease associated with a grave prognosis. Cats are often critically ill and appear disoriented, recumbent, weak, dyspneic, and have systemic hypotension. These cases are best managed in the critical care setting, and consultation with a criticalist or cardiologist is recommended. In cats with HCM that have normal myocardial function but systemic hypotension not caused by hypovolemia, dopamine is a preferable choice over dobutamine. Pimobendan should not be given to cats with severe HCM and significant SAM of the mitral valve, since it may worsen the severity of the left ventricular outflow tract obstruction and increase pressure overload to the already hypertrophied left ventricle. Pimobendan is a controversial therapy for cats with refractory heart failure secondary to advanced HCM with systolic dysfunction, but it may be considered for refractory therapy since SAM often is less of a component of the disease in this group of cats. These are cats who continue to accumulate cardiogenic pleural effusion or pulmonary edema despite high or maximal furosemide doses. Pimobendan has been anectodally used in cats but not extensively researched for potential adverse effects in cats, and it is not licensed for use in cats. Adverse side effects may be uncommon (5/161 cats, 3% in a retrospective, uncontrolled survey) and may include vocalization, agitation, anorexia, vomiting, and constipation (MacGregor et al. 2010). In cats with myocardial failure that have been chronically maintained on atenolol, the dose should be decreased and possibly weaned off. However, empirically weaning all HCM cats that decompensate off beta blockers is not necessary, unless heart failure becomes intractable. Reduction in the atenolol dose may be pertinent in cats on chronic beta blocker therapy that have relative bradycardia of <160 bpm in the face of active heart failure.

Often cats with life-threatening heart failure necessitating aggressive diuretic dosages are dehydrated and have prerenal azotemia as well as electrolyte depletions (sodium, chloride, potassium, and calcium). During the aggressive diuretic stage, once to twice a day renal panels (consisting of BUN, creatinine, and electrolytes) and PCV/TS may be considered to follow the degree of azotemia. Mild to moderate azotemia (BUN <60 mg/dl [21 mmol/l], creatinine <2.5 mg/dl [220 mmol/l]) is expected and is typically tolerated without requiring fluids or a change in therapy. Concurrent use of furosemide and intravenous fluids for routine treatment of heart failure is ineffective and counterproductive. Fluid administration is reserved for cats that develop severe prerenal azotemia that requires temporary discontinuation of furosemide and careful fluid administration (1/4–1/2 maintenance rate intravenously of 0.45% NaCl supplemented with potassium if indicated, or 50–75 ml of subcutaneous fluids). Chronic concurrent diuretic and fluid administration, since they are counterproductive, should rather be handled with reduction of one and abolition of the other: a cat that is thought to need high-dose diuretics and "a small dose of fluids to protect the kidneys" in fact is receiving two treatments that negate each other. An appropriate approach would be to administer a lower dose of diuretics and no fluids (same result). The analogy is administering hydromorphone for sedation and concurrently to give naloxone (the reversal agent) to protect against respiratory center depression, which is not as logical as simply administering a lower dose of hydromorphone alone. Titration and monitoring are essential because overzealous fluid administration can result in the return of congestive heart failure. See Chapter 24. Mild to moderate hypokalemia is also expected during aggressive diuresis and often improves as diuretic therapy is tapered. Potassium supplementation with potassium gluconate may be considered in hospitalized cats when the potassium concentration is ≤3 mEq/l. An ACE inhibitor should be withheld during the acute diuresis stage of heart failure treatment, because it may greatly exacerbate azotemia in the dehydrated animal. Ideally, an ACE inhibitor is started after rechecking the cat several days to a week after initial heart failure treatment, after a new baseline renal panel is done with the cat receiving furosemide.

Repeat radiographs may be taken during the course of acute therapy, usually 1–2 days after starting furosemide, to assess for remaining amount of pulmonary edema and help guide the dose of oral furosemide for home care. Another option is to monitor resting respiratory rate and respiratory effort for normalization as evidence of resolution of pulmonary edema. Depending on the amount of dehydration, azotemia, and residual fluid, cats may be

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discharged with furosemide 12.5 mg PO q 12 h for a few days, if mild dyspnea is still present at the time of discharge, and then the furosemide can be decreased to the minimal tolerated dose to achieve RR <40 and normal effort (6.25 mg PO q 12 h is a typical maintenance dose). In cats with significant azotemia (BUN 70 mg/dl (25 mmol/l) or higher, creatinine 3 mg/dl (264 mmol/l) or higher) and resolved heart failure, a lower starting dose of furosemide of 6.25 mg PO q 12–24 h may be more appropriate. The owner should be taught how to count the resting respiratory rate and qualitatively assess respiratory effort at home and instructed to keep a daily written log. This is highly beneficial for making decisions regarding dosage adjustment in individual patients.

Refractory congestive heart failure

Refractory heart failure is present when clinical signs of dyspnea continue occur due to persistent pulmonary edema and/or pleural effusion despite increasing doses or maximal dose of furosemide (3–4 mg/kg PO q 8–12 h) in a compliant patient that is reliably receiving the medication. Cats commonly have progressive heart failure over time, requiring up-titration of the furosemide dose, yet refractory heart failure requiring 4 mg/kg PO q 8 h is unusual. In cats requiring maximal furosemide doses, the issue of owner and patient compliance with medication administration should be investigated, and compounding the furosemide may be an option in cats that resent the pill form. Mild to moderate prerenal azotemia and dehydration are expected in cats receiving high doses of furosemide but are a necessary evil compared to life-threatening dyspnea from progressive heart failure. Some cats are intolerant to high furosemide doses and develop symptoms referable to dehydration and azotemia. The furosemide dose may be decreased in these cases, and if there is a lack of improvement in symptoms of dehydration, one or two subcutaneous fluid administrations with low volumes (50–60 ml) may be given temporarily but not on an ongoing basis. In cats with concurrent symptoms from severe dehydration and azotemia as well as severe dyspnea from congestive heart failure, no effective therapy exists and euthanasia may be a feasible option.

Cats with significant heart failure despite maximal furosemide doses may benefit from addition of hydrochlorothiazide (1–2 mg/kg PO q 12–24 h) starting at the low end of the dose and increasing as necessary. Spironolactone is not a very effective diuretic but may provide adjunctive treatment to reduce hypokalemia and reduce some of the deleterious effects of aldosterone. In a study of 26 cats with asymptomatic HCM, 1/3 of cats treated with spironolactone developed severe ulcerative facial dermatitis 2.5 months after treatment, so careful monitoring for adverse skin reactions is recommended. Aldactazide is a combination of hydrochlorothiazide and spironolactone, which is used in dogs with refractory heart failure, but it may not be as attractive for use in cats given the possibility of an adverse reaction to spironolactone.

A low salt diet may be implemented, if palatable, in cats receiving moderate furosemide doses and an ACE inhibitor. Low salt cardiovascular diets contain 0.15–0.2 g sodium/1000 kcal, and help limit sodium and water retention. The nutritional priority in cats is to maintain an adequate caloric intake, rather than forcing an unpalatable low-salt diet to a cat that remains anorexic. Low-salt diets are available as prescription commercial diets (Purina CV or Hills H/D) or one can be formulated by a nutrition service. Owner-formulated home-cooked diets are discouraged unless they are balanced by a veterinary nutritionist (useful resources include balanceit.com; Home-prepared Dog and Cat Diets, The Healthful Alternative, DR Strombeck, 1999.) Low-salt diets also activate RAAS, so cats should also be given an ACE inhibitor. Renal diets are protein restricted, which may hasten development of cachexia in heart failure patients. They may be indicated in patients with concurrent moderate to severe renal disease and heart failure.

Prophylactic anticoagulant therapy

Prophylactic anticoagulant therapy is indicated in cats that have had a history of ATE or have echocardiographic evidence of spontaneous contrast (i.e., red blood cell aggregation) or intracardiac thrombus. Some cardiologists, including the authors, use prophylactic anticoagulant therapy in cats with moderate or severe left atrial dilation, who are likely at greater risk of developing ATE. The incidence of ATE in cats with HCM is 16–18% (Rush et al. 2002; Atkins et al. 1992). Anticoagulant choices include low-dose aspirin (5–81 mg PO q 3 days), clopidogrel (18.75 mg PO q 24 hr with food), low molecular weight heparin (Lovenox 1.5 mg/kg SC BID-TID), or warfarin. There are no controlled studies comparing effects of the most commonly used anticoagulants (aspirin, clopidogrel, and enoxaparin) on development of arterial thromboembolism in cats, although a large multicenter study in cats suffering from ATE that were treated with aspirin versus clopidogrel has been conducted and results are pending. In cats with spontaneous contrast seen by echocardiography, repeat echocardiographic assessment of spontaneous contrast should be done after anticoagulant therapy is started, and combination therapy may be needed for cats with persistent spontaneous contrast.

Medications Not Indicated or Contraindicated

Because taurine and carnitine deficiencies do not cause or contribute to development of HCM, their supple-

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mental use is not indicated for treatment of HCM. Positive inotropic agents such as digoxin or digitalis-like homeopathic therapies (hawthorne, compounds including strophanthus, foxglove, lily-of-the-valley, rhododendron, oleander, milkweed) should not be given to cats with HCM, because they may worsen the severity of SAM and increase pressure overload to an already hypertrophied left ventricle. Based on current knowledge, inodilators such as pimobendan are relatively contraindicated in cats with HCM unless there is end-stage myocardial failure or possibly in refractory heart failure. This relative contraindication may change with greater research on the potential risk versus benefit analysis of inodilators in cats with HCM. Pimobendan is never a substitute for an ACE inhibitor in cats with congestive heart failure, and if indicated, it is given in addition to standard therapy with furosemide and an ACE inhibitor. The use of long-acting corticosteroids, such as methylprednisolone acetate, is contraindicated in cats with HCM, since it may significantly increase plasma-circulating volume and may precipitate development of heart failure.

Considerations for General Anesthesia

Cats with HCM may require anesthesia for routine procedures (dental prophylaxis, dental extractions) or for diagnostic/therapeutic procedures of other more significant systemic disease. The main concerns regarding anesthesia are minimizing fluid overload, avoidance of hypotension, and avoidance of pharmacologic agents that may worsen the severity of left ventricular outflow tract obstruction in cats with SAM or exert proarrhythmic effects. In a study of cats with congestive heart failure, the most common precipitating event was fluid administration (28%), followed by anesthesia/surgery (25%) and recent corticosteroid administration (21%) (Rush et al. 2002). Ketamine was the most common anesthetic administered in 89% of anesthetized cats that developed CHF, but it was probably the most common anesthetic drug used in cats during the time of that study. Ketamine increases heart rate and contractility, which may worsen left ventricular outflow tract obstruction in cats with significant SAM. Worsened SAM increases systolic left ventricular pressure and may decrease myocardial perfusion and increase left ventricular filling pressure. Despite the "dogma" that cats with heart disease should not be given ketamine, there is a paucity of data detailing specific significant deleterious cardiac effects.

Cats with severe HCM and heart failure have a much higher risk of adverse anesthetic or postanesthetic events than cats with compensated heart disease, and elective procedures should be avoided. However, cats with mild HCM and normal left atrial size have less risk of adverse cardiac events, and are less likely to become fluid overloaded compared to cats with left atrial dilation and/or heart failure. However, even cats with HCM and normal left atrial size are at risk for fluid overload, since they have reduced left ventricular compliance and diastolic dysfunction. For specific protocols and details regarding sedation and anesthesia of cats with HCM, see Chapter 27.

COMPLICATIONS AND MONITORING

Key Points

- Congestive heart failure, arterial thromboembolism, and sudden cardiac death are the most common and devastating clinical sequelae in cats with HCM
- Prerenal azotemia and dehydration are common in heart failure patients treated with furosemide ± an ACE inhibitor and are typically well tolerated unless severe.
- Mild functional azotemia is common following ACE inhibitor therapy, and does not require altering the therapeutic plan. Severe functional azotemia is addressed by stopping the ACE inhibitor, temporarily stopping the furosemide, and cautious fluid diuresis.
- Supraventricular tachyarrhythmias such as atrial fibrillation or supraventricular tachycardia require treatment with either atenolol or diltiazem. Ventricular tachycardia should be treated with atenolol. Sotalol ± mexiletine may be used for refractory ventricular arrhythmias.
- Monitoring of asymptomatic cats with HCM includes repeat echocardiograms every 4–12 months depending on the severity and progression of the disease. To evaluate for early heart failure, radiographs should be obtained periodically (every 3–6 months) in cats with significant left atrial dilation. These recommendations must be balanced against the patient's anxiety and the client abilities in all cases individually.
- Monitoring of cats with HCM and heart failure includes repeat thoracic radiographs and renal panels to assess clinical response and guide medical therapy. Thoracic ultrasound can be done to evaluate severity of pleural effusion and guide location for thoracocentesis. Targeted repeat echocardiograms are done periodically (every 3–6 months) to assess for presence of an intracardiac thrombus, or spontaneous contrast, and to evaluate myocardial function.
- Systolic blood pressure and thyroxine levels should be periodically evaluated in middle-aged to older cats that are at risk for developing systemic hypertension or hyperthyroidism.

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The most common devastating sequelae to severe HCM are congestive heart failure, arterial thromboembolism, or sudden cardiac death due to a severe arrhythmia or large intracardiac thrombus. Complications may also arise secondary to medical treatment of heart failure. Progressive prerenal azotemia, dehydration, and hypokalemia are the most common complications of heart failure therapy. Cats with underlying renal insufficiency may be precarious heart failure patients, and may develop significant exacerbation of azotemia and dehydration on heart failure therapy. Cats with known renal insufficiency that are diagnosed with heart failure are cautiously treated with lower doses of furosemide, and renal values are more frequently monitored—initially in 5–7 days after starting medications, then a 2–4 weeks later and then potentially every 3 months. Once the heart failure is stabilized, low-dose ACE inhibitor therapy may be started (consider benazepril or ramipril since their blood levels are not increased by presence of renal insufficiency), and a renal panel checked before and after up-titration. ACE inhibitor induced functional azotemia may occur in some cats and is identified as moderate to severe azotemia that develops after starting an ACE inhibitor. Cats with moderate or severe azotemia are often anorexic, which worsens dehydration and perpetuates the vicious circle of azotemia. These patients often require temporarily stopping the furosemide, permanently discontinuing the ACE inhibitor, and judicious use of fluids. Daily subcutaneous fluids can be administered for several days (50–75 ml SC) and then stopped, and then the furosemide restarted and slowly up-titrated. Potassium gluconate or spironolactone can be given to cats with significant hypokalemia secondary to diuretic therapy.

Chronic weight loss is another complication of heart failure, and is likely due to poor nutritional intake and catabolic influences of inflammatory cytokines such as tumor necrosis factor. Renal prescription diets that are moderately sodium restricted are sometimes given to cats with heart failure, and may be appropriate provided they contain sufficient protein and energy. See Chapter 24.

Cats with HCM may develop significant tachyarrhythmias as the heart disease progresses. These cats may have episodes of weakness, syncope, or marked lethargy. Atrial fibrillation or supraventricular tachycardia may develop secondary to severe left atrial dilation and pathologic remodeling. Antiarrhythmic therapy is indicated for treatment of rapid and/or symptomatic supraventricular tachyarrhythmias and ventricular tachycardia (see Chapter 18). Supraventricular arrhythmias (atrial fibrillation and supraventricular tachycardia) can be treated with atenolol, diltiazem, or sotalol. Concurrent use of both a beta blocker and calcium channel blocker is to be avoided since it may cause severe negative inotropic and chronotropic effects and hypotension. Ventricular arrhythmias that require treatment include ventricular tachycardia, frequent ventricular couplets and triplets, or frequent multiform ventricular premature complexes with R on T phenomenon. Atenolol is the first choice ventricular antiarrhythmic, followed by sotalol or mexiletine. A combination of a beta blocker and mexiletine may be necessary. Omega 3 fatty acids may provide adjunctive treatment for ventricular arrhythmias, and may also aid in treatment of cardiac cachexia by reducing endogenous levels of tumor necrosis factor.

Monitoring the Asymptomatic Cat

Echocardiography is the main tool for monitoring progression of ventricular hypertrophy and diastolic dysfunction in asymptomatic cats with HCM. Progressive concentric hypertrophy (moderate to severe) and worsened SAM (moderate to severe) may indicate the need to start a beta blocker or calcium channel blocker. Progressive left atrial dilation occurs when there are increased diastolic filling pressures with progressive heart disease, and heart failure or arterial thromboembolism may be sequelae. Radiographs may be taken in cats with echocardiographic evidence of severe left atrial dilation to assess for presence of congestive heart failure. Repeat echocardiograms can be done every 4–12 months, depending on the disease severity, whether there is static or progressive cardiac disease, and financial considerations. Often young purebred cats require more frequent follow-up (every 3–6 months) since they tend to have more severe and rapidly progressive heart disease. Progressive left atrial dilation is an ominous sign of progressive diastolic dysfunction and elevated left atrial pressure, with high risk of heart failure or arterial thromboembolism. Cats with significant left atrial dilation should have repeat thoracic radiographs every 3–5 months to identify early heart failure, so heart failure medications can be started prior to development of significant dyspnea. Perceptive and engaged owners can be trained to monitor resting respiratory rate and respiratory effort, and may alert the doctor if there is a persistently elevated respiratory rate (≥40 breaths/min) on multiple consecutive measurements several hours apart. Owners can be counseled that a mildly increased resting respiratory rate and effort may not necessarily represent a cardiac emergency, but it may necessitate reevaluation to assess for development of heart failure.

Echocardiographic assessment of spontaneous contrast should also be done periodically in cats with HCM and left atrial dilation and if present, this finding would

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warrant the initiation or intensification of anticoagulant therapy. Periodic measurement of blood pressure, renal values, and thyroxine level should be done in middle age to older cats. Hypertension and hyperthyroidism may develop over time independently from HCM and exert deleterious cardiac effects.

Monitoring the Symptomatic Cat with HCM and Heart Failure

Follow-up thoracic radiographs are essential to monitor efficacy of diuretic therapy and identify reaccumulation of pulmonary edema or pleural effusion. Pulmonary venous distension and subtle perihilar interstitial infiltrates are early signs of heart failure, which would dictate mildly increasing the furosemide dose. Although serial BNP blood tests are helpful to monitor people with heart failure, serial monitoring in cats with heart failure is not established and no clinical data is available on its utility for aiding dose titration of diuretics in feline heart failure. Radiographs may be taken after a week of initiating diuretic therapy, and then intermittently (every 3–4 months) in compensated cats on heart failure therapy. In cats that have persistent heart failure despite medical therapy, repeat radiographs are done a week after increasing the diuretic dose. Renal panels are also followed at the same rechecks as radiographs. In cats that develop pleural effusion as the main cause of dyspnea, ultrasound may be useful to quickly assess the severity of pleural effusion and whether thoracocentesis is necessary. If there is not significant pleural effusion, thoracic radiographs are recommended to evaluate whether pulmonary edema is present. Review of the resting respiratory rate and effort log may be very informative in cats that are unable to have routine recheck radiographs, with high suspicion of recurrent heart failure if the resting respiratory rate is persistently >40 breaths/minute or the respiratory effort is persistently increased. Although unusual, some cats have more than mild congestive heart failure demonstrated on radiographs despite normal resting respiratory rate.

Periodic thoracocentesis is often needed to remove pleural effusion in cats with heart failure. The rapidity of pleural effusion accumulation serves as a prognostic indicator for early cardiac death. The furosemide dose usually should be significantly (and aggressively) increased in cats with rapidly progressive pleural effusion requiring thoracocentesis more than twice a month. Most cats tend to tolerate thoracocentesis for palliative treatment of pleural effusion on a monthly or longer basis (ideally the longer the better), and tractability of the cat, and the owner's ability to return for the procedure, may play a pivotal role in centesis frequency. Chronic deleterious effects of pleural effusion include pleural fibrosis or loculated small pockets of pleural effusion, which are less amenable to removal and palliation by thoracocentesis.

Recheck echocardiograms in cats with severe HCM and heart failure are targeted to specifically evaluate whether there is spontaneous contrast or an intracardiac thrombus and confirm that there is still adequate myocardial function. It is rare but possible that cats with severe HCM may develop myocardial failure in the end-stage of disease (i.e., "burnt-out" HCM), and these cats may benefit from addition of pimobendan and possibly reducing or tapering of atenolol.

OUTCOME AND PROGNOSIS

Survival time is highly variable in cats diagnosed with HCM. Young, male, purebred cats (especially Ragdoll cats) tend to have more severe disease that is rapidly progressive. In a study of homozygous affected Maine coon cats with familial HCM, severe concentric hypertrophy was usually present by 12 months of age, heart failure by 20 months of age, and most cats died by 4 years of age (Kittleson et al 1999). In a study of 260 cats diagnosed with HCM, median survival time of cats surviving more than 24 hours from time of diagnosis was 709 days (range 2–4418 days) (Rush et al. 2002). Median survival time was 1129 days (range 2–3778 days) in asymptomatic cats, 563 days (range 2–4418 days) in cats with heart failure, and only 184 days (range 2–2278 days) in cats suffering from ATE. Each cat is an individual, and the bell curve is wide with marked range in survival times, so diagnosis does not equal imminent death. As in people, increased left atrial size and age were negative predictors of survival (Rush et al. 2002). Another study of 74 cats with HCM reported median survival time of >1830 days in asymptomatic cats, but only 92 days for cats in heart failure, and 61 days for cats with ATE (Atkins et al. 1992). Half of cats with heart failure and all cats with ATE were not alive after 6 months. Based on clinical experience, the prognosis is good for cats with mild static HCM that have normal left atrial size and minimal progression in ventricular hypertrophy over 12–16 months, and these cats often have normal life spans. Once significant left atrial dilation occurs, there is a high likelihood of development of heart failure within months to 2 years. Once heart failure develops, it is the authors' experience that cats tend to live for between several weeks and 18 months, and most fewer than 8 months depending on presence of reversible trigger for heart failure (better prognosis), rapid progression of structural cardiac changes (worse prognosis), and owner participation, abilities, and insight (better prognosis).

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12

Restrictive/Unclassified Cardiomyopathy

Key Points

- Restrictive cardiomyopathy is a form of cardiomyopathy characterized by normal ventricular wall thickness and myocardial dysfunction that is primarily diastolic (filling).
- In the cat it is an adult-onset disorder, with an average age of diagnosis of approximately 7 years.
- Echocardiographic diagnosis is based on the presence of a dilated left or left and right atria with a fairly "normal" appearance to the ventricle in the absence of other structural defects (ventricular septal defect, mitral valve dysplasia, etc.).
- Treatment is palliative and based on the clinical signs of the individual cat.

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy (RCM) is an adult-onset myocardial disease that appears to be less prevalent than hypertrophic cardiomyopathy but more prevalent than dilated cardiomyopathy in cats. One report of 106 cats with cardiomyopathy identified RCM in approximately 20% of them, compared to 58% for hypertrophic cardiomyopathy (Ferasin et al. 2003). Restrictive cardiomyopathy is characterized by a normal or mildly reduced myocardial systolic function, normal wall thickness, and diastolic (filling) dysfunction. Because it can have both systolic and diastolic dysfunction it was sometimes referred to as an "intermediate cardiomyopathy," but *restrictive cardiomyopathy* is the more proper term. In some cases, endomyocardial fibrosis is also observed and has resulted in the division of RCM into two possible forms: myocardial and endomyocardial restrictive cardiomyopathy. By definition, RCM is demonstrated to exist via the confirmation of a restrictive diastolic ventricular filling pattern, typically with Doppler echocardiography. Due to various circumstances (tachycardia causing wave fusion, poor technique, lack of availability of the Doppler modality, postmortem specimens, etc.), such a filling pattern may not always be demonstrable in a given cat.

ETIOLOGY, PATHOPHYSIOLOGY, AND GROSS PATHOLOGY

Etiology

It has been suggested that RCM may actually be the end result of other forms of cardiomyopathy including severe, end-stage hypertrophic cardiomyopathy that has been complicated by a myocardial infarction or myocardial failure (Bonagura and Fox 1995). An alternative theory might be that RCM is the result of an infectious organism since histopathologic evidence of myocarditis and viral DNA from panleukopenia virus was observed in a small number of cats with RCM (Meurs et al. 2000). Finally, in human beings, one form of RCM is associated with infiltration of eosinophils into the myocardium (Kushwaha 1997). This is not likely to be a common cause of RCM in the cat, although it has been observed in a few case reports (Fox 2004; Saxon 1991). In 1 case, it was observed with a significant peripheral eosinophilia (Saxon 1991).

Some human beings develop RCM as a familial trait, and causative mutations have been identified in cardiac troponin I, cardiac troponin T, and cardiac actin genes (Sen-Chowdhry et al. 2010) The importance of an inheritable etiology of RCM in the cat is not yet known.

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Pathophysiology

A stiffened left ventricle leads to elevated left ventricular diastolic pressure, dilation of the left atrium, pulmonary venous congestion, and left heart failure. Some cats appear to develop pulmonary hypertension, and severe right atrial dilation may be noted. Many cats have greatly dilated left and right atria and develop thromboembolic episodes as well as atrial tachyarrhythmias including atrial fibrillation (Côté et al. 2004).

Pathology

Heart weight and heart weight to body weight are generally mildly to moderately increased (Fox 2004). The left ventricular wall thickness should be normal, but there may be some regional areas of thinning or hypertrophy. The left atrium is typically severely dilated. The left ventricular endocardium may be covered with an opaque, white-gray fibrous material, particularly in the left ventricular outflow or on the papillary muscles. Some cats will have an irregular endocardial fibrosis in the left ventricle that bridges to the interventricular septum (Figure 12.1). Focal or diffuse fibrous tissue through the endocardium, subendocardium, and myocardial regions are characteristic for the disease (Liu 1985) (Figure 12.2). Inflammatory cells consistent with myocarditis may be present. In advanced cases, arteriosclerosis in the intramural coronary arterioles may be observed in the left ventricular free wall and septum (Liu 1985).

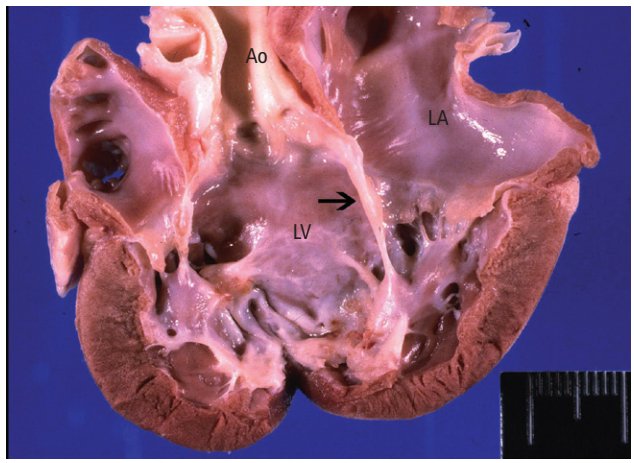


Figure 12.1. Gross pathology of a heart from a cat with restrictive cardiomyopathy. A large fibrotic bridging band (arrow) tethers the papillary muscles and left ventricular free wall to the basilar interventricular septum. Diffuse, severe endomyocardial fibrosis is evident as a thickened, white appearance of the endomyocardium with a dense hyperechoic scar in the left ventricle (LV). Left atrial (LA) dilation is observed. Ao = aorta.

SIGNALMENT

This is an adult onset disease. The average age at diagnosis has been reported as 7 ± 3 years (Ferasin et al. 2003). Specific breed predispositions have not been identified, although it has been reported in Birmans, Siamese, and Persians as well as domestic shorthair and longhair (Meurs et al. 2000; Ferasin et al. 2003).

HISTORY AND CHIEF COMPLAINT

The presenting complaints may be vague and include dyspnea, tachypnea, and anorexia. Restrictive cardiomyopathy does have a high incidence of secondary thromboembolic disease, so hindlimb paralysis may be noted.

PHYSICAL EXAMINATION

A gallop sound has been suggested as a common auscultatory abnormality in some reports although a soft heart murmur is often heard over the left apex or at the sternum as well. In one report, a murmur was recorded in 36% of the cases (Ferasin et al. 2003). A tachyarrhythmia may be heard. Importantly, many affected cats will not have any auscultable abnormalities, which may explain the perceived severity of this disease if it generally escapes notice until overt clinical signs are present.

DIFFERENTIAL DIAGNOSIS

Unclassified cardiomyopathy may have a similar presentation. In general, the term unclassified cardiomyopathy is used when there are structural hallmarks of RCM without proof of impaired diastolic ventricular filling.

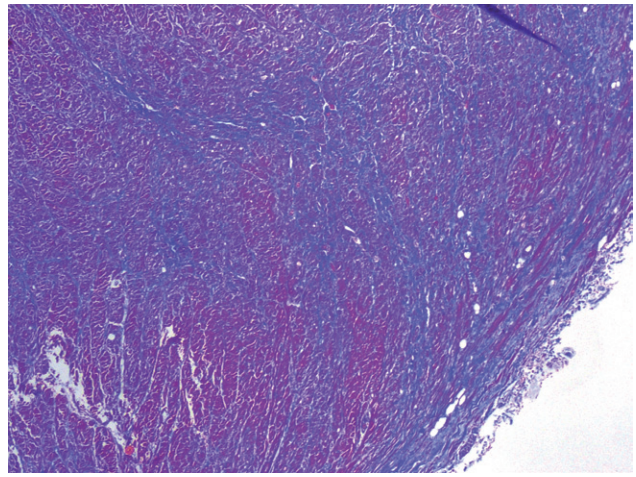


Figure 12.2. Histopathologic sample from the left ventricle of a cat with restrictive cardiomyopathy. The tissue is stained with a trichrome stain which causes the fibrous tissue to appear blue. Note the diffuse fibrous tissue throughout the myocardium.

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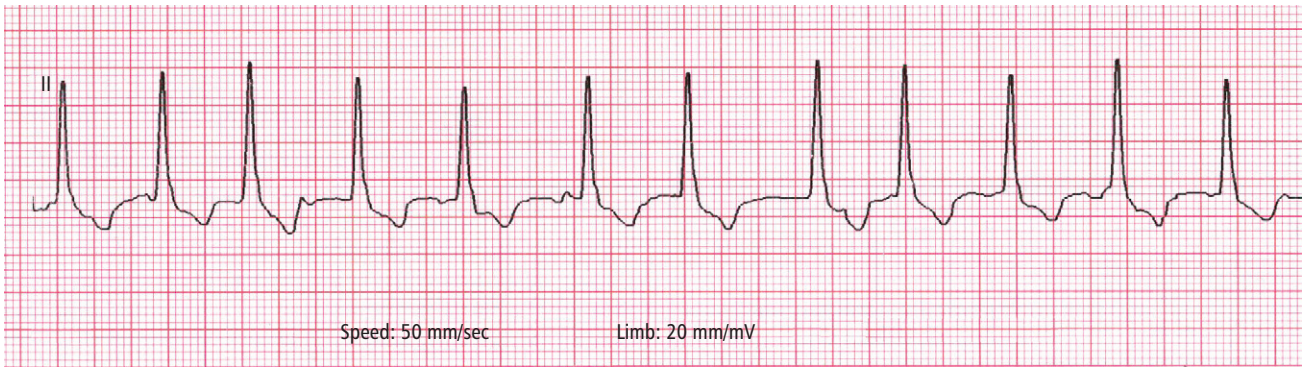


Figure 12.3. Lead II electrocardiogram from a cat with restrictive cardiomyopathy. Atrial fibrillation is noted due to the lack of P waves and the irregular rhythm.

Additionally, in some cases, end-stage hypertrophic cardiomyopathy with ventricular wall thinning secondary to a myocardial infarct may have a similar presentation to RCM. There may be some cases in which it is not possible to state with certainty that a specific diagnosis of RCM, unclassified cardiomyopathy, or end-stage HCM exists. However, at this time, the distinction is clinically negligible because the disorders are treated identically and have the same prognosis.

DIAGNOSTIC TESTING

Electrocardiography

There are no specific electrocardiographic findings for RCM although a left axis shift may be observed. Supraventricular or ventricular premature complexes may be identified. Atrial fibrillation has been frequently observed and is likely associated with the very large atria that are often observed with this disease (Figure 12.3) (Côté et al. 2004).

Radiography

Evidence of moderate to severe left atrial or biatrial enlargement is often seen (Fox 2004). Left or biventricular heart failure may be observed, including pulmonary edema or pleural effusion.

Echocardiography

Moderate to severe left atrial or biatrial enlargement is the most common finding, and when observed in the face of normal left ventricular wall thickness and normal or mildly decreased systolic function, a diagnosis of RCM should be considered (Figure 12.4). Pericardial effusion is sometimes observed in severe cases with congestive heart failure.

Some cats have a form of RCM characterized by endomyocardial fibrosis. This may be identified by endocardium involvement, with obvious thickening or scarring that may obstruct some of the left ventricular lumen. An irregular hyperechoic endocardial region that obstructs some of the left ventricular lumen may be observed.

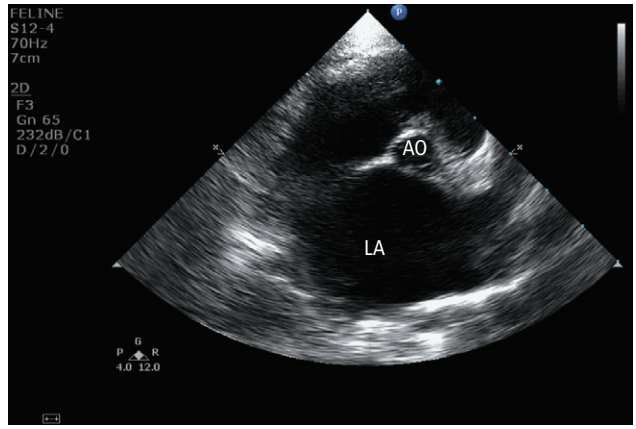


Figure 12.4. 2D short-axis echocardiographic view from a cat with restrictive cardiomyopathy. Note the large dilated left atrium (LA) in comparison to the aorta (Ao).

Doppler echocardiography may identify mitral regurgitation, typically mild. Transmitral flow velocities may be used to help assess diastolic function (see Chapter 13). Abnormal relaxation patterns including an increased isovolumetric relaxation time, an E wave with reduced peak velocity, and an increased A wave velocity (low E:A ratio) may be observed. More commonly, a restrictive filling pattern with a shortened relaxation time, increased E wave, and shortened A wave (high E:A ratio) is present (Luis Fuentes 2003) (Figure 12.5). However, transmitral flow velocities may be difficult to identify in the cat with a rapid heart rate.

Diagnosis

Ultimately the diagnosis of RCM will be dependent on echocardiographic findings of severe left atrial

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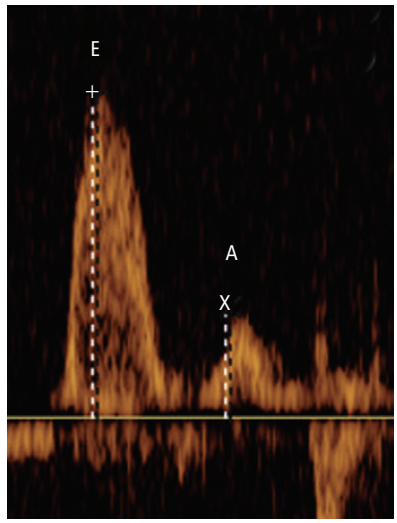


Figure 12.5. Transmitral flow velocities from a cat with restrictive cardiomyopathy. Note the restrictive filling pattern with increased E wave and shortened A wave (high E:A ratio) (see Chapters 7 and 11).

enlargement and typically normal ventricular wall thickness. A hyperechoic appearance to the endocardial surface may be observed as well as moderately decreased systolic dysfunction.

Pathologic findings should include an increase in heart weight, and biatrial dilation with normal wall thickness and an absence of other structural defects (ventricular septal defect, mitral valve dysplasia, etc.) that could explain the changes.

TREATMENT

There is no specific therapy for RCM. Treatment is directed at palliation of clinical signs that may be present from arrhythmias or congestive heart failure. If heart failure is present, diuretics including furosemide and an ACE inhibitor should be considered (see Chapter 19).

If myocardial dysfunction is observed, pimobendan may be considered at a dose of 1.25–1.5 mg/cat PO q 12 hours, although its use in cats is not yet approved in the United States (Sturgess and Ferasin 2007, MacGregor et al. 2010).

Because cats with RCM are at a high risk of thromboembolic disease, consideration of anticoagulents for possible prevention of embolic disease is warranted, particularly for cats with significant left atrial enlargement (usually a left atrium to aorta ratio of 1.9 or greater) (see Chapter 20).

If a supraventricular arrhythmia resulting in an elevated heart rate is present, medical therapy to control the heart rate may be indicated, including digoxin or diltiazem (see Chapter 18). Cats that are being treated for rapid supraventricular tachyarrhythmias (atrial fibrillation, etc.) should be managed to ideally have a heart rate of 140–160 beats per minute on medication when examined at the hospital.

COMPLICATIONS AND MONITORING

Because cats with RCM appear to be at an increased risk of thromboembolic disease, owners should be advised to observe for signs of sudden paralysis, most commonly of the hindlimbs, but sometimes of a forelimb.

Congestive heart failure is often a complication. Owners should monitor the respiratory rate at home in a resting state once a day if possible; ideally it should be less than 30 breaths per minute. An increase in respiratory rate may be an indication of the development of pulmonary edema or pleural effusion.

Once the initial diagnosis is made, reevaluation and adjustment of medications is typically directed at control of the clinical signs of heart failure. Much of this can be based upon history (owner's record of daily respiratory rate at home) physical examination, radiographs, and blood pressure. A renal profile to monitor BUN, creatinine, and electrolytes is also helpful to guide drug therapy. Rechecking echocardiography may be needed only if acute changes occur, such as sudden decompensation, or acute development of signs suggestive of thromboembolism.

OUTCOME AND PROGNOSIS

Unfortunately, the long-term prognosis is generally poor. Many cats succumb to heart failure or a thromboembolic episode. The extensive degree of the lesion at the time of presentation suggests that most cats with RCM present late in the course of disease. Treatment of congestive heart failure and/or aortic thromboembolism prophylaxis is successful in many cats but response rate and time to recurrence are highly variable, and they likely depend on owner commitment. The median survival of 16 cats with RCM was 132 days in one study (Ferasin et al. 2003).

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13

Dilated Cardiomyopathy

Key Points

- Dilated cardiomyopathy is an adult onset myocardial disease characterized by systolic dysfunction.
- Dilated cardiomyopathy was most commonly associated with taurine deficiency but this is now rarely observed in cats on a balanced, feline diet. The etiology of many cases is unknown.
- Affected cats that are eating a taurine-deficient diet may respond well to taurine supplementation.

INTRODUCTION

Dilated cardiomyopathy is an adult onset primary myocardial disease characterized by dilation of the left ventricular lumen and decreased systolic myocardial function. Occasionally dilated cardiomyopathy is referred to by other names, including *congestive cardiomyopathy* or *myocardial systolic dysfunction*. Dilated cardiomyopathy used to be the most common form of feline myocardial disease until it was determined that many cats suffered from taurine deficiency due to insufficient levels of taurine in commercial pet food (Pion et al. 1987). It is now considered an uncommon feline myocardial disease.

ETIOLOGY, PATHOPHYSIOLOGY, AND GROSS PATHOLOGY

Etiology

The prevalence of dilated cardiomyopathy in the cat is not well known but it is certainly much less than that of hypertrophic cardiomyopathy. One report of the prevalence of dilated cardiomyopathy in the late 1990s found a prevalence of about 5–7% (Fox et al. 1999). The prevalence of this form of cardiomyopathy has significantly decreased now that commercial pet foods are properly supplemented with taurine, but it is still occasionally diagnosed even in cats on a normal diet. Dilated cardiomyopathy associated with taurine deficiency is still observed in cats receiving unbalanced diets (vegetarian, certain homemade diets, diets designed for other species [i.e., dog food]). Interestingly, there is some indication that there may be a heritable component to the development of dilated cardiomyopathy associated with taurine deficiency with some families at greater risk of developing cardiomyopathy than others (Lawler et al. 1993; Novotny et al. 1994).

Additionally, feline dilated cardiomyopathy is still recognized in small numbers of cats eating an appropriate diet; the etiology of dilated cardiomyopathy in these cases is unknown. A recent report of feline cardiomyopathy that included 11 cats with dilated cardiomyopathy did not find any to be associated with taurine deficiency (Ferasin et al. 2003).

Viral nucleic acid and histopathologic findings consistent with myocarditis were identified in a small number of cats with dilated cardiomyopathy; therefore, an infectious etiology has been suggested for some cases (Meurs et al. 2000). Viral myocarditis is also associated with the development of dilated cardiomyopathy in humans and other species (Hare 2008).

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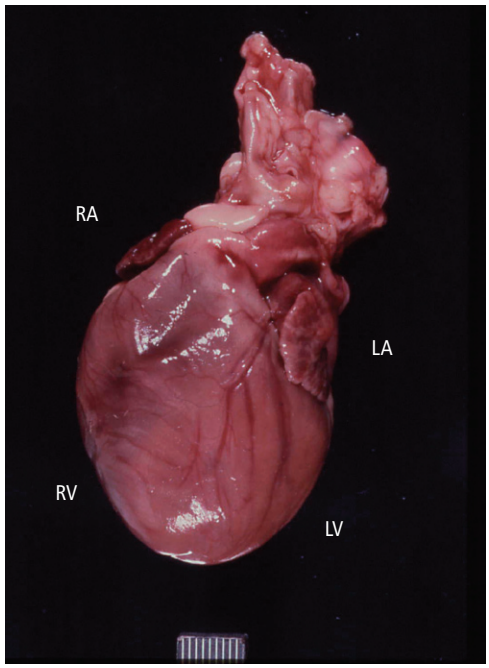


Figure 13.1. Heart from an adult cat with dilated cardiomyopathy. Note the large dilated left auricle (LA) and left ventricle (LV). RA = right auricle; RV = right ventricle.

Pathophysiology

Dilated cardiomyopathy is a progressive myocardial disease that appears to begin with a decrease in myocardial systolic function and progresses to left ventricular dilation. Increased left atrial pressure, pulmonary venous congestion, and pulmonary edema develop as a result of the myocardial dysfunction and dilation. Biventricular failure with pleural effusion is also often noted. Thromboemboli and arrhythmias may also develop.

Pathology

The left atrium and ventricle are typically dilated and in severe cases all 4 chambers can be dilated (Figure 13.1). The left ventricular wall may appear to be thin but generally measures normally. Histopathologic findings are nonspecific but can include myocytolysis, myofibril fragmentation, and fibrosis.

SIGNALMENT

Strong breed predispositions have not been observed; DCM has been reported in Persian, domestic shorthair, domestic longhair, Birman, Siamese, and Burmese breeds (Ferasin et al. 2003). Dilated cardiomyopathy is an adult onset disease with an average reported age in one study of 9 years of age (Ferasin et al. 2003).

HISTORY AND CHIEF COMPLAINT

Presenting complaints may include those consistent with heart failure, including dyspnea, tachypnea, and anorexia. Thromboembolic episodes do occur and hindlimb paralysis may be noted. In some cases, although much less commonly, the embolus may go to a forelimb or to the brain where it results in asymmetric neurologic signs.

PHYSICAL EXAMINATION

A soft heart murmur of mitral regurgitation may be heard over the left apex and was detected in 13/77 cats in one study (Sisson et al. 1991). An arrhythmia may be ausculted and gallop sounds are frequently heard (79%) (Sisson et al. 1991).

Cats with taurine deficiency may have central retinal lesions so a retinal evaluation may help identify increased suspicion of taurine deficiency (Pion et al. 1987).

DIFFERENTIAL DIAGNOSIS

The most common differential diagnoses include unclassified cardiomyopathy and hypertrophic cardiomyopathy with an infarct resulting in regional wall hypokinesis.

DIAGNOSTIC TESTING

Electrocardiography

The electrocardiogram may be within normal limits; however, many arrhythmias have been observed including sinus tachycardia and atrial or ventricular premature complexes. Atrial fibrillation has been observed with feline DCM (Côté et al. 2007).

Bradyarrhythmias including AV blocks have been observed. Enlargement patterns consistent with left atrial (P wave duration >0.04 seconds) and/or ventricular (R wave >0.9 mV in lead II) enlargement may be observed.

Radiography

Radiographs may be consistent with cardiac disease but are not diagnostic for the specific form of cardiomyopathy. Evidence of left or biventricular heart failure may be observed including pulmonary edema or pleural effusion (Figure 13.2).

Echocardiography

Dilated cardiomyopathy is diagnosed when the left ventricle is found to be dilated (>11 mm at systole and/or >16 mm in diastole). Systolic function is decreased with

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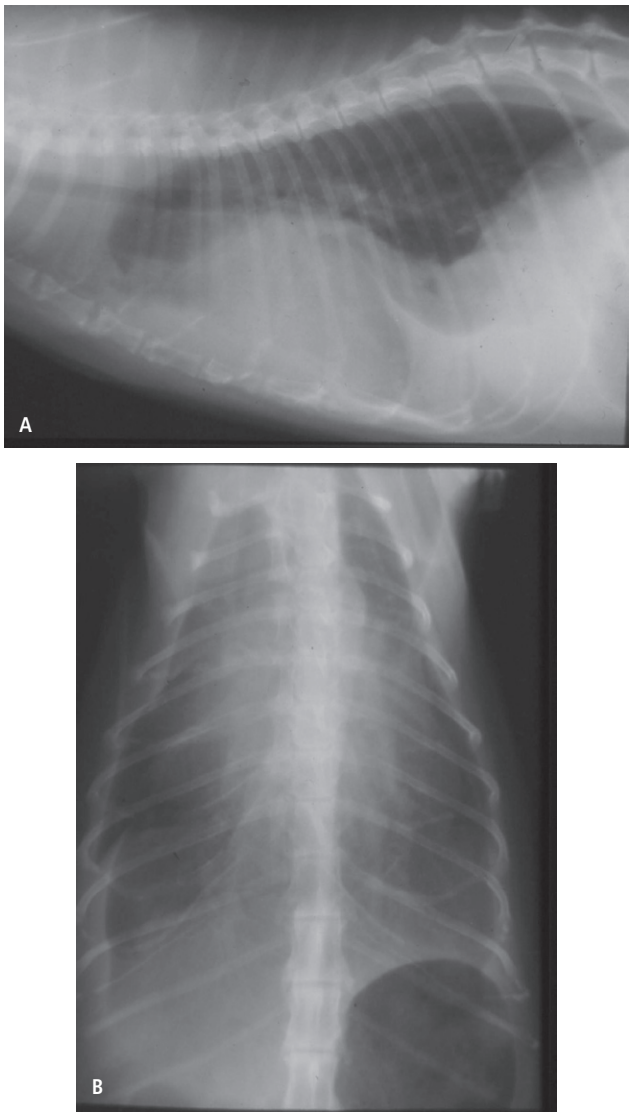


Figure 13.2. Radiographs from a cat with dilated cardiomyopathy and congestive heart failure; both pleural effusion and pulmonary edema are present. **(A)** = lateral view; **(B)** = dorsoventral view.

a left ventricular fractional shortening <20% (Figure 13.3). Usually the systolic dysfunction precedes the dilation. Left atrial enlargement is often observed as well. In some cases, right atrial and ventricular dilation may be observed.

Doppler findings typically demonstrate mitral regurgitation. Mitral valve inflow velocities may demonstrate relaxation abnormalities including an increased isovolumetric relaxation time, an E wave that may have a reduced peak velocity, and increased A wave velocity (low E:A ratio) (see Chapter 11) as well as systolic dysfunction (Luis Fuentes 2003).

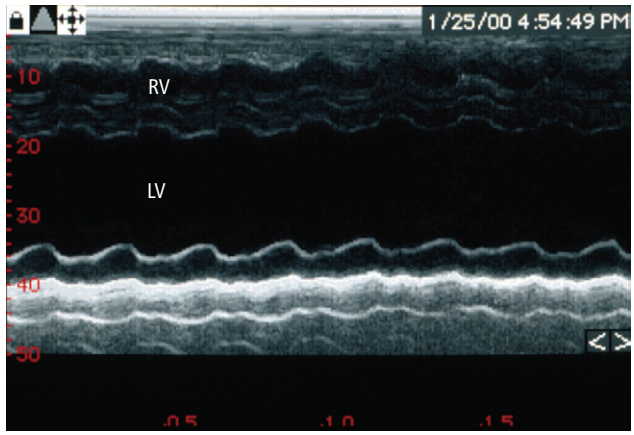


Figure 13.3. M-mode echocardiogram of left ventricle from an adult cat with dilated cardiomyopathy. Note the large dilated left ventricle (LV) with decreased wall motion. RV = right ventricle.

Additional Diagnostics

Due to the possibility that dilated cardiomyopathy may be associated with taurine deficiency, taurine should always be measured even in cats whose owners report that they are on a balanced feline diet. Taurine may be measured in plasma (>60 nmol/ml) and/or whole blood (>250 nmol/ml). Whole blood may be less affected by fasting, which could be associated with an inappetant cat (Pion et al. 1991). Taurine can be released from platelets if the plasma sample is not separated quickly enough and it might appear falsely elevated. Other apparent reasons for false elevation can include skeletal muscle necrosis as might be observed with thromboembolic disease.

Some cats with taurine deficiency have evidence of central retinal degeneration, so an optic exam may be helpful. However, the absence of retinal degeneration does not exclude taurine deficiency.

Diagnosis

Evidence of left ventricular systolic dysfunction with a fractional shortening of less than 20% is highly suggestive of feline dilated cardiomyopathy, particularly with evidence of left ventricular dilation. Early reports suggested that measurement of wall thickness for wall thinning might be a reliable criteria but this has not been found to be reliable. In many cases, the wall appears thinner simply due to the ventricular dilation but actually is a normal thickness.

Decreased taurine levels taken in conjunction with echocardiographic evidence of systolic dysfunction suggests taurine-related dilated cardiomyopathy.

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TREATMENT

Given that cats with dilated cardiomyopathy may be taurine-deficient, taurine supplementation should always be given until the taurine levels have been proven to be normal. Supplementation should be provided at 250 mg orally twice day and can typically be purchased by the owner at a health food store.

A positive inotrope to aid the decreased systolic dysfunction should be provided. Digoxin, 0.03125 mg (1/4 of a 0.125 mg tablet PO q 48 hours) can be used. Pimobendan, a stronger positive inotrope, appears to be well tolerated in the cat at a dose of 1.25 mg orally twice a day. At least in the dog, pimobendan also appears to have other positive effects, including increased appetite, that may be beneficial in a cat with heart failure. However, pimobendan is not approved for use in the cat in the United States and use of this drug in cats should be supported by client understanding and consent for off-label use.

Treatment should include additional medications, including furosemide and an ACE inhibitor, as needed for the symptoms associated with congestive heart failure if it is present (see Chapter 19).

Thoracocentesis and/or abdominocentsis should be performed if pleural effusion or ascites is having an effect on respiration (see Chapter 3).

If atrial fibrillation or an atrial tachycardia is observed, treatment may be may be needed to slow the heart rate (ventricular response rate) as described (see Chapter 18).

Prevention of possible thromboembolic complications should also be considered as described (see Chapter 20), because cats with dilated cardiomyopathy are at risk of thromboembolic complications.

COMPLICATIONS AND MONITORING

Because cats with dilated cardiomyopathy are at an increased risk of thromboembolic disease owners should be advised to observe for signs of sudden paralysis, most commonly of the hindlimbs, but sometimes of a forelimb, or atypical neurologic signs.

Congestive heart failure is a common complication. Owners should be advised to monitor the respiratory rate at home in a resting state. An increase in resting respiratory rate may be a sign of developing pulmonary edema or pleural effusion.

Cats that are being treated for atrial fibrillation with Digoxin should ideally have a heart rate of 140–160 beats/minute on medication when at the clinic.

After the initial diagnosis is made, periodic reevaluation could include physical examination (heart rate and respiratory rate), radiographs (for evidence of heart failure), and blood pressure monitoring (for hypotension). A renal profile to monitor BUN, creatinine, and electrolytes is also helpful to monitor for complications associated with therapy. Recheck echocardiography may be needed only if an acute change occurs (sudden decompensation to heart failure, development of signs of thromboembolic disease).

OUTCOME AND PROGNOSIS

The prognosis for cats with dilated cardiomyopathy is varied. Some cats progress very rapidly, and others have a more gradual progression. In many cats, if taurine deficiency is identified and treated before severe heart failure has developed the disease will begin to reverse. Cats that are successfully treated and survive the first 30 days have an excellent chance of survival (Pion et al. 1992). Substantial improvement in a cat's attitude and appetite is often observed even within the first few weeks of treatment (Pion et al. 1992).

In general, prognosis is poor unless taurine deficiency is present.

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14

Arrhythmogenic Right Ventricular Cardiomyopathy

Key Points

- Arrhythmogenic right ventricular cardiomyopathy is an adult onset, uncommon myocardial disease in the cat.
- Radiographic and echocardiographic findings consist of right atrial and ventricular enlargement; pleural effusion may be present.
- Congenital tricuspid valve dysplasia is an important differential diagnosis.

INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy is an adult onset primary myocardial disease characterized by fibrofatty infiltration of the right ventricular myocardium. It is observed in cats, dogs, and human beings, although the disease does have some species differences (Fox et al. 2000; Basso et al. 2004; Harvey et al. 2005). Arrhythmogenic right ventricular cardiomyopathy is thought of as predominantly a right sided heart disease, but in some cases the disease includes the left ventricle and interventricular septum as well. In dogs and human beings the disease may ultimately lead to left ventricular dysfunction as well, but this has not been well described in the cat (Basso et al. 2004).

ETIOLOGY, PATHOPHYSIOLOGY, AND GROSS PATHOLOGY

Etiology

Although the disease is noted to be familial in human beings and dogs, the etiology in the cat is unknown (Basso et al. 2004).

Arrhythmogenic right ventricular cardiomyopathy is an uncommon disease that is increasing in clinical recognition. The prevalence is unknown, but one report estimated that it represented 2–4% of feline myocardial diseases diagnosed at the Animal Medical Center, a large referral hospital in New York (Fox 1999). A recent study that screened apparently healthy cats for the presence of heart disease identified ARVC in 1 out of 103 cats (1%) (Paige et al. 2009).

Pathophysiology

The disease is characterized by right ventricular enlargement with thinning of the ventricular free wall and right atrial enlargement. Right heart failure may be observed (Fox et al. 2000).

Pathology

A diagnosis of feline ARVC is confirmed by pathologic evaluation. Right atrial and ventricular dilation are observed as well as focal or diffuse thinning of the wall. Aneurismal bulges may be observed in the apical, subtricuspid, or infundibular regions. Key histopathologic findings include right ventricular myocardial atrophy and fibrous or fibrofatty replacement. Although the findings are most commonly observed in the right ventricle, they can also be observed in the other chambers as well. Lymphocytic infiltrates are also commonly observed.

SIGNALMENT

This is an adult onset form of cardiomyopathy with an age at diagnosis ranging from 1–20 years of age (Fox

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et al. 2000). No breed predisposition has been noted (Fox et al. 2000; Harvey et al. 2005).

HISTORY AND CHIEF COMPLAINT

The majority of affected cats have presented for vague clinical signs, including lethargy and anorexia; additionally, signs of right heart failure including dyspnea and tachypnea may be observed. Syncope may be observed but appears to be uncommon (Fox et al. 2000; Harvey et al. 2005). Sudden death is possible. ARVC may be detected incidentally in cats not showing overt clinical signs, but the majority of cases are identified due to presentation related to overt clinical signs (Fox 1999; Paige et al. 2009).

PHYSICAL EXAMINATION

Physical examination findings are often consistent with right heart failure including hepatosplenomegaly, abnormal jugular distension and pulsation, and a soft holosystolic right apical murmur associated with tricuspid valve regurgitation. In some cats, a murmur may not be detected. Tachyarrhythmias may be ausculted.

DIFFERENTIAL DIAGNOSIS

A differential diagnosis for ARVC is the congenital heart defect tricuspid valve dysplasia (see Chapter 10). Arrhythmogenic right ventricular cardiomyopathy is an adult onset form of myocardial disease, so it should be recognized by detection of a murmur or tachyarrhythmia in an adult cat. Because tricuspid valve dysplasia is a congenital heart defect and is present at birth, one would expect that at least a soft systolic right apical murmur should be present at a very young age. However, some cats with tricuspid valve dysplasia may have only a very soft murmur that could be missed (see Chapter 1). Echocardiography would be the best test to differentiate the two diagnoses. Although both ARVC and tricuspid valve dysplasia cause tricuspid valve regurgitation, it would be expected to have higher velocity in tricuspid valve dysplasia. Additionally tricuspid valve dysplasia should have abnormal valve morphology and fairly normal right ventricular systolic function in most cases.

DIAGNOSTIC TESTING

Electrocardiography

Arrhythmias are commonly observed in feline ARVC. Ventricular premature complexes, ventricular tachycardia, atrial fibrillation, atrial standstill, supraventricular premature complexes, right bundle branch block, first-degree AV block, and third-degree AV block may be observed alone or in combination (see Chapter 18).

Radiography

Right atrial and ventricular enlargements are almost always observed, and findings consistent with right heart failure (pleural effusion, caudal caval distention) are frequently present.

Echocardiography

Echocardiography is needed to confirm the diagnosis. The significant right-sided lesions consist of right atrial and right ventricular enlargement and decreased right ventricular wall motion (Figures 14.1, 14.2). Paradoxical

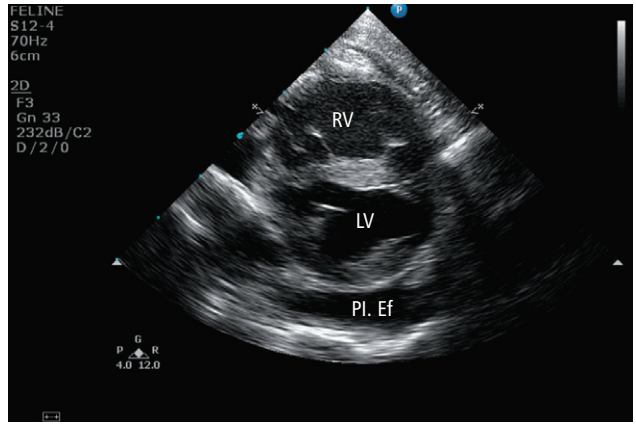


Figure 14.1. Short-axis echocardiogram of a cat with ARVC. Note the right ventricular enlargement and presence of pleural effusion in the thorax. RV = right ventricle; LV = left ventricle; Pl.Ef = pleural effusion.

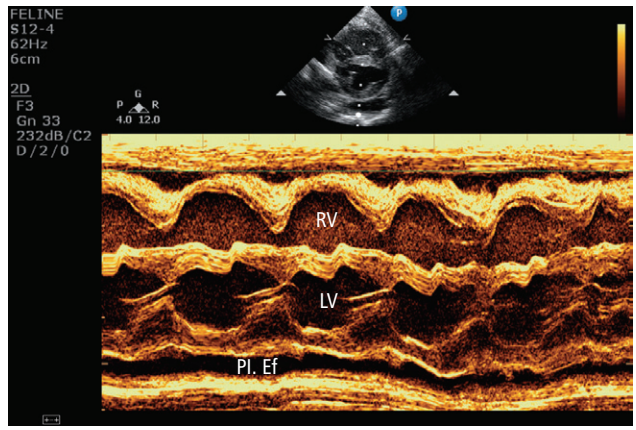


Figure 14.2. M-mode echocardiogram of a cat with ARVC. Note the right ventricular enlargement and presence of pleural effusion in the thorax. RV = right ventricle; LV = left ventricle; Pl.Ef = pleural effusion.

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septal motion may be observed. Aneurysmal bulges in the apical or subtricuspid region are uncommon but are characteristic of ARVC. Mild myocardial dysfunction of the left ventricle may be observed, but function is more commonly within normal limits.

The Doppler echocardiogram often identifies mild tricuspid valve regurgitation due to the dilated right ventricle and tricuspid valve annulus. As mentioned above, a differential diagnosis for feline ARVC would be congenital tricuspid valve dysplasia, which should have higher velocity tricuspid valve regurgitation as well as abnormal valve morphology.

TREATMENT

There are no specific treatments for arrhythmogenic right ventricular cardiomyopathy in the cat.

Treatment should include medications as needed for the symptoms associated with congestive heart failure if it is present. This might include furosemide and an ACE inhibitor as described in Chapter 19.

Thoracocentesis and/or abdominocentesis should be performed (see Chapter 3) if pleural effusion or ascites is present and is negatively impacting respiration.

If clinical signs are present that are thought to be associated with the ventricular tachycardia (syncope, exercise intolerance, lethargy) or if the tachycardia is sustained, an antiarrhythmic like sotalol should be considered. Sotalol may be prescribed at 1–2 mg/kg orally q 12 hours. The efficacy of this drug for feline ARVC has not been extensively studied. However, sotalol has been used for treatment of the arrhythmias associated with ARVC in both dogs and human beings (Meurs et al. 2002; Marcus et al. 2009). The sotalol caplets come in 80 mg, 120 mg, and 240 mg but it is possible to have them compounded for accurate dosing in the cat.

If atrial fibrillation or an atrial tachycardia is observed, antiarrhythmics such as digoxin or diltiazem may be indicated to slow the heart rate (ventricular response rate) (see Chapter 18) with an ideal target heart rate of 140–180 on medication.

If the right ventricle is very dilated and ventricular dysfunction is suspected, pimobendan, a positive inotrope, may be useful at a dose of 1.25 mg–1.5 mg/cat PO q 12 hours, although its use in cats is not yet approved in the United States. Therefore, use of this drug in cats should be supported by client understanding and consent for off-label use.

Right atrial enlargement could lead to the development of an atrial thrombus, and prevention of possible thromboembolic complications should also be considered including treatment with aspirin or clopidogrel as described (see Chapter 20).

COMPLICATIONS AND MONITORING

After the initial diagnosis is made, reevaluation and control of treatment will be based on control of respiratory rate and heart rate that can be determined by physical examination, radiographs, and electrocardiogram. A renal profile to monitor BUN, creatinine, and electrolytes is also helpful to monitor for development of azotemia. Recheck echocardiography is needed only if the case seems to be progressing unusually rapidly or in an unusual fashion. It should be remembered that a trip to the veterinary hospital for reevaluation is almost always associated with increased stress for a cat and may in some cases result in a well-controlled cat suddenly decompensating. Therefore the benefits and indications for a hospital revaluation should be carefully weighed with possible risks and it should not be recommended unless truly medically indicated. Additionally, the reevaluation appointment should be done as efficiently and as calmly as possible to minimize stress.

Congestive heart failure, right or biventricular, is a common complication of this disease. Owners should be instructed to monitor the respiratory rate at home in a resting state. A target resting respiratory rate for a cat should be less than 16 breaths per minute. If the respiratory rate is maintained in a low range and the cat is eating and appears comfortable, a recheck may not yet be needed. If an owner detects a persistently elevated respiratory rate it may be a sign of developing pleural effusion and indicates a need for a reevaluation with thoracic radiographs.

OUTCOME AND PROGNOSIS

Generally, feline ARVC carries a grave prognosis. Many cats are euthanized for right heart failure within 4 months of clinical onset (Fox et al. 2000; Harvey et al. 2005). Cats are also at risk of thromboembolism.

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SECTION E

Other Forms of Structural Heart Disease

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15

Acquired Valvular Disease

Key Points

- Acquired primary valve disease is usually degenerative in cats, although it is far less common than in dogs.
- Infective valve disease is even less common in cats.
- Many cats with infective endocarditis present with congestive heart failure due to severe mitral and/or aortic valve insufficiency. If, during echocardiography, an oscillating, echogenic mass is visibly associated with either of these valves, the clinician should be highly suspicious of infective endocarditis, and blood cultures are warranted.
- Treatment of congestive heart failure secondary to valve disease includes furosemide, an ACE inhibitor, and possibly pimobendan. Long-term therapy (6–8 weeks) of broad-spectrum antibiotics is needed in patients with infective endocarditis.

DEGENERATIVE VALVE DISEASE

Degenerative valve changes that lead to significant valvular regurgitation often result in myocardial remodeling due to the volume overload. Because cats with degenerative valve disease rarely develop the severe valve thickening or prolapse that is frequently noted in canine valve disease, the cardiac changes secondary to ventricular volume overload (left atrial enlargement, left ventricular enlargement) may be incorrectly ascribed to cardiomyopathy, in particular unclassified cardiomyopathy since ventricular wall thickness is normal. Secondary valve disease can also occur due to primary myocardial disease. For example, mitral regurgitation and structural changes to the anterior mitral valve leaflet often occur secondary to systolic anterior motion of the mitral valve with hypertrophic obstructive cardiomyopathy. Moreover, the mitral valve leaflets, chordae tendineae, and papillary muscles may be distorted in cats with endomyocarditis or restrictive cardiomyopathy. Functional, or secondary, mitral regurgitation may occur secondary to ventricular volume overload and annular dilation associated with diseases such as dilated cardiomyopathy or left-to-right shunts, and in the absence of structural valve abnormalities.

Animals with mitral and tricuspid regurgitation usually present with systolic murmurs due to the blood leaking back into the left or right atrium during systole. The murmur is left-sided if the mitral valve is involved and right-sided with tricuspid valve degeneration. A subset of feline patients will present without an auscultable murmur, with factors including a small volume of regurgitant blood, eccentric regurgitant jet away from the body surface, or a low pressure gradient driving the regurgitation in cats with elevated right atrial pressure due to severe tricuspid regurgitation. Other physical limitations to ausculting a murmur may include purring, obesity, fractious behavior, etc. However, in most patients with degenerative valve disease, the presence of a murmur increases suspicion that the patient has heart disease.

Valve regurgitation can be mild and inconsequential or it can be severe and lead to congestive heart failure (CHF). Severe mitral or tricuspid regurgitation is

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uncommon in cats, but it occurs sporadically. Mitral regurgitation leads to an increase in the left atrial pressure, which can lead to left atrial enlargement. This extra volume of blood then returns to the left ventricle during diastole resulting in a volume overload of the left ventricle as well as the left atrium. In this scenario, ventricular dilation and hypertrophy occur, in which the ratio of wall thickness and chamber size remains essentially unchanged. This pattern is termed *eccentric hypertrophy*. Ultimately, CHF secondary to elevated pulmonary venous pressure may occur. When the mitral valve is involved, CHF is expressed as cardiogenic pulmonary edema and/or pleural effusion (Figure 15.1A,B). When the tricuspid valve is affected, ventricular volume overload occurs on the right side of the heart and it is associated with systemic venous congestion causing pleural effusion and ascites. For more in-depth discussion on CHF, see Chapter 19.

DIAGNOSIS

The presence of a left apical holosystolic murmur is not specific for mitral valve degeneration, and an echocardiogram is needed for definitive diagnosis. Thoracic radiographs may reveal left-sided cardiomegaly primarily evident as left atrial dilation, and possibly pulmonary venous distension, pulmonary edema, and/or pleural effusion if congestive heart failure is present.

Echocardiography is the essential diagnostic tool for the diagnosis of degenerative valvular disease. The hallmark echocardiographic abnormalities of mitral valve degeneration and insufficiency include identification of mitral regurgitation on color-flow Doppler (Figure 15.2), which is often eccentric in nature, left atrial dilation (Figure 15.3), and an increased left ventricular diastolic diameter (i.e., eccentric hypertrophy) due to the volume overload to the ventricle. There may be mild to moderate secondary myocardial failure of the left ventricle, which is evident as decreased left ventricular free wall motion and an increased end-systolic diameter. However, fractional shortening is typically normal to high, due to the increased ventricular volume and reduced afterload (because of the mitral valve leak). The septal systolic wall motion is often hyperdynamic. Unlike small dogs with myxomatous valve degeneration, mitral valve prolapse is rarely seen in cats with degenerative valve disease, and the valves may appear only slightly thickened (Figure 15.4). It is important to rule out systolic anterior motion of the mitral valve as a cause of mitral regurgitation since, in association with hypertrophic obstructive cardiomyopathy, it is much more common than degenerative valve disease and therapy tends to be different.

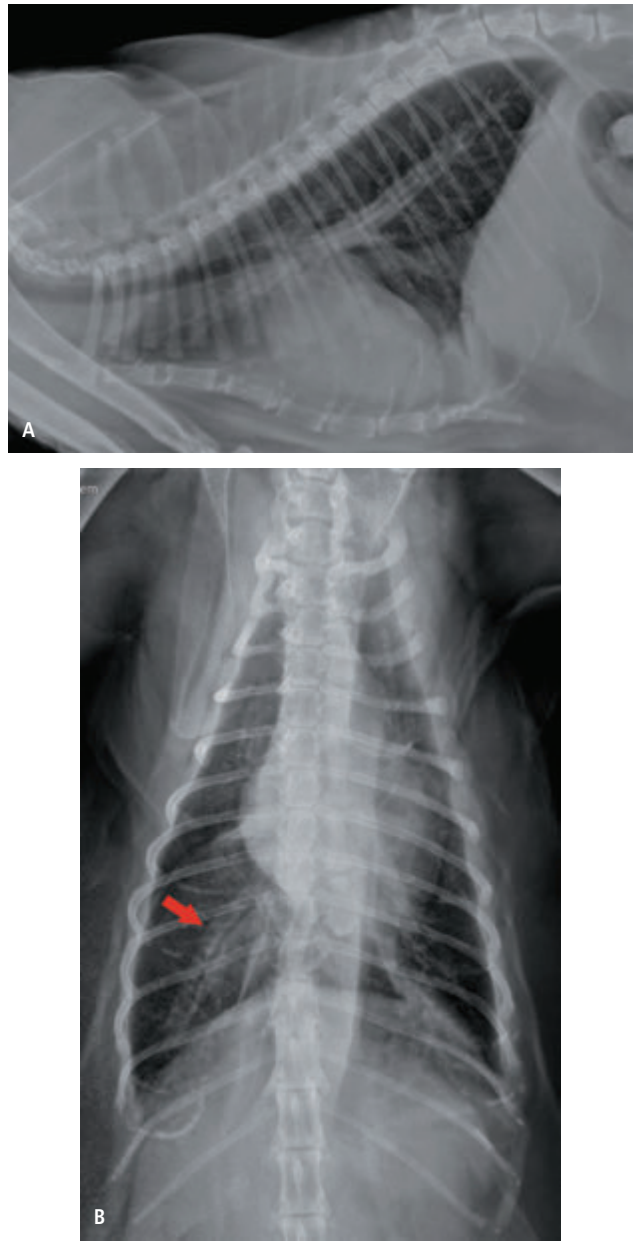


Figure 15.1. **(A)** Lateral thoracic radiograph from a cat with degenerative mitral valve disease, mitral regurgitation, and congestive heart failure. Note the generalized heart enlargement and increased pulmonary interstitial pattern. **(B)** VD thoracic radiograph from the same cat as in (A). Note the generalized cardiomegaly, the increased pulmonary interstitial pattern, and the dilated pulmonary vasculature (arrow).

DIFFERENTIAL DIAGNOSIS

The most common cause of mitral regurgitation in middle-aged to older cats is systolic anterior motion (SAM) of the mitral valve, which is seen in some cats with hypertrophic cardiomyopathy. The key difference in distinguishing degenerative valve disease from SAM of the mitral valve is the identification of anterior dis-

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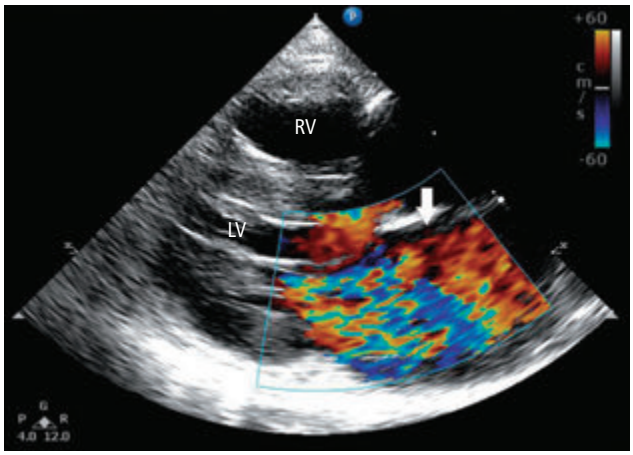


Figure 15.2. Right parasternal long-axis color-flow Doppler echocardiogram of the mitral valve. Note that the aliased color-flow pattern representing the high-velocity jet of mitral regurgitation is filling the left atrium. This echocardiogram was obtained from the same cat as the radiographs in Figure 15.1. LV = left ventricle; RV = right ventricle.

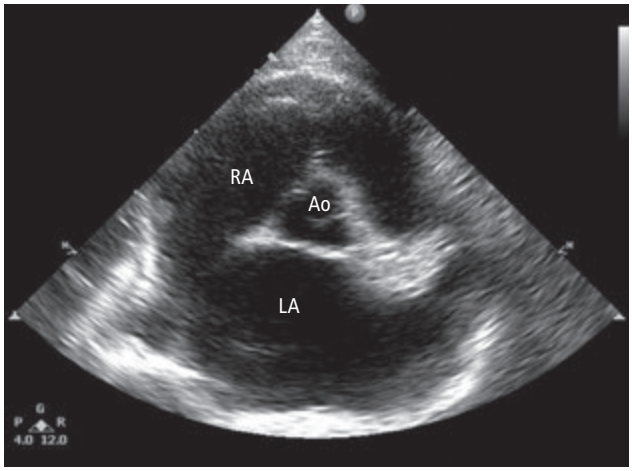


Figure 15.3. Right parasternal short-axis echocardiogram of the heart base. Note the left atrial (LA) enlargement. The right atrium (RA) also appears enlarged. This echocardigram was obtained from the same cat as the radiographs in Figure 15.1. Ao = aorta.

placement of the anterior mitral leaflet in cats with SAM, where it approaches or touches the interventricular septum during systole. On color-flow Doppler interrogation, SAM produces two turbulent jets: one ascending into the aorta as a result of the left ventricular outflow tract obstruction and the other in the left atrium as a result of mitral regurgitation. The jets arise from the same point where the valve leaflet causes the obstruction. Mitral valve dysplasia is the most common cause of mitral regurgitation in kittens or juvenile cats. The mitral valve typically has characteristic morphologic abnormalities including short, thick chordae tendinae, which may tether the abnormally shaped thickened mitral

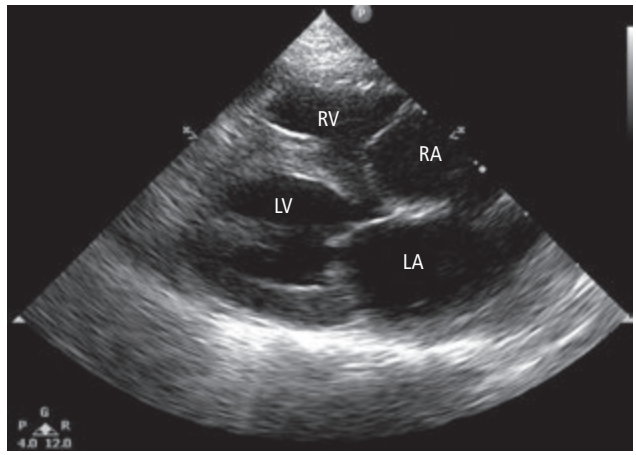


Figure 15.4. Right parasternal long-axis 4-chamber echocardiogram from the same cat as the previous images. Note the enlarged left atrium (LA) and right atrium (RA) and thickening of the mitral valve. RV = right ventricle; LV = left ventricle.

valve. Sometimes with mitral dysplasia the anterior leaflet appears elongated and misshapen, and papillary muscles may be abnormal in shape and position in the left ventricle. Another common cause of mitral regurgitation is functional, secondary mitral regurgitation due to other cardiac diseases such as dilated cardiomyopathy, unclassified cardiomyopathy, or left-to–right shunts, which lead to left ventricular enlargement. Secondary, or functional mitral regurgitation, is typically mild or moderate and often is symmetrical and centrally arising (in the valve orifice), with a normal mitral valve structure.

INFECTIVE ENDOCARDITIS

Infectious endocarditis (IE) is extremely rare in cats with an incidence of 0.006 to 0.018% of cats presented for examination in one retrospective report (Sisson 1994). The mitral and/or aortic valves are most commonly affected, which is similar to dogs. Several factors are important in the pathogenesis of infective valvular endocarditis:

- Endothelial damage
- Activation of clotting factors
- Bacteremia and colonization of a noninfective thrombus on the valve surface

Healthy endothelium is not particularly receptive to bacterial attachment. However, when it is damaged, the development of platelet-fibrin aggregates provides a susceptible nidus for bacterial colonization. Valvular endothelium is rich in fibronectin, a glycoprotein produced following endothelial injury. Many pathogenic bacteria associated with IE have surface receptors for fibronectin (Peddle and Sleeper 2007), and *Staphylococcus aureus*, which possesses fibronectin receptors, has been

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reported to cause mitral endocarditis in the cat (Yamaguchi 1983). Gram-positive bacteria are most often implicated in the development of IE (*Streptococcus* spp. and *Staphylococcus* spp.) (Peddle and Sleeper 2007). Valvular infection with gram-negative organisms is less common but is possible (Peddle and Sleeper 2007). Clusters of microorganisms in vegetations are protected by layers of fibrin from the circulating blood pool. Moreover, the valves are minimally vascularized, which limits the access of the host immune response as well as antibiotics.

In a large feline pathology study which included results from 4933 necropsied cats between 1962 and 1976, 13 cases of IE were identified (Liu 1977). These cases were always associated with focal or systemic bacterial infections, and the mitral valve, aortic valve, or both were most commonly involved. In severe cases, valve perforation was noted and concurrent arterial thromboembolism occurred in 3 of the 13 cats (Liu 1977). None of the cats had evidence of concurrent congenital heart disease (nor have any studies since), suggesting that there is not likely an association with subaortic stenosis, which has been recognized in dogs and humans. However, since both diseases are rare in cats, it is possible that a relationship has simply not been recognized due to the low number of reported cases. In a retrospective study that included cats diagnosed antemortem with sepsis (and confirmed by postmortem histopathologic evidence of multiorgan bacterial infection) over a 12-year period, 4 of 29 cats were found to have infective endocarditis (Brady et al. 2000). Therefore, IE is a rare but significant disease in the cat.

In dogs, the definitive diagnosis of IE is often complicated, although most affected patients show signs consistent with sepsis (fever, malaise, inflammatory leukogram), evidence of systemic embolization (septic arthritis, uveitis, myocarditis), and signs of severe valve insufficiency (murmurs, arrhythmias, bounding pulses, congestive heart failure). Moreover, the disease course in dogs tends to be acute to subacute (Peddle and Sleeper 2007). Cats presenting with IE can present with similar signs to those described for dogs. Because the mitral and aortic valves are most commonly involved, a left parasternal systolic murmur or a left basilar diastolic murmur is often present. However, diastolic murmurs in cats can be challenging to identify, particularly in the presence of sinus tachycardia. There have been sporadic case reports of IE in cats causing unusual sequelae such as a dissecting aortic aneurysm (Laurenço et al. 2002) and cerebellar infarction (Cherubini et al. 2007). Systemic arterial embolization and CHF appear to be particularly common findings in cats affected with IE. However, most case reports suggest disease progression may be slower than what is seen in dogs, with extensive remodeling and calcification of infected valves in some affected cats (Noakes 1988; Malik et al. 1992), which suggests the disease is sufficiently chronic to allow time for remodeling to occur. Chronicity is supported by a case series of 6 cats with IE, in which 4 of the cases were presented primarily due to signs of congestive heart failure and had normal leukograms and body temperatures. The aortic vegetation was documented to have mineralized by the time of examination in one of the cats in this series. The other 2 cats presented with a more typical acute pattern of sepsis and multisystemic disease following recent histories of abscessation, and gram-positive cocci were documented postmortem. The aortic valve was most frequently involved (5/6), followed by the mitral valve (4/6); the tricuspid valve was involved in 1 case. *Streptococcus* species were detected via gram-stain of valve lesions in 1 case and gram-positive cocci were demonstrated in valve vegetations of another cat; 2 cats had positive blood cultures for a *Bartonella* species, suggesting a possible link to *Bartonella* (Malik et al. 1999).

Bartonella are fastidious, hemotropic gram-negative bacteria that are primarily transmitted by arthropod vectors and possibly fleas. Domestic cats are the primary reservoir for *B. henselae* and infected cats can have bacteremia for more than a year (Chomel et al. 2006). In recent years, *Bartonellae* have been implicated as an important cause of endocarditis in humans and dogs. Cats had previously been believed to be healthy carriers of the pathogen; however, since Malik's report in 1999, several *Bartonella* endocarditis cases, including *B. henselae* have been reported in cats (Malik et al. 1999, Chomel et al. 2009). Four types of *B. vinsonii* subsp. *berkhoffi*, *B. clarridgeiae*, *B. washoensis*, *B quintana*, and *B. rochalimae* have all been associated with endocarditis in the dog. In Malik's case series from Australia, although *Bartonella* sp. were isolated from 2 cats with endocarditis of the aortic valve, no direct causality was proven (Malik et al. 1999). However, 1 feline *B. henselae* endocarditis case was reported in California several years later with PCR evidence of the organism in the aortic valve (Chomel et al. 2003), and the same group reported another feline case from New York (Chomel et al. 2009). The pattern of disease in these feline cases was similar to human and canine *Bartonella* endocarditis, with large vegetative lesions involving the aortic valve. The mitral valve was also involved but less severely affected. Seropositive cats are also more likely to have kidney disease and urinary tract infections, stomatitis, and lymphadenopathy (Chomel et al. 2006). In humans (and cats), the disease follows a northern to southern gradient with the highest prevalence in southern latitudes (Chomel et al. 2006, 2009). Antibody titers for *Bartonella spp*. have also been detected in numerous wild felid populations (Chomel et al. 2006).

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Diagnosis in cases of IE depends on documentation of markedly elevated serum antibodies to *Bartonella* and demonstration of *Bartonella* antigens using polymerase chain reaction testing for Bartonella spp DNA (often a postmortem finding on valve tissue). Definitive diagnosis is difficult because many cats are carriers and are therefore seropositive. Because *Bartonellae* are extremely fastidious intracellular bacteria, they are rarely cultured from blood or body tissues even using specialized culture medium and long incubation periods. With endocarditis, identification of the causative organism is often challenging, whatever the etiologic agent. Although multiple sets of blood cultures (3 samples over 3 hours) are recommended to evaluate patients in whom IE is suspected, the small body size of cats means volumes of blood withdrawn should be considered carefully. Most blood culture media bottles require 5–15 ml for each sample, and the effect on a debilitated patient must be considered when planning this diagnostic test. A urine culture is always indicated and may identify the causative organism. If the patient is already receiving antibiotic therapy, samples for cultures should be drawn when antibiotic blood levels are at trough levels (Miller and Sisson 1999).

Retrospective human studies demonstrated that using a combination of laboratory data and echocardiographic and clinical findings resulted in the best sensitivity and specificity, and this scheme has been slightly modified for the veterinary patient (Miller and Sisson 1999). A diagnosis of IE is likely in an individual patient when two major criteria, one major and three minor, or five minor criteria are met (Tables 15.1, 15.2). Serial echocardiographic examinations are sometimes helpful because the valve can appear structurally normal in the early stages of disease. Over time, vegetations often develop into an irregular and pedunculated mass arising from the tip of the valve leaflet, and the hemodynamic consequences (aortic and/or mitral regurgitation) can be readily appreciated. Aortic or mitral stenosis secondary to large, space-occupying vegetations, rarely occur in feline IE cases. In cats, the vegetation will often mineralize, making it appear hyperechoic on ultrasound.

Therapy of IE is directed at controlling sepsis and management of cardiac dysfunction secondary to valvular insufficiency and/or stenosis. Congestive heart failure is an important sequela of this disease in cats. More than half of the cases in Malik's series presented for veterinary care secondary to signs referable to CHF rather than signs of sepsis. See Chapter 19 for discussion of congestive heart failure therapy. Antimicrobial therapy is most

Table 15.1. Major vs minor criteria for diagnosis of infectious endocarditis

Major Criteria	Minor Criteria
Two separate, positive blood cultures with organisms likely to cause IE (*Staph* spp, *Strep* spp, *Corynebacterium* spp, *Erysipelothrix rhusiopathiae* [typically serovar 7], *Pseudomonas aeruginosa*, *Pasteurella* spp)	Predisposing factor (subaortic stenosis in dogs, unknown whether factor in cats; long-term in-dwelling catheter)
	Fever (historical or at presentation)
Three or more separate, positive blood cultures with common skin contaminants	Thromboembolic disease (pulmonary, central nervous system, or arterial emboli)
Positive echocardiographic findings for IE (oscillating intracardiac mass on valve or valve apparatus in the absence of alternative explanation, i.e., thrombus); erosive lesion	Immunologic disease (glomerulonephritis, vasculitis, polyarthropathy)
New valvular regurgitation	Microbiologic evidence (positive blood culture[s]) that does not meet "major criteria"
	Echocardiographic evidence (findings consistent with IE, but which do not meet "major criteria")
	Identification of *Bartonella* antigens using polymerase chain reaction testing on bacterial isolates or valve tissue

Modified from Miller and Sisson 1999, p. 572.

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Table 15.2. Criteria for diagnosis of infective endocarditis

Definite Infective Endocarditis

• Pathologic criteria
  • Micororganisms demonstrated by culture or histology in vegetation (of valve or embolization)
  • Active endocarditis confirmed on histology
• Clinical criteria (see Table 15.1)
  • Two major criteria
  • One major and three minor criteria
  • Five minor criteria

Possible Infective Endocarditis
• Findings consistent with infective endocarditis, but which fall short of "definitive" description above
Reject Infective Endocarditis Diagnosis
• Good alternative diagnosis • Clinical signs resolve with <4 days of antimicrobial therapy • No pathologic evidence of infective endocarditis at surgery or postmortem (after <4 days of antimicrobial therapy)

Modified from Miller and Sisson 1999, p. 572.

likely to be successful if the organism is identified on culture and sensitivity testing of whole blood samples. Therefore, blood cultures should be performed in cats with clinical suspicion of IE or echocardiographic evidence of a vegetative lesion of IE. Unfortunately, blood cultures are often negative and empirical treatment is necessary. When antimicrobial therapy must be initiated without identifying the organism, initial therapy using a combination of gentamicin (or amikacin) and ampicillin (or a cephalosporin) is a reasonable approach. It is optimal to use intravenous agents initially to obtain high serum levels of the drugs quickly. Long-term therapy (6–8 weeks) is recommended, so patients are often switched to oral medications after 1 or 2 weeks of intravenous therapy. Nephrotoxicity may be potentiated in cats treated with concurrent aminoglycosides and furosemide, warranting extra vigilance or avoidance of this combination. Amoxicillin + clavulanate or enrofloxacin are reasonable options for chronic oral therapy. Azithromycin may be a good alternative if IE is due to *Bartonella* spp. In some patients, even longer-term therapy is necessary. It is likely the valve will remain thickened on repeat echocardiographic examinations, and an enlarging vegetation or valve insufficiency suggests a poorer prognosis. Regardless, prognosis is poor for affected cats. Even if the lesion can be sterilized by antimicrobial therapy, which is difficult, valve remodeling often results in severe valvular incompetency and progressive CHF. In a case series, two cats that were treated with antimicrobials and congestive heart failure therapy survived 5 and 11 months, whereas the other 4 cats died within 2 weeks of diagnosis (Malik et al. 1999).

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16

Cardiac Neoplasia

Key Points

- Benign and malignant tumors of the cardiovascular system are rare in cats.
- The most common types are lymphoma and aortic body chemodectoma; the latter appears to occur more commonly than was previously reported.
- Cardiac tumors in cats are more commonly associated with respiratory or nonspecific signs of ill thrift, or they may be incidental findings at necropsy.
- The prognosis is generally poor, although successful regression of lymphoma with standard chemotherapy has been reported.

INTRODUCTION

Cardiac tumors (cardiac neoplasms) are uncommon diseases in feline cardiology. Nevertheless, certain characteristics appear to separate this location of neoplasia from its equivalent in other species. In contrast to dogs, for example, cardiac hemangiosarcoma is extremely rare in the cat. Lymphoma and chemodectoma, however, are well-recognized, and although large case series do not exist, some observations have been made allowing limited conclusions to be drawn.

PREVALENCE, ETIOLOGY, PATHOPHYSIOLOGY, AND GROSS PATHOLOGY

Cardiac neoplasia encompasses primary tumors of the heart and secondary tumors, which originate elsewhere and metastasize to the heart. Historically, primary cardiac tumors were considered very rare in cats (e.g., n = 1/30, 3% in one case series) (Aupperle et al. 2007). Several recent case reports of chemodectoma in the cat seem to alter this prevalence, and greater attention has been devoted lately to these heart base tumors (e.g., 7 cases published in 1994–2004 versus 2 cases in a search of the Veterinary Medical Database covering 210,888 feline admissions from 1982–1993) (Ware 1995).

The etiology of these tumors is unclear, with the exception of lymphoma, which can be caused by the feline leukemia virus (FeLV).

Gross lesions are characteristic of the tumor type. Lymphoma may affect the heart diffusely (Liu et al. 1989; Brummer and Moïse 1989) or focally (Shinohara et al. 2005) (Figure 16.1). It is almost always identifiable in other tissues once the diagnosis of cardiac lymphoma is made. Chemodectoma may affect the carotid body (2 reported cases) or the aortic body (heart base; 13 reported cases). These heart base masses are located between the aorta and either atrium; one was found adjacent to the cranial vena cava.

SIGNALMENT

Cardiac lymphoma is described in cats of all ages (5–13 years of age when noted in case reports) and both genders. Chemodectoma is similarly described in adult cats (4–13 years old) of both genders.

HISTORY AND CHIEF COMPLAINT

In dogs, cardiac tumors routinely cause clinical signs via pericardial effusion producing signs of cardiac tamponade such as acute collapse and abdominal distension

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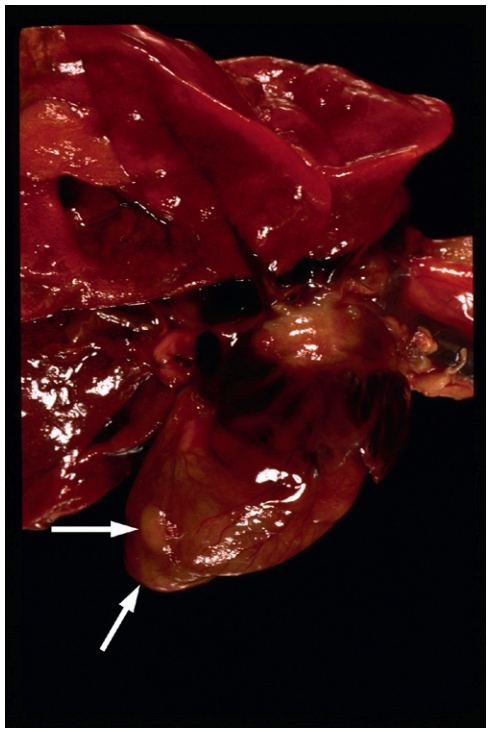


Figure 16.1. Pluck from a cat with lymphoma. Discrete, pale, raised lesions are present on the epicardial surface (arrows), consistent with lymphoma. Photo courtesy of Dr. Kristin MacDonald.

from ascites. In cats, by contrast, this expression of cardiac neoplasia appears to be uncommon. Rather, the most widely reported chief complaints are tachypnea and/or dyspnea that most commonly has been noted by owners for a few days to one week, or rarely more. Concurrently, such systemic signs as anorexia and lethargy occur, and these typically are noted for a few days before the onset of severe respiratory signs prompts the owners to seek veterinary attention.

A number of cases of cardiac tumors are diagnosed incidentally at necropsy, suggesting that the cardiac neoplasia produces no characteristic clinical signs or causes signs that are mild and that pass unnoticed.

PHYSICAL EXAMINATION

Cats with cardiac tumors may present with few or no signs referable to the lesion, and the diagnosis is made when the tumor is found incidentally at necropsy. Conversely, severe respiratory signs are present in some cats in whom marked pleural effusion is present. Information regarding the presence of general demeanor, body condition, heart sounds, arrhythmia, pulse quality, signs of right-sided heart failure, and many other important physical findings is generally lacking from the literature.

DIFFERENTIAL DIAGNOSIS

Echocardiographically, circumscribed masses may be abscesses, granulomas, cysts, or neoplasms. Chemodectomas typically are mixed echogenicity masses that may best be identified between the aorta and either atrium, or adjacent to the cranial vena cava in 1 case. Myocardial infiltration may be focal (Shinohara et al. 2005) or diffuse (Brummer and Moïse 1989; Liu et al. 1989). Diffuse infiltration may be mistaken for hypertrophic cardiomyopathy if attention is not paid to the variable echogenicity that is usually present and the hypokinesis (reduced motion) of the infiltrated myocardium.

DIAGNOSTIC TESTING

Cardiac neoplasia in cats arises in three clinical contexts:

1. A patient shows clinical signs (e.g., respiratory problems) that ultimately are found to be caused by the effects of the neoplasm
2. A patient with cancer that shows no overt signs of cardiac dysfunction, but diagnostic testing reveals cardiac abnormalities consistent with cardiac neoplasia
3. A patient in which the finding is made incidentally at necropsy

For the first and second scenarios, a diagnosis is pursued beginning with the least invasive, most rewarding tests first. Depending on results, further testing often proceeds through minimally invasive (e.g., needle-sampling and cytologic examination) and can extend to tissue-based analysis (biopsy) with confirmatory intent; curative intent is rarely feasible due to extensive infiltration or adhesion. The extent to which a confirmatory diagnosis is sought depends on the following features of the case: patient's stability and capacity to tolerate testing; opportunity to confirm the diagnosis by lesser invasive means, including test repetition (e.g., a second centesis later); client wishes and abilities, both financial and emotional; and to some degree expected prognosis, although speculating on prognosis can be dangerous.

Initial Tests

Abnormalities of routine laboratory tests (complete blood count, serum biochemical profile, urinalysis) are not usually noted in cats with cardiac tumors. Serologic testing for FeLV is variable: 3 of 5 reported cats with cardiac lymphoma had a negative FeLV test result and 2 had a positive result.

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The few cases describing thoracic radiographic findings in cats with cardiac tumors show that marked enlargement of the cardiac silhouette is possible, but evidence of pulmonary metastases is not described. Pleural effusion could be expected if a cat had concurrent mediastinal disease (e.g., lymphoma) or congestive heart failure induced by a mass effect interfering with normal blood flow.

Echocardiography is the noninvasive diagnostic test of choice. In cats with lymphoma, a spectrum of lesions is possible, ranging from focal myocardial infiltrates or a mass lesion (Shinohara et al. 2005) to massive, diffuse infiltration. Myocardium that is infiltrated with lymphoma cells is generally mixed in echogenicity and may be slightly hyper-, iso-, or hypoechoic to surrounding normal myocardium. Pericardial effusion is present in some cases and not in others. Signs suggesting that cardiac tamponade might be likely, such as collapse of the right ventricular free wall, have been present (Brummer and Moïse 1989) or absent (Shinohara et al. 2005).

Cats with chemodectoma have echocardiographic findings that mirror the gross findings listed above: a characteristically located mass, which is usually of mixed echogenicity, with or without pericardial effusion.

Advanced Testing

A cytologic or histopathologic diagnosis is required for definitive confirmation of the nature of these unusual lesions. Fine-needle aspiration and cytologic exam of pleural or pericardial effusion (lymphoma), and of cells retrieved from an echocardiographically apparent mass (chemodectoma), have provided a conclusive diagnosis in some cases of feline cardiac tumors. With lymphoma, pericardiocentesis typically reveals serosanguineous to bloody effusion, with effusion hematocrits reported as 6% (Zoia et al. 2004) or 16% initially and then 3% 1 month later (Shinohara et al. 2005).

Immunophenotyping of feline cardiac lymphoma was undertaken in 2 cases; both were B-cell lymphoma (Aupperle et al. 2007).

TREATMENT

Medical and surgical therapies are described for cardiac tumors in cats. Chemotherapy for lymphoma was successful in at least 2 cases. In the first, treatment with a protocol consisting of cyclophosphamide, vincristine, and prednisone led to disappearance of initial clinical signs of lethargy and depression and dramatic resolution of the myocardial infiltrate on echocardiography, all by the 12th day after initiation of treatment. Similarly, a 5-year-old FeLV-positive cat with cardiac lymphoma received treatment with a protocol comprising L-asparaginase, cyclophosphamide, vincristine, doxorubicin, and prednisone, and clinical recovery was excellent with resolution of clinical signs and effusions (Brummer and Moïse 1989). Conversely, in another case treated with prednisone only, no improvement was seen by the 5th day of treatment and the cat was euthanized (Meurs et al. 1994).

Surgical removal of a chemodectoma is described in 1 case (Paltrinieri et al. 2004). The procedure was completed successfully but the patient died suddenly 24 hours postoperatively.

OUTCOME AND PROGNOSIS

The prognosis for cardiac lymphoma is highly variable: the two dramatically positive responses noted above ended with deterioration and euthanasia of the first cat after 4 weeks but survival beyond the 30th week in the second.

For chemodectoma, treatment appears to be undertaken rarely, and therefore too few instances of treatment response are known to allow a conclusion to be drawn.

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17

Miscellaneous Myocardial Disease

Key Points

- Myocarditis is an uncommon myocardial disease in the cat and the clinical importance likely depends on the underlying etiology.
- Endocardial fibroelastosis is an uncommon endomyocardial disorder observed in young cats (usually <6 months of age) and carries a poor prognosis. Burmese and Siamese cats appear to be predisposed.
- Excessive moderator bands can be observed in the left ventricle in cats of a wide age range. The clinical importance of them is not well understood.

MYOCARDITIS

Myocarditis is a rare form of myocardial disease characterized by the presence of myocardial necrosis and/or degeneration and inflammation. In the cat, infectious agents are most likely to be the etiology and can lead to damage to the myocardium and the induction of the inflammatory response. Chamber enlargement, myocardial dysfunction, and arrhythmias can develop.

Etiology, Pathophysiology, and Gross Pathology

Etiology

Toxoplasmosis has been reported to be a cause of myocarditis in both human beings and cats (Dubey and Carpenter 1993; Kirchhoff et al. 2004; Simpson et al. 2005). In one report a cat with presumed toxoplasmosis myocarditis had elevated IgG and IgM titers to *Toxoplasma gondii* (Simpson et al. 2005). The cat presented for dyspnea, and a heart murmur was identified. Echocardiography demonstrated pericardial effusion and increased echogenicity and hypertrophy of the myocardium with both left and right ventricular involvement. Treatment with clindamycin was initiated and echocardiographic changes and clinical signs resolved.

Streptococcus canis myocarditis was reported in two cats. In 1 case, the cat died shortly after a diagnosis of lameness (Sura et al. 2008). At necropsy bacteria were identified in the myocardium, lungs, kidneys, brain, subcutaneous tissue, and biceps femoris. In a separate case, an 11-year-old cat was diagnosed with mitral valve endocarditis and myocarditis (Matsuu et al. 2007). At necropsy, *Streptococcus canis* was isolated.

Lymphoplasmacytic myocarditis was observed in eight cats that were experimentally infected with *Bartonella*; however, clinical signs suggestive of cardiac disease were not observed (Kordick et al. 1999). Therefore, the clinical importance of this finding is unknown.

Pathophysiology

The presence of inflammation, myocardial necrosis, and degeneration can lead to systolic and/or diastolic dysfunction, ventricular and atrial dilation, and the development of both tachyarrhythmias and bradyarrhythmias. Myocardial fibrosis may also develop.

Pathology

Myocarditis is a pathologic diagnosis that requires histopathological identification of inflammation, necrosis, and fibrosis.

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Signalment

There is no specific signalment or breed predisposition for myocarditis.

History and Chief Complaint

The history may be vague and include such findings as inappetence and lethargy. However, some cats may present with more advanced signs of cardiac involvement, including signs of heart failure (dyspnea, tachypnea) or an arrhythmia (syncope).

Physical Examination

Affected cats may be dyspneic or tachypneic. Some cats may have a heart murmur if the myocarditis has resulted in ventricular dilation or if the infectious agent has involved a heart valve. A bradyarrhythmia or tachyarrhythmia may be detected.

Diagnostic Testing

Electrocardiography

Cardiac arrhythmias may be observed depending on the location and diffuseness of the inflammation. Supraventricular and ventricular tachyarrhythmias may be observed as well as bradyarrhythmias including atrioventricular block.

Radiography

Radiographs may be within normal limits or may demonstrate atrial or ventricular dilation and evidence of heart failure (pulmonary edema, pleural effusion).

Echocardiography

Echocardiography may demonstrate ventricular or atrial dilation. The inflammation may affect the right and/or left side of the heart. Cardiac function may be impacted by the inflammation and may include systolic and/or diastolic dysfunction. In many cases, alterations in echogenicity may be observed. Most frequently this is a hyperechogenicity. In some cases a nodular or granular appearance of the myocardium may be observed.

Diagnosis

Myocarditis is an uncommon cause of myocardial disease in the cat. Diagnosis would depend on consideration of a number of factors, including history, physical examination, and—importantly—echocardiogram to look for alterations in echogenicity, ventricular morphology, and cardiac function. Serum cardiac troponin -I concentrations would be expected to be high, based on human, equine, and canine myocarditis (see Chapter 8) Ultimately though, myocarditis is a pathologic diagnosis that is confirmed only at time of death with a necropsy.

Treatment

Treatment is dependent on the suspected etiology of the myocarditis. If heart failure is present, treatment should be as described (see Chapter 19).

Outcome and Prognosis

Outcome and prognosis is dependent on the underlying etiology and the response to therapy. A case report of suspected *Toxoplasma* myocarditis demonstrates a good response to medical therapy with clindamycin (Simpson et al. 2005). In contrast, two reports of cats with a myocarditis associated with *Streptococcus canis* described a grave prognosis (Matsuu et al. 2007; Sura et al. 2008).

ENDOCARDIAL FIBROELASTOSIS

Endocardial fibroelastosis is a rare cardiac disease defined as diffuse thickening of the left ventricular endocardium secondary to proliferation of fibrous and elastic tissue.

Etiology, Pathophysiology, and Pathology

Etiology

The etiology of endocardial fibroelastosis is poorly understood. It appears to be inherited (primary endocardiofibroelastosis) in some breeds including Siamese, Burmese, and some domestic shorthair cats (Rozengurt 1994; Bonagura and Lehmkuhl 1999). Primary endocardial fibroelastosis is best described in the Burmese cat, where the heritable form has been observed to be a rapid progression from normal histology at birth to symptomatic fibroelastosis by 2 months of age (Zook and Paasch 1982).

Pathophysiology

Excessive fibroblast proliferation occurs in the left ventricular endocardium, which produces collagen and elastin fibers. Marked lymphatic dilation and accumulation of edema within the endocardium are other features of the disease and may occur secondary to impaired cardiac lymphatic drainage. The end result is left or biventricular heart failure, which develops secondary to myocardial failure and ventricular dilation. Pulmonary edema and pleural effusion may be observed. When the right ventricular endocardium is involved, hepatic congestion and ascites may develop.

Pathology

Detailed comparative pathologic studies have been done in a colony of Burmese cats that were bred for this

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defect. Kittens were evaluated from 2 days to 3 months of age at the end-stage of the disease (Paasch and Zook 1980). Affected cats had an increased heart weight with left ventricular and often left atrial dilation. The endocardium appeared grossly opaque and diffusely thickened, secondary to proliferation of fibrous and elastic tissue and edema formation (Bonagura & Lehmkuhl 1999). Histologic abnormalities include a diffuse hypocellular fibroelastic thickening of the endocardium, with thin collagen and elastic fibers, and marked accumulation of edema. Dilated endocardial lymphatics are present until the end-stage disease, when they likely become compressed or obliterated. Purkinje cells, and often the left bundle branch, become incorporated into the fibroelastic thickening, and undergo atrophy or necrosis.

Signalment

Burmese and Siamese kittens were the original breeds reported; however, it has been reported in a colony of domestic shorthair cats as well (Rozengurt 1994; Bonagura and Lehmkuhl 1999).

History and Chief Complaint

A family history of the disease is likely, given the heritable nature of the defect. Clinical signs consistent with congestive heart failure typically develop in cats between 1 and 6 months of age (Bonagura and Lehmkuhl 1999; Fox 1999). Sudden death may occur (Zook and Paasch 1982; Rozengurt 1994).

Physical Examination

Physical examination findings may include a left apical holosystolic murmur of mitral regurgitation, tachycardia, and a gallop rhythm (Zook and Paasch 1982; Fox 1999).

Differential Diagnosis

Because the disease affects young kittens, the most common differential diagnoses include various congenital heart defects such as mitral valve dysplasia, ventricular septal defect, and endocardial cushion defects, which may result in similar clinical presentation.

Diagnostic Testing

Electrocardiography

The most common ECG abnormality is increased R wave amplitude suggestive of left ventricular enlargement (Fox 1999).

Radiography

Left atrial and ventricular enlargement has been observed, often with evidence of congestive heart failure, including pulmonary edema and/or pleural effusion (Fox 1999).

Echocardiography

Echocardiography has not been well described for this uncommon defect. Myocardial failure and left ventricular eccentric hypertrophy may be present. The endocardium may appear thickened and hyperechoic due to the accumulation of fibroelastic tissue.

Diagnosis

Given the uncommon nature of the defect, the diagnosis is primarily based on pathology findings.

Treatment

There is no specific treatment for endocardial fibroelastosis. Therapy consists of treating congestive heart failure when present (see Chapter 19).

Outcome and Prognosis

The prognosis is grave, and most affected cats die of heart failure or suddenly at a young age.

EXCESSIVE LEFT VENTRICULAR MODERATOR BANDS

Excessive moderator bands ("false tendons") are prominent muscular bands that cross from the interventricular septum to the left ventricular free wall (Liu et al. 1982; Wray et al. 2007). A single one is commonly seen in the right ventricle of many species. A single moderator band or a network of small moderator bands has been reported occasionally in the left ventricle of the cat (Wray et al. 2007; Fox 1999). Early reports suggested that left ventricular moderator bands were typically associated with cardiac disease; however, they have also been found as an incidental finding (Fox 1999). Therefore, the importance of moderator bands in the left ventricle of the normal cat is controversial.

Etiology, Pathophysiology, and Pathology

Etiology

The etiology of excessive moderator bands is unknown, and it is unclear if it is caused by a "silent" congenital anomaly (Liu et al. 1982) or is simply a variant of normal in normal cats (Fox 1999).

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Pathophysiology

The function of the moderator band is not known, but proposed functions include preventing overdilation of the ventricle during diastole and passage of Purkinje fibers from IVS to the left ventricular free wall (Liu et al. 1982).

Pathology

The moderator band can be a large trabecular band or many small trabecular bands that divide the ventricle. Histologically the moderator band is characterized by central Purkinje fibers and dense parallel collagenous fibers covered by endothelium (Liu and Fox 1999).

Signalment

Excessive moderator bands have been observed in very young kittens as well as cats as old as 13 years (Liu et al. 1982). A gender predisposition has not been observed.

History and Chief Complaint

There is no specific clinical presentation for excessive moderator bands. In a large study of 21 cats with excessive moderator bands, the most common clinical signs included lethargy, dyspnea, paraparesis, and syncope (Liu et al. 1982). However, since many of the cats also had additional cardiac disease, it is possible that the clinical signs were associated with concurrent cardiac diseases.

Physical Examination

Physical examination findings include hypothermia, a heart murmur, and a gallop. Cats may display clinical signs of left heart failure including tachypnea, dyspnea, or lethargy.

Differential Diagnosis

Endomyocardial fibrosis, a form of restrictive cardiomyopathy, may be confused with excessive moderator bands because it often involves a large fibromuscular band bridging the left ventricle from the papillary muscle to the interventricular septum. Other differentials include other cardiomyopathies or congenital heart diseases.

Diagnostic Testing

Electrocardiography

Conduction disturbances may include right bundle branch block, left anterior bundle branch block, atrioventricular block, and sinus bradycardia (Liu et al 1982; Wray et al. 2007).

Radiography

Radiographs are nonspecific and may indicate evidence of heart failure, including pulmonary edema and/or pleural effusion.

Echocardiography

Characteristic echocardiographic features of this disease include one or multiple isoechoic bands of tissue extending from the left ventricular free wall to the septum. Papillary muscle involvement may be observed.

Diagnosis

Definitive diagnosis of this disease is by necropsy identification of muscular bands dissecting the left ventricle, which are characterized on histopathology as moderator bands. Characteristic echocardiographic abnormalities provide a supportive but not definitive diagnosis of this disease.

Treatment

Excessive moderator bands may be an incidental finding in an asymptomatic cat. In these cases, no treatment is needed. If clinical signs of heart failure are observed, standard heart failure therapy and possible prophylactic anticoagulation may be initiated (see Chapters 19 and 20).

Outcome and Prognosis

Prognosis and clinical importance of excessive moderator bands is poorly understood and likely depends on the presence of other additional cardiac disease.

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SECTION F

Arrhythmias and Other Electrocardiographic Abnormalities

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18

Arrhythmias and Other Electrocardiographic Abnormalities

Key Points

- Although at opposite ends of the heart rate spectrum, tachycardias and bradycardias may produce similar overt clinical signs (e.g., syncope); however, most cardiac arrhythmias in cats produce no detectable signs and instead are incidental findings.
- The electrocardiogram (ECG, EKG) remains the diagnostic test of choice to confirm or rule out cardiac arrhythmias. If a resting ECG is insufficient, portable or implantable ECG monitors may confirm the diagnosis.
- Myocardial disease is often present in cats with ventricular tachyarrhythmias (premature ventricular complexes, ventricular tachycardia) or atrial fibrillation.

INTRODUCTION

Cardiac arrhythmias (dysrhythmias) are defined as disturbances in the rhythm of the heartbeat (Tilley 1993; Mirvis and Goldberger 2008; Fox and Harpster 1999; Côté 2010). In cats, as in other species, a range of severity exists in terms of the significance of an arrhythmia to the patient: arrhythmias may be normal physiologic variants, such as sinus tachycardia in the exam room; individual variants of no concern, such as right bundle branch block; markers for underlying structural heart disease, such as many cases of third-degree AV block or atrial fibrillation; or the principal cause of the patient's chief complaint: episodic weakness, syncope, or even sudden death.

ETIOLOGY, PATHOPHYSIOLOGY, AND GROSS PATHOLOGY

Broadly, arrhythmias can be divided into those disorders where the creation or conduction of impulses is greater than normal, and those where it is less than normal. Both situations can cause identical clinical manifestations: arrhythmias that involve an excessively high heart rate (tachycardias, also called tachyarrhythmias) are indistinguishable in their clinical manifestations from those arrhythmias that cause an excessively slow heart rate (bradycardias, also called bradyarrhythmias). The rapid fluctuations in heart rate brought on by sporadic arrhythmias can alter cardiac output faster than a patient's homeostatic mechanisms can offset these changes. Therefore, forward cardiac failure, manifested classically as syncope, is the chief complaint of cardiac arrhythmias in cats, in contrast to chronic mechanical pump failure, such as with the cardiomyopathies or congenital malformations, where backward (congestive) heart failure occurs as a result of the lesion exceeding the body's longstanding compensatory mechanisms.

The rarity of syncope in the cat attests to the severity of arrhythmia needed to cause an observable change. When bradycardias limit cardiac output, they do so by compromising heart rate (cardiac output [ml/min] = heart rate [beats/min] × stroke volume [ml/beat]). When tachycardias limit cardiac output, they do so by limiting stroke volume: the physiologic maximum heart rate (the fastest rate of sinus tachycardia possible in a healthy cat, subjectively 260–280 beats/min for periods of several seconds to minutes) ensures adequate diastolic filling time for the ventricles, but pathologic

Feline Cardiology, First Edition. Etienne Côté, Kristin A. MacDonald, Kathryn M. Meurs, Meg M. Sleeper.
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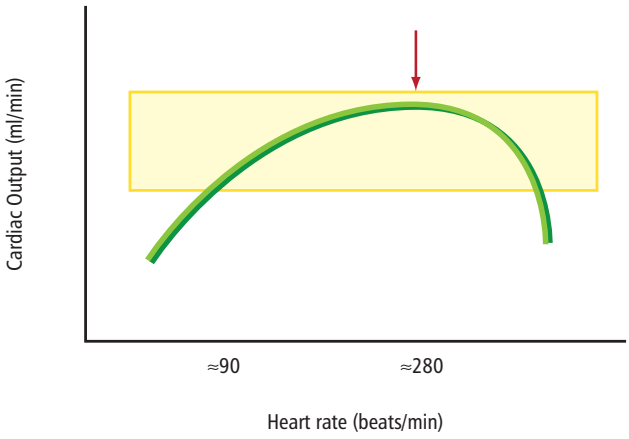


Figure 18.1. Effect of heart rate on cardiac output. As heart rate increases, cardiac output increases, because the volume of blood ejected by the heart to the circulation per minute depends exactly on the amount of blood in the ventricles for each beat times the number of beats per minute (cardiac output = stroke volume × heart rate). This direct relationship is constructive up to a point (red arrow), after which further increases in heart rate lead to a decrease in cardiac output. Yellow box: range compatible with life (hemodynamic stability and adequate perfusion of vital organs in the cat).

tachycardias that exceed this maximum rate may force the heart to beat at a rate that leaves the ventricles insufficiently filled from one beat to the next. In this way, ventricular tachycardia at 360 beats/min is expected to produce a lower cardiac output than ventricular tachycardia at 260 beats/minute (Figure 18.1). The clinical implication is that a cat exhibiting clinical signs such as suspected or confirmed syncope needs to have ECG confirmation of the heart rhythm during those clinical signs, in order to identify whether a bradycardia or a tachycardia is responsible, and choose a treatment that corrects, rather than adds to, the problem.

A number of clinically important points can be understood from the relationship in figure 18.1:

- An increase in heart rate triggered by physical exercise or by sympathetic stimulation to maintain an individual in an asymptomatic state despite cardiomyopathy, for example, increases the cardiac output (desirable effect). This is represented by the ascending limb of the curve in the left part of the yellow box.
- Too low a heart rate, even when the myocardium is healthy, is inadequate for hemodynamic stability. Examples include marked sinus bradycardia during general anesthesia, or third-degree AV block and a slow ventricular escape mechanism. This is represented by the tail of the curve in the bottom left, outside the yellow box. In this instance, measures to reverse the cause of the bradycardia (e.g., reduce the concentration of inhalant anesthetic), and if not sufficient, treatment to increase the heart rate directly (e.g., glycopyrrolate for sinus bradycardia under anesthesia, or pacemaker implantation for AV block and a low ventricular escape rate) are essential in order to promptly raise the heart rate and return the cardiac output to a level compatible with life.
- A physiologic maximum exists for the sinus heart rate (peak heart rate), beyond which the heart rate cannot reach even under maximal sympathetic stimulation. This innate maximum heart rate limit (red arrow) varies from one individual to another but broadly exists at a point at which cardiac output is maximized. Examples of reaching this peak heart rate are sinus tachycardia during extreme physical activity or in a cat with life-threatening pulmonary edema/congestive heart failure. In most cats this maximum is likely between 260 and 300 beats/minute.
- Too high a heart rate compromises diastolic ventricular filling to a disproportionately greater degree than the benefit of the rise in heart rate, resulting in a fall in cardiac output. That is, the benefit of the cardiac output relationship (cardiac output = heart rate × stroke volume) is compromised by a lower stroke volume when ventricles are "told to contract faster than they can fill." This range of heart rates exceeds the maximum sinus rate (red arrow), which means it only occurs due to an arrhythmia (classically atrial tachycardia, atrial fibrillation, or ventricular tachycardia). Therein lies the risk associated with these arrhythmias, since they are not confined to the normal range of heart rate and may produce very rapid tachycardias that markedly reduce cardiac output (the descending limb on the right side of the curve within the yellow box). This region of the curve illustrates that tachycardias generally produce negative hemodynamic effects that are more severe when the heart rate is higher. Therefore, arrhythmias warrant treatment with an antiarrhythmic more promptly (or at all) if the heart rate they produce is very high, whereas a less aggressive treatment approach is more often taken when the arrhythmia produces a heart rate that is not much different from the normal range of heart rate. The curve also shows that similar reductions in cardiac output (bottom of the yellow box) may occur with severe tachycardias, on the right, or severe bradycardias, on the left; thus, a patient with a presenting complaint of syncope, reflective of cerebral hypoperfusion, requires an ECG diagnosis to identify the arrhythmia because exactly the same clinical signs can arise from tachycardias requiring treatments that reduce the heart rate (bottom right of yellow box) and

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bradycardias requiring treatments that increase the heart rate (bottom left of yellow box).

- Extreme increases in heart rate may render the ventricles essentially non-functional; so little time is available between beats for diastolic filling that the ventricles ultimately quiver rather than contracting and filling. Examples of such a situation are very rapid ventricular tachycardia (e.g., >400 beats/minute in the cat) or ventricular fibrillation. Cardiac output falls below a level that can sustain perfusion of vital organs and cardiac arrest occurs (segment of the curve at the bottom right corner, outside the yellow box). Treatment requires immediate elimination of the tachycardia, such as with electrical defibrillation, so that normal sinus rhythm may reemerge spontaneously.

This curve illustrates the relationship and concepts associated with heart rate and cardiac output in the cat, but exact numerical values for each parameter vary from one cat to the next depending on the structure of the myocardium, presence of euvolemia/hypovolemia, and electromechanical association, among other factors.

Pathophysiologic mechanisms underlying arrhythmias are varied and are discussed for each individual arrhythmia.

CLINICAL ELECTROCARDIOLOGY

Diagnostic Decision-Making and Electrocardiography

The ECG is the uncontested cornerstone of evaluation of the cardiac rhythm. Two central questions govern its use: when should one be performed, and what is to be done if it reveals an abnormality?

An ECG is warranted under any of the following circumstances:

- When an irregular heart rhythm is ausculted or palpated during physical exam
- When the heart rate is noted to be unusually rapid or unusually slow considering the cat's immediate environment and medical status
- When overt clinical signs suggest compromised circulatory function (e.g., syncope or near-syncope)
- As part of monitoring a patient under general anesthesia, in an intensive care unit, or in any setting where acute changes in cardiovascular function are considered likely
- As part of a comprehensive cardiovascular evaluation

The value of ECG as a clinical screening test remains debated. Some practitioners obtain ECGs from cats as part of routine geriatric, preoperative, asymptomatic murmur, or other stable patient evaluations; some experts and medical device companies support such screening, while others, including many cardiologists, do not advocate this extent of preemptive use of the ECG. Certain changes are indeed apparent on ECG that are associated with underlying heart disease, and detecting these can lead to earlier diagnosis of heart disease. For example, 22% of cats with atrial fibrillation (AF) are diagnosed with this arrhythmia incidentally during a routine physical examination (Côté et al. 2004) and the vast majority of cats with AF have myocardial disease, typically cardiomyopathy. Perhaps more cases of AF and cardiomyopathy could be identified through a more widespread use of ECG in cats. Similarly, third-degree AV block is detected as an incidental finding in otherwise normal-appearing cats in 29% of cases (Kellum and Stepien 2006); a wider application of early identification could conceivably lead to pacemaker implantation and prevention of sudden death in some patients. However, these arrhythmias are often detected on auscultation and the expense associated with early diagnosis and intervention may be reasonable when ECGs are performed on a select population (e.g., those cats with an audible arrhythmia); the expense and other drawbacks may become dramatically—perhaps prohibitively—greater when applied to the feline hospital population as a whole. Another example is ST segment changes, which occur on the ECGs of 43–47% of cats with cardiomyopathy (Schwerin et al. 2002a, b). Although this high prevalence is important, its clinical application as a screening test means that trusting the ECG to accurately identify a cardiomyopathic cat amounts to the flip of a coin (50% likelihood). Therefore, despite the technical simplicity and appeal of an ECG, these examples demonstrate that the role of ECG as a screening tool is not supported by current data. Its use should be confined to patients meeting one or more of the criteria in the list, above, until studies identifying the cost-to-benefit ratio of systematic ECG screening are performed in the feline population.

Evaluating the Arrhythmic Feline Patient

When the ECG has identified an abnormality, defined as a clinically relevant finding not explained by normal physiologic changes (excluding sinus tachycardia caused simply by excitement, for example), then the following diagnostic investigations are appropriate in all cats (Côté and Harpster 2009):

- History
- Physical exam
- Thoracic radiographs
- Echocardiography
- Arterial blood pressure

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- Complete blood count
- Serum biochemistry profile
- Urinalysis

Serum thyroxine levels, feline leukemia testing, and feline immunodeficiency virus testing may be appropriate depending on age, environment, and physical exam findings. Additional testing is pursued based on results and on the particular features of a case. These diagnostic evaluations allow the clinician to identify underlying or concurrent disorders and develop a treatment plan and prognosis. The specific prioritization of these tests is detailed below for each arrhythmia.

Heart Rate

The adult cat's intrinsic heart rate (where the heart is artificially deprived of both sympathetic and parasympathetic inputs by concurrent propranolol and atropine treatment) is 158 ± 4 beats/minute, as compared to 218 ± 3 beats/minute in the same cats in a laboratory setting prior to treatment (Diepstra et al. 1980). These values confirm what is apparent to most clinicians, namely that the autonomic input to the heart of a cat undergoing examination is usually characterized by a predominance of sympathetic tone over parasympathetic tone, likely through the same increase in cardiac sympathetic nerve activity that is noted in cats during physical exercise (Tsuchimochi et al. 2002). Most normal cats seen in the veterinary setting have a heart rate that ranges from 140 to 260 beats/minute (Côté et al. 2004), with a mean of 150 ± 23 beats/minute at rest in a veterinary teaching hospital and 187 ± 25 beats/minute during restraint for echocardiography (Abbott 2005). By contrast, normal cats at home have a mean heart rate of 118 ± 11 bpm when ausculted by their veterinary student-owners (Hamlin 1989) and routinely have heart rates <100 beats/minute (presumably during sleep) when assessed by Holter monitor (Abbott 2005; Hanås 2009; Ware 1999). Therefore, while some sources describe normal sinus rhythm and its defined rate of 110–180 beats/minute as the normal cardiac rhythm for the cat, context is critical and normal sinus rhythm, sinus bradycardia, and sinus tachycardia are to be expected in normal cats in appropriate environments.

Kittens have a higher heart rate (median: 247 beats/minute during the first week of life) (Gomes Lourenço and Ferreira 2003) whereas adult cats conserve a similar range of heart rates across all ages, from young adulthood to geriatric age. As cats age from kittenhood (6 weeks) to geriatric (18 years), SA nodal cycle length increases, dependent on diastolic depolarization rate and action potential duration (Alings and Bowman 1993). The size of the adult feline SA node does not change over time (Alings and Bowman 1993). There is no established gender difference in heart rate.

It should be remembered that normal sinus rhythm may constitute a bradycardia if the patient is in an environment or has a medical status that would normally be expected to elicit sinus tachycardia. An example is the cat that appears aroused or anxious but whose exam-room heart rate is only 140 beats/minute. While some healthy cats may have naturally high vagal tone even when anxious, any cat with a resting heart rate <160 beats/minute in an examination room should be evaluated like a sinus bradycardia patient, beginning with an ECG to rule out pathologic bradycardias (see below).

An elevated heart rate alone rarely is indicative of heart disease in the cat. Although it is true that cats with heart disease may have heart rates exceeding 240 beats/minute, healthy cats or cats with noncardiac illness also routinely have sinus tachycardia at such rates. For example, in a study of 103 overtly healthy cats, 16 had cardiomyopathy and 87 did not, but their mean heart rates were essentially identical: 189 vs 188 beats/minute (Paige et al. 2009). Thus, rate alone cannot be used for suspecting or ruling out heart disease in cats. Exceptions include 1) the concurrent presence of an irregular rhythm, and 2) when the heart rate is sustained at >240 beats/minute for 60 seconds or more despite a calm environment and no identifiable systemic illness. With such unrelentingly high heart rates, pathologic tachycardias including ventricular tachycardia, atrial tachycardia, atrial fibrillation, and macroreentry need to be ruled out with an ECG.

SPECIFIC ARRHYTHMIAS

Normal Sinus Rhythm

The normal heartbeat originates in the sinoatrial (SA) node, a region of specialized impulse-forming cells located in the dorsolateral right atrium. In the domestic cat, a cluster of fewer than 2000 (possibly <500) cells comprises the primary pacemaker within the SA node (Opthof et al. 1986). Unifocal impulse generation, a predominance of collagen, and a paucity of gap junctions are characteristics of the feline SA node. Its morphology resembles that of the dog and human but not the rabbit or guinea pig; however, electrophysiologic properties of the SA node of the cat and rabbit are similar (Opthof et al. 1986).

A combination of sodium influx through the I_f current, decay in potassium influx through I_{Kr} and I_{Ks} currents, and intramyocyte sodium-potassium exchange (transmembrane $I_{Na–Ca}$ current) in SA nodal cells raises the cells' membrane potential past the threshold level.



Figure 18.2. Normal sinus rhythm in a 17-year-old male castrated domestic short-haired cat with peritoneopericardial diaphragmatic hernia. Heart rate = 160 beats/minute. 25 mm/sec, 1 cm = 1 mV.

The result is an influx of calcium through the $I_{Ca–T}$ (transient) and $I_{Ca–L}$ (long-lasting) currents, causing depolarization. A spontaneous, inherent ability to depolarize is called *automaticity*, and this is a hallmark feature of the normal SA node. The end of depolarization is indicated by activation of the repolarizing outward rectifier current, I_K, which evacuates potassium ions from the cell.

The wave of electrical activity created in the SA node spreads outward through the atria, creating the P wave on the ECG. A portion of this electrical activity reaches the atrioventricular (AV) node in the floor of the right atrium. The AV node is a functional filter that prevents excessive numbers of supraventricular impulses from reaching the ventricles and delays the conduction of each normal impulse slightly in order to allow optimal ventricular filling via the completion of atrial contraction. This AV node-associated delay is expressed as the PR segment, the period of electrical quiescence between the P wave and QRS complex. For purposes of nomenclature, note that the PR *interval* consists of the PR *segment* plus the P wave proper. Passage through the AV node triggers ventricular depolarization through the His-Purkinje system's arborization into the right and left bundle branches, the latter of which may further divide into the left anterior and left posterior fascicles. This division has been demonstrated in many species and remains controversial in the cat, particularly as concerns left anterior fascicular block. The ECG expression of ventricular depolarization is the QRS complex. Repolarization is necessary to prepare the myocardium for a subsequent depolarization; in the ventricles, it occurs transmurally (from the endocardial surface toward the epicardium, as well as from the epicardial surface to the endocardium, such that the components of repolarization meet midmurally) and creates the T wave on ECG. An equivalent process occurs in the atria, producing the T_a ("T sub-a") wave, but the extremely small amplitude of this wave in the cat, and its frequent overlaying by the QRS complex, mean that it is rarely seen. Uncommonly, abnormal atrial repolarization may produce a visible T_a wave in the terminal part of the PR segment.

In the normal cat, this sequence of cardiac depolarization and repolarization occurs consistently for each beat, and the interval from one beat to the next is constant, creating normal sinus rhythm (NSR). The ECG characteristics of NSR are monomorphic (same-shaped) P waves, monomorphic QRS complexes, the presence of a P wave for every QRS complex and a QRS complex for every P wave with a consistent P-R interval, and a constant R-R interval (i.e., a *regular rhythm*) at a rate between 110–180 beats/minute outside a stimulating or stressful environment (Figure 18.2) (Côté and Harpster 2009).

Sinus Tachycardia

Withdrawal of vagal tone, and an increase in sympathetic tone, are the factors that underlie sinus tachycardia in the cat (Diepstra et al. 1980; Tsuchimochi et al. 2002). Sinus tachycardia is a rapid, regular rhythm in which the ECG findings are identical to those of NSR except for rate, which is defined as >180 bpm (Figure 18.3). The upper limit of heart rate for sinus tachycardia in the cat is 260–280 bpm (Côté et al. 2004; Ware 1999), although anecdotal reports of sinus tachycardia at 300 bpm exist in cats.

Sinus tachycardia is essentially never the cause of clinical signs, nor is it frequently observed as an isolated rhythm abnormality. Rather, sinus tachycardia is almost always the consequence of a more generalized disturbance, such as anxiety, pain, medication/toxicosis, hypovolemia, anemia, or hypoxemia. Therefore, the history of patients with sinus tachycardia is vital because it helps to pinpoint the underlying cause of the tachycardia. Sinus tachycardia itself is not expected to produce any owner-observed abnormalities.

The physical examination findings specific to sinus tachycardia consist essentially of an elevated heart rate. The pulse is synchronous and may be of the same,



Figure 18.3. Sinus tachycardia in an anxious cat with compensated hypertrophic cardiomyopathy. Heart rate = 210 beats/minute. 25 mm/sec, 2 cm = 1 mV.

weaker, or stronger intensity than normal depending on diastolic filling time, presence or absence of structural heart disease, and intravascular volume status, among other factors.

Other findings, such as an anxious demeanor with stress-associated sinus tachycardia, or pallor in anemia cases, are often apparent to varying degrees on the extracardiac physical examination. A heart murmur may sometimes be heard only when a cat's heart rate is elevated. Since heart rate and inotropy (force of ventricular contractility) are both increased by sympathetic stimulation, the clinician's impression may be that a cat's increased heart rate is responsible for the generation of the murmur, when in fact the increased systolic force is more likely causative. Importantly, this phenomenon may be harmless, as in many cases of dynamic midright ventricular obstruction (Rishniw and Thomas 2002), or may be indicative of structural heart disease, as in the obstructive form of hypertrophic cardiomyopathy. A cat with a murmur audible only when provoked or aroused is 6.1 times more likely to have dynamic ventricular outflow tract obstruction than a cat that does not develop a murmur under the same circumstances (Paige et al. 2009). Therefore, the presence of a heart murmur noted only during sinus tachycardia is neither diagnostic of heart disease nor reassuring of its absence, and when a murmur is noted only when a cat's heart rate is high, investigation of cardiac structure, beginning with echocardiography, is warranted.

Sinus tachycardia is the most common cause of an elevated heart rate in overtly healthy cats in a clinical setting. ECGs performed on 27 normal cats identified rhythms of sinus origin at a mean heart rate of 182 ± 20 beats/minute (Hamlin 1989), indicating that more than half of healthy cats have sinus tachycardia when restrained for the purpose of ECG evaluation.

Differential diagnoses include atrial tachycardias, ventricular tachycardia, and rarely atrioventricular reciprocating tachycardias (macroreentry such as the Wolff-Parkinson-White syndrome). The ECG is the diagnostic test of choice, and it is generally performed if a patient's heart rate seems inappropriately high given the patient's context; if the rate remains elevated in a sustained manner (>60 seconds at >240 beats/minute despite calm environment and no identifiable illness); if the rhythm is irregular; or if overt clinical signs suggestive of syncope are observed, since none of these features is consistent with sinus tachycardia.

Importantly, treatment of sinus tachycardia should consist of correcting its inciting causes, not treating the arrhythmia. Suppression of sinus tachycardia itself, such as with a beta-blocker or calcium-channel blocker, may prove to be catastrophic when the rhythm was a natural compensatory response (reflex tachycardia) providing a necessary increase in cardiac output in a systemically ill patient.

Sinus Bradycardia

A rhythm that is sinus in origin but that occurs at a rate lower than that of NSR (<110 bpm) is termed *sinus bradycardia* (Figure 18.4). Sinus bradycardia is a rhythm that virtually always occurs as a consequence of an extracardiac influence, generally one that increases vagal tone. Examples include spontaneous factors (e.g., sleep), medical effects (e.g., opiate drugs), and systemic disorders such as hypoglycemia (Little 2005). Subjectively, cats commonly develop sinus bradycardia in shock syndromes such as severe hypovolemia (Boothe et al. 1985) or septic peritonitis (16% of cases) (Costello et al. 2004). Interestingly, in cats experimentally made hypovolemic through massive phlebotomy (bled 25 ml/kg), the heart rate decreases, and replacement with equal or larger volumes of lactated Ringer's solution causes an increase in heart rate—the opposite sequence of events expected from baroreceptor reflex predominance, as in dogs (Costello et al. 2004). This phenomenon is well-recognized in feline practice; the mechanisms remain to be clarified, but potential explanations include SA nodal hypoperfusion, rapid downregulation or disturbance of catecholamine receptors, cervical/thoracic trauma



Figure 18.4. Sinus bradycardia. This cat sustained a tarsal fracture and was receiving opiate analgesia (hydromorphone), which increases vagal tone. Heart rate = 100 beats/minute. 25 mm/sec, 1 cm = 1 mV. Tracing courtesy of Dr. Cate Creighton, Atlantic Veterinary College, UPEI, Canada.

causing cardiac sympathetic denervation or spinal cord trauma, and central nervous system disturbances causing massive central vagal discharge (Ornato and Peberdy 1996). Massive release of cardiac nucleosides has been documented in experimental myocardial hypoxia in cats (Berne 1963), and such nucleosides, notably adenosine, can decrease myocardial contractility, pacemaker automaticity, and AV nodal conduction (Ornato and Peberdy 1996). The lack of responsiveness to atropine by adenosine-mediated bradycardias, but successful in vitro response with methylxanthine drugs (Ornato and Peberdy 1996), helps explain the common prescription of drugs such as theophylline in an attempt to treat sinus bradycardia when it is part of the sick sinus syndrome (sinus node dysfunction). Such treatment has not been evaluated objectively in cats with hypotensive shock-associated bradycardia (nor sick sinus syndrome), however.

As noted previously, a *relative* sinus bradycardia may be said to exist in a cat that has normal sinus rhythm (e.g., at a heart rate of 130/minute) in a context that would be expected to produce sinus tachycardia (e.g., noisy treatment area). Therefore, the textbook definition of sinus bradycardia involves a rate of <110 bpm, but the practical clinical concept of sinus bradycardia—and the desire to investigate a surprisingly low heart rate with ECG—is more fluid and must factor in the influences of environment and medical status.

The history and physical exam of cats with sinus bradycardia essentially always reflect the underlying cause rather than the arrhythmia itself. A rare exception is the cat with sinus node dysfunction (sick sinus syndrome), which is a very uncommon disorder in this species (see below).

Physical examination of cats with sinus bradycardia reveals a slow, regular rhythm with a synchronous pulse, the strength of which varies depending on the underlying cause of the bradycardia. In a cat with a low heart rate, the main differential diagnoses are sinus bradycardia and second- or third-degree AV block, and the ECG is diagnostic. Further diagnostic testing in sinus bradycardia is indicated only for identifying its underlying cause if it is not apparent and accounted for by the history and physical examination.

Treatment of sinus bradycardia is almost never necessary, inasmuch as treatment should concentrate on correction of the underlying cause. Therapy that alters the heart rate (e.g., parasympatholytic drugs such as atropine) may be indicated if sinus bradycardia is associated with hypotension and the underlying cause is already being addressed; the most common clinical example is probably an excessively deep plane of general anesthesia, where reduction of inhalant anesthetic is followed by a lag period, and sinus bradycardia causing hypotension is treated with glycopyrrolate or atropine to temporarily raise the heart rate while the level of anesthesia normalizes.

Respiratory Sinus Arrhythmia

A cyclical variation in heart rate characterized by faster heart rate during inspiration and slower heart rate during expiration, but otherwise normal ECG characteristics of normal sinus rhythm, is termed *respiratory sinus arrhythmia* (RSA; Figure 18.5). Respiratory sinus arrhythmia is primarily vagally mediated, with negative intrathoracic pressure of inspiration causing less pressure on the paired vagus nerves and therefore lower vagal tone (heart rate increases), and the reverse sequence causing a decrease in heart rate during expiration. Additional factors involved in generating RSA include the Bainbridge reflex (atrial stretch stimulates receptors in the atrial wall, increasing heart rate via vagal inhibition; countermechanism to baroreceptor reflex), the Bezold-Jarisch reflex (venous pooling causing arterial hypotension, which triggers an increase in heart rate via baroreceptor activation), respiratory muscle stretch reflexes, and interaction of respiratory and cardiac



Figure 18.5. Respiratory sinus arrhythmia. This cat displayed severely exaggerated inspiratory and expiratory efforts due to near-complete upper airway obstruction by a very large nasopharyngeal polyp. Note that the rhythm accelerates and decelerates cyclically, a pattern that was repeated continuously. Blue = expiration; red = inspiration. 25 mm/sec, 1 cm = 1 mV.

centers in the medulla (Rishniw and Bruskiewicz 1996). It occurs commonly when cats are asleep (Schechtman et al. 1985) and in the home environment in general (Hanås et al. 2009; Ware 2009). As described above, cats in a clinical setting generally have a dominantly sympathetic influence on the cardiovascular system, and feline RSA is therefore very rarely observed in the exam room. Pathologically high elevations in vagal tone, such as those observed with intoxications (e.g., digoxin, organophosphate), central nervous system disorders, or gastrointestinal disturbances, can cause RSA in cats (Rishniw and Bruskiewicz 1996; Ware 1992), as can upper airway obstructions that force the cat to create abnormally elevated and decreased intrathoracic pressures on expiration and inspiration, respectively (see Figure 18.5). These same mechanisms are also responsible for the wandering pacemaker, which, when it occurs, often coexists with RSA. Occasionally, RSA is observed in normal cats in the clinical environment (Rishniw and Bruskiewicz 1996; Ware 1992). Respiratory sinus arrhythmia does not warrant antiarrhythmic treatment, and no clinical signs are expected due to RSA itself. Identification of this arrhythmia in cats simply justifies investigation of possible underlying causes. The high degree of vagal tone required to overcome sympathetic influences in the hospital setting likely explains both the rarity of RSA in the cat, and the observation that the nature of the inciting cause is usually apparent on physical exam alone—such as severe upper respiratory distress or signs of marked CNS dysfunction.

Premature Atrial Complexes

As described above, every normal heartbeat begins as a wavefront of organized electrical activity that originates in the SA node and activates the atria in a wavelike sequence. A premature atrial complex (PAC; synonyms: atrial premature complex/contraction/depolarization) preempts this rhythm. A PAC begins as a solitary impulse originating from atrial tissue outside the SA node. If the abnormal impulse originates *prior* to emergence of the normal heartbeat from the SA node, the impulse has occurred prematurely and a true PAC exists. The abnormal impulse takes control of the atria for that beat and depolarizes them and then conducts to the ventricles, with the entire heartbeat therefore occurring sooner than expected: a premature atrial complex. Note that if the abnormal impulse were to arise from the atrial tissue later, *after* the normal heartbeat has already emerged from the SA node, then the normal wavefront controls the atrial and the abnormal impulse fails to conduct; the normal heartbeat carries through to the AV node and a normal heartbeat occurs instead of a PAC. Thus, the term "premature atrial complex" nicely explains the features of this arrhythmia: atrial impulses that are ectopic (originating outside the SA node) trigger a complete heartbeat and are apparent on ECG if they occur sooner than a normal heartbeat should (i.e., prematurely; Figure 18.6). A temporary pause in recording the ECG may give the false impression of a PAC, and this type of misinterpretation must be avoided (Figure 18.7). The ECG representation of atrial activity in a PAC is termed a *P' wave*, and it may be of mildly or markedly different morphology (shape) than the patient's normal sinus P waves depending on the distance of the ectopic focus of origin from the SA node: how different the P' wave looks depends on how different the path of atrial depolarization was compared to that seen in a normal sinus beat.

In cats, PACs are associated with structural atrial abnormalities (Boyden et al. 1984). As a general concept, atrial lesions may be responsible for one of 3 types of functional disorders, giving rise to PACs: spontaneous impulse formation in atrial myocardium where no impulse should normally begin ("abnormal automaticity"), abnormal perpetuation of an existing impulse that should normally have been transient ("reentry"), or spontaneous depolarization during repolarization ("afterdepolarizations," causing "triggered activity") (Blömstrom-Lundqvist et al. 2003; Nattel 2002). These

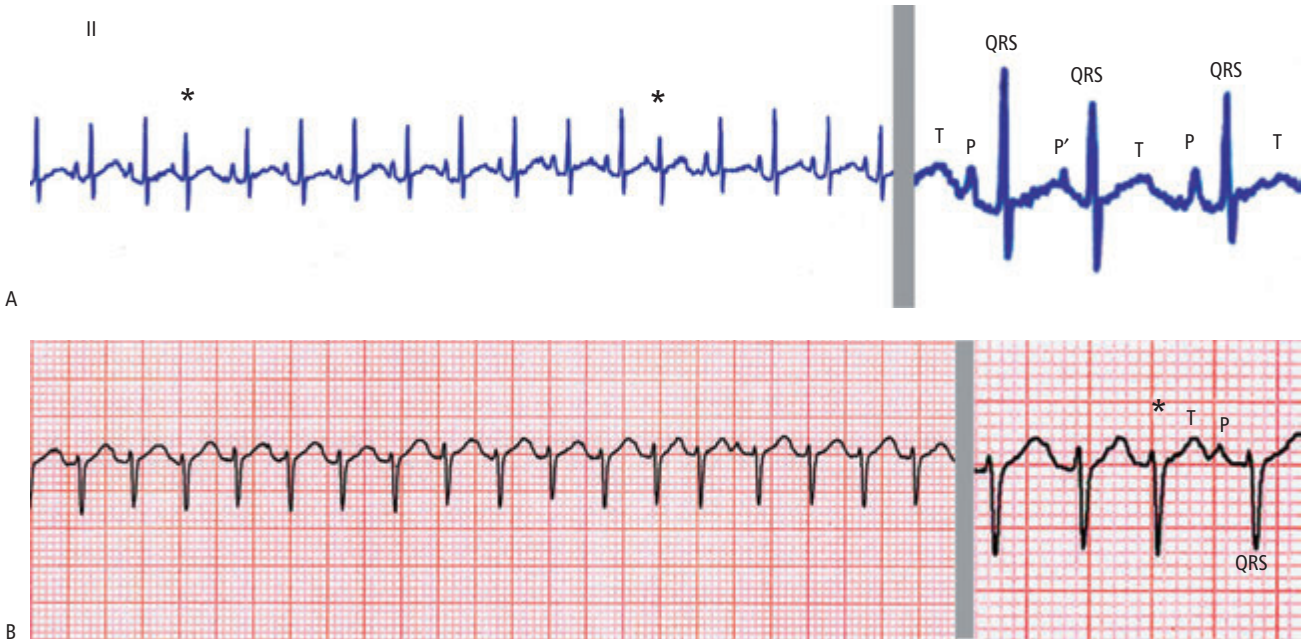


Figure 18.6. **(A)** Two premature atrial complexes (PACs; asterisks) in this 15-year-old domestic long-haired cat with left ventricular concentric hypertrophy. By definition, the PACs occur sooner than expected (shorter R-R interval than other beats), but the QRS complex and T wave morphology are only slightly different than that of the sinus QRS complexes and T waves. The premature P wave (P′) is superimposed on the preceding T wave. The slight variation in QRS morphology for the second premature beat could suggest it is a PVC, but the T wave is of the same shape as sinus T waves, and the QRS is not wider than normal, both of which are inconsistent with a PVC. **(B)** One PAC in a cat. The regular rhythm is interrupted by a PAC (fifth heartbeat from the right; also inset [asterisk]). This subtle finding underscores the need for careful examination of ECG tracings; otherwise, such abnormalities may be missed. The pause that immediately follows the PAC reveals the normal shape of the P and T waves (inset), which are otherwise superimposed on each other during the rest of the tracing. Heart rate = 200 beats/minute. The diagnosis is sinus tachycardia or atrial tachycardia, with one PAC; S waves in this lead II tracing suggest an axis deviation. 25 mm/sec, 1 cm = 1 mV.

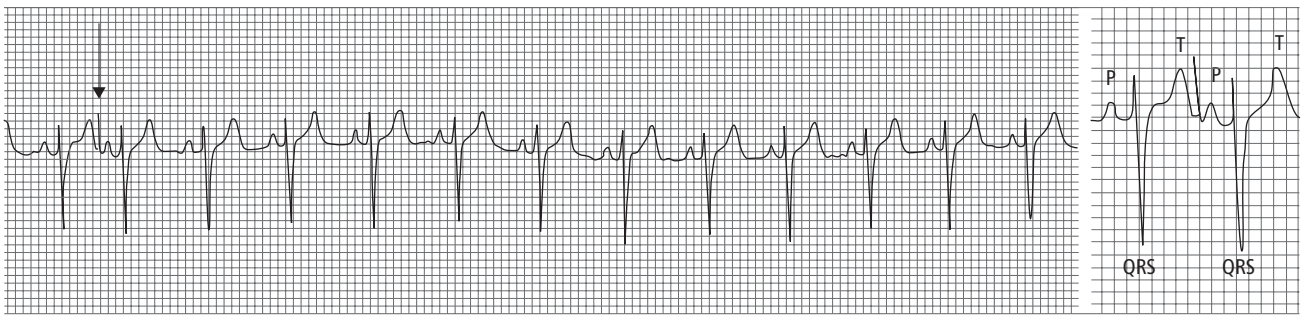


Figure 18.7. Artifact mimicking a premature atrial complex in a cat. Pausing during a rhythm strip and then restarting can be associated with a shorter R-R interval at the time of restart, giving the erroneous impression of a premature beat. In this figure, the ECG acquisition was stopped and then restarted between the first and second beats. Typically, a sharp vertical line or other ECG stylus marking is present at the point of pausing (arrow). Lead II; 25 mm/sec, 1 cm = 1 mV.

mechanisms are explained in detail and with great clarity by Nattel (2002). Through variations within these mechanisms, PACs may occur singly or repetitively, with variable degrees of prematurity.

Premature atrial complexes in cats are classically considered a marker for atrial enlargement. For example, in 34 cats with atrial enlargement associated with cardiomyopathy, 5 (15%) had PACs on routine ECG (Boyden et al. 1984). There was a reduction in the resting membrane potential, decreased action potential amplitude, and decreased velocity of phase 0 depolarization of some atrial cells in these cats, and other atrial myocytes were electrically inexcitable (Boyden et al. 1984). These changes, associated with interstitial fibrosis and cellular hypertrophy and degeneration, increase in severity with increasing atrial size in cardiomyopathic cats and thus

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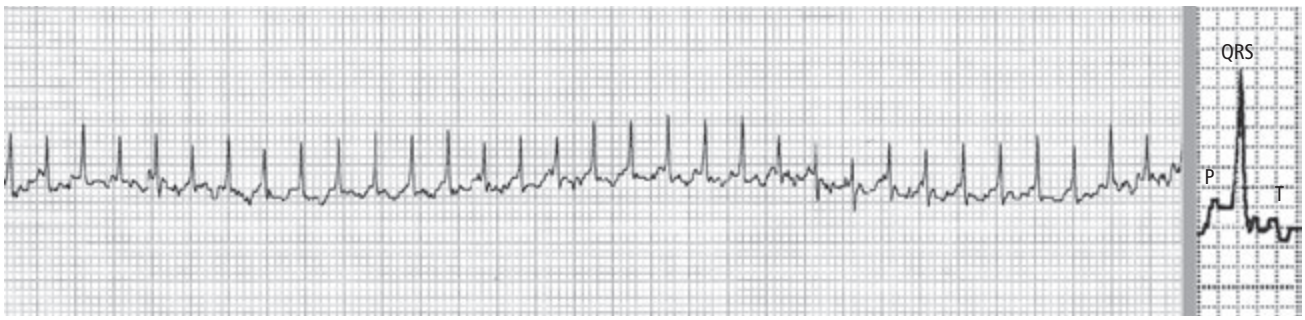


Figure 18.8. Supraventricular tachycardia/atrial tachycardia in a 4-year-old Persian cat with unclassified cardiomyopathy. QRS complexes are narrow and upright in this lead II tracing, consistent with a supraventricular origin of the arrhythmia. P waves are sometimes difficult to see because of fine artifact altering the baseline. The heart rate is 320 beats/minute. 25 mm/sec, 1 cm = 1 mV.

may explain the occurrence of atrial arrhythmias through microreentry: heterogeneous depolarization and repolarization of diseased atrial myocytes predisposes to reentry, especially if an obstacle exists (inexcitable atrial myocytes) around which the reentry may occur (Boyden et al. 1984).

Premature atrial complexes are thus associated with diseases that can cause atrial enlargement, cardiomyopathy, or both: a case series of 59 cats with cardiomyopathy from the early 1970s revealed a prevalence of PACs of 12% (Harpster 1977). Premature atrial complexes also occur in association with noncardiomyopathic disorders, including 11% (Peterson et al. 1982) to 15% (Moïse et al. 1986) of cats with hyperthyroidism; feline endocarditis (Kovacevic et al. 2002); and in association with ventricular preexcitation (Rishniw 2000). Healthy cats have 0–21 PACs daily, with the higher number occurring in older individuals (Ware 1999). The clinical significance of PACs in cats primarily is their role as a marker for atrial disease. The underlying cause must be managed, but antiarrhythmic treatment is not warranted for PACs alone, unless clinical signs such as syncope exist and it is suspected that PACs are only the tip of the supraventricular tachyarrhythmia iceberg. In such cases, extended ECG monitoring such as Holter assessment or in-hospital telemetry is recommended to confirm that clinical signs coincide with a sustained arrhythmia, and to identify the causative arrhythmia at the time of clinical episodes.

Atrial Tachycardia (AT)

Supraventricular tachycardias are broadly defined as any tachycardia originating from the SA node, atrial myocardium, AV node/junction, or great vessels connecting to the atria (venae cavae, pulmonary veins, coronary vein) (Blömstrom-Lundqvist et al. 2003). Specifically included are sinus tachycardia, sinus node reentrant tachycardia, automatic atrial tachycardia, intra-atrial reentrant tachycardia, atrial flutter, atrial fibrillation, AV nodal reentrant tachycardia (AVNRT), orthodromic atrioventricular reciprocating tachycardia (OAVRT), and automatic junctional tachycardia (Wright 2009). Of these, sinus tachycardia has been discussed (above). Atrial flutter, atrial fibrillation, AVNRT, and OAVRT (the latter two being forms of preexcitation) are presented separately (see below). The remaining arrhythmias are generally grouped in the broad category of "atrial tachycardia." This simplification would be excessive for patients whose tachycardia might be cured with radiofrequency catheter ablation, but is adequate for practical purposes in feline cardiology given the current practical limitations to performing therapeutic catheter ablations in cats due to their small body size. An atrial tachycardia may be defined as a series of 3 or more consecutive PACs (Figure 18.8), some or all of which may successfully cross the AV node. When atrial activity is excessively rapid, the filtering function of the normal AV node may limit the number of P' waves admitted into the ventricles, a protective mechanism called *physiologic AV block*. For example, a cat with an ectopic atrial focus that fires at a rate of 420 beats/minute would have a ventricular rate (heart rate) of 420 beats/minute if each atrial impulse crossed the AV node normally into the ventricles ("1:1 conduction"). Such a rapid heart rate could be expected to cause a substantial decrease in cardiac output due to severely limited diastolic filling time (see Figure 18.1). Physiologic 2:1 or 3:1 second-degree AV block in this patient would commonly occur, producing heart rates much closer to the normal range: 210 or 140 beats/minute, respectively, and such physiologic block has a beneficial effect in AT that explains why some patients may tolerate AT better than others.

The mechanism for AT is the same as for PACs. In cats, atrial tachycardia has been associated with hypertrophic cardiomyopathy (Boyden et al. 1984; Liu and Tilley 1980), dilated cardiomyopathy (Liu and Tilley 1980), and hyperthyroidism (Peterson et al. 1982; Kovacevic et al. 2004), and is always considered abnor-

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mal because it is not reported in healthy cats undergoing Holter monitoring (Hanås 2009; Ware 1999). Since AT may occur in short bursts lasting 1–60 seconds or may be sustained (uninterrupted for >60 seconds), it may cause clinically relevant decreases in cardiac output and even overt clinical signs. It is uncommon for AT to cause syncope in the cat or human (Delacrétaz 2006) but AT has been diagnosed in a syncopal cat using an implantable cardiac event monitor (Ferasin 2009). Underdiagnosis of AT in cats is likely, since the most common clinical signs in humans with AT are sensations without overt manifestations: light-headedness, palpitations, and chest pain (Delacrétaz 2006).

The diagnostic test of choice is ECG, which should be a 10-lead baseline tracing initially since feline P waves and QRS complexes are often very small and difficult to interpret on single-lead tracings (see Figure 18.8). The sporadic occurrence of AT means that establishing the diagnosis may require extended ECG monitoring, such as in-hospital telemetry, or ambulatory ECG (Holter or event monitoring). The differential diagnosis for AT includes sinus tachycardia (for which a distinct P wave of the same morphology as sinus P waves is present for every QRS complex at a fixed PR interval) and ventricular tachycardia (for which the QRS complexes should be different in morphology from sinus QRS complexes). Clinically, bradycardias may also cause syncope and are a differential diagnosis for AT in patients with undiagnosed syncope. Probably the most common ECG differential diagnosis for AT is motion artifact, notably purring (see Figure 18.10, later in this chapter) (Ware 1992). Other forms of motion artifact (shivering/tremor) and electrical interference also may mimic AT (see Figure 18.11, later in this chapter).

Confirmation of AT may be aided with a vagal maneuver (Wright 2009). The purpose of a vagal maneuver is to increase parasympathetic tone predominantly to the SA and AV nodes, since they receive a large proportion of the autonomic inputs to the heart. Slowing of the sinus rate, and/or transient physiologic AV block, are the most common and desired effects. Ventricular rhythms such as ventricular tachycardia are less easily influenced by vagal maneuvers, if at all.

Vagal maneuvers can be performed safely and consistently. One form of vagal maneuver, carotid sinus massage, involves the simple application of gentle, sustained digital pressure by the clinician to the external region of the neck overlying one or both of a cat's carotid sinuses, located just caudal to the dorsal aspect of the larynx (sometimes to the point of eliciting a gag reflex), for 5 to 10 seconds, while the ECG tracing is being recorded. Such a maneuver should be tolerated by the patient, and signs of discomfort, resentment, or a marked change in heart rate warrant immediate termination of the maneuver. Because cats very rarely suffer from carotid artery atherosclerosis, concern for thromboembolic consequences of carotid sinus massage as expressed in human cardiology is unlikely to be relevant to small animal practice. The other form of vagal maneuver used routinely in feline medicine is ocular pressure. It consists of applying firm but controlled gentle digital pressure to both globes through closed eyelids. The distance of retropulsion of the globes depends on the shape of the orbit, typically 5–15 mm in a cat (lower value for brachycephalic breeds with shallow orbits). Subjectively, the amount of pressure applied is the best guide: it should not exceed the digital pressure one would place on a ripe grape without rupturing it. Likewise, this should be acceptable to the patient, and signs that it is not warrant immediate termination. Ocular pressure is contraindicated in patients with ocular problems. There appears to be interindividual variation in response to vagal maneuvers, with some individuals demonstrating a stronger effect during carotid sinus massage and others during ocular pressure. Overall, the effect of a vagal maneuver should be manifested at some point during the application of pressure (typically within 5–15 seconds of initiation of the maneuver). It must be remembered that vagal maneuvers increase parasympathetic tone but are not a guarantee of parasympathetic override; that is, an anxious, distraught, or otherwise strongly sympathetically stimulated cat may not respond to a vagal maneuver simply because of the sympathetic stimulus, not because the arrhythmia is independent of the SA and AV nodes. Therefore, the value of vagal maneuvers lies mainly in the diagnostic help provided by slowing a very rapid heart rate to make the rhythm decipherable on ECG.

Treatment of AT requires correction of the underlying problem when possible (e.g., hyperthyroidism) and administration of medications that reduce the ventricular rate if it is excessive. Although formal guidelines do not exist for the cat, ATs that produce a sustained heart (ventricular) rate of >260 beats/minute for several consecutive minutes or longer, that are shown to be associated with overt signs of syncope or near-syncope via ECG recordings during the clinical signs, or both, should be treated with antiarrhythmic medications. Beta-blocking drugs (e.g., atenolol 1–1.5 mg/kg PO q 12h, or sotalol 2 mg/kg PO q 12h) are the first line of treatment except when AT is associated with hypovolemia/dehydration, anemia, congestive heart failure, or other condition in which primary reduction of the heart rate might be detrimental. A cat that is unstable (unconscious and/or recumbent with a weak or absent pulse) during AT should be approached as follows: 1) confirm AT, since sinus tachycardia occurs much more commonly and

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suppression of sinus tachycardia could cause hemodynamic collapse; 2) with AT confirmed, determine whether AT alone appears responsible for the unstable state, which mainly depends on the heart rate (is it >260 beats/minute?). If so, identify and correct systemic abnormalities that increase sympathetic tone (hypovolemia, anemia, hypoxemia, etc.); 3) in an unstable cat with confirmed AT at a rate >260/minute and in whom extracardiac disorders are controlled or absent, intravenous diltiazem (0.125 mg/kg IV infusion over 1 minute), propranolol (0.1 mg total bolus/cat, once), or esmolol 25–200 mcg/kg/min intravenous infusion (begin low and gradually increase to achieve desired effect) may be administered with continuous ECG monitoring. The time to effect for any of these drugs is typically <2 minutes, and a decrease of 5–20% in heart rate is considered a satisfactory response, together with either no change, or an improvement, in the cat's demeanor, pulse strength, and other hemodynamic parameters. If no effect is seen, the dose can be increased (esmolol) or repeated twice in 10 minutes (diltiazem, propranolol). If this approach remains ineffective, the diagnosis should be questioned (repeat 10-lead ECG, including with a vagal maneuver) and logistical errors should be sought and corrected (is the IV catheter patent?) before additional doses are considered. A cat with AT that is stable (conscious, breathing comfortably, fair or good pulse strength) at the time of evaluation may be treated with atenolol 6.25 mg PO q 12h; uptitration to 12.5 mg PO q 12h is a robust increase that may be considered after several days if AT persists. This higher dosage has been used by some cardiologists but may be excessive (causing inappetence, lethargy, and weakness) in some cats, particularly if there is concurrent structural cardiac disease or other illness. Dilated cardiomyopathy is a relative contraindication, especially to the higher dosages. Alternatives to atenolol include diltiazem hydrochloride (regular formulation) 7.5 mg PO q 8h, or sotalol 2 mg/kg PO q 12h. Sustained-release diltiazem (Cardizem-CD, Dilacor-XL) is not recommended in cats due to unpredictable bioavailability and toxicosis (Johnson et al. 1996; Wall et al. 2005).

With either acute (IV) or chronic (PO) treatment, the therapeutic goal is to reduce or eliminate extremes of tachycardia that would reduce cardiac output—i.e., to provide medication at a level that prevents HR >260 and stops AT-associated syncope or other arrhythmia-associated clinical signs if present. Pharmacologically forcing the heart rate beyond these parameters and into the range of normal sinus rhythm (110–180 beats/minute) would likely require excessive dosages of medication and is not recommended.

Follow-up is warranted after 7–14 days of antiarrhythmic therapy, or sooner if clinical signs worsen or new clinical signs appear. Such follow-up should consist of physical exam, 10-lead resting ECG, and repetition of laboratory tests as indicated to evaluate ongoing abnormalities if they were noted.

Atrial tachycardia does not clearly confer a worse prognosis, and the prognosis for cats with AT is not distinguishable from the prognosis of its underlying disorders (cardiomyopathy, hyperthyroidism, others) when AT is absent.

Atrial Fibrillation

Atrial fibrillation (AF) is said to represent a state of electrical chaos in the atria. The atria depolarize from multiple foci at a rate of several hundred impulses per minute, many or most of which never cross the AV node to the ventricles. The result is a heart rate that varies from normal to elevated (e.g., 260/minute) and an irregular rhythm due to the patternless selection of impulses that are admitted through the AV node to the ventricles (Figure 18.9).



Figure 18.9. Atrial fibrillation in a cat. There are no identifiable P waves (nor were they present in any other lead); the QRS complexes are monomorphic, slender, and upright in this lead II tracing, and the rhythm is irregularly irregular. The left panel (50 mm/sec) demonstrates that faster paper speeds show the variable R-R interval more clearly than slow paper speeds (25 mm/sec; middle panel). The negative wave preceding each QRS complex is necessarily a T wave from the previous beat (rather than a P wave) because every QRS must be followed by a T wave; ventricular repolarization is required for subsequent depolarization. This physiologic fact helps to distinguish whether a deflection is a P wave, a T wave, or both superimposed. The heart rate is 320 beats/min. 1 cm = 1 mV.

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Historically perceived as a series of spontaneous electrical discharges in either or both atria or a single large reentrant circuit, AF is now understood to be a series of microreentrant electrical circuits that propagate in the atria in a spiral fashion, with important additional paramechanisms including cranial and caudal vena caval, pulmonary venous, and left atrial contributions that continue to be investigated (Nattel 2002).

The loss of atrial contribution to ventricular filling, and especially the high ventricular rate that often results from AF, can cause decompensation (congestive heart failure and/or syncope) in previously compensated patients with preexisting heart disease: AF can push a patient "over the edge" from asymptomatic to symptomatic (Nattel 2002). This phenomenon is well-recognized in humans and dogs, but appears less common in cats, perhaps because of the comparative rarity of AF in this species, or because ventricular rates are not dramatically higher in cats with AF versus cats in normal sinus rhythm/sinus tachycardia.

Equally or more important than the loss of effective atrial contraction to ventricular filling is the rapid ventricular response rate (heart rate) that commonly occurs in AF. A patient's AV node represents the filter that determines whether the heart rate in a cat with atrial fibrillation will be less than 260 beats/minute (resulting in fairly normal cardiac output) or greater than 260 beats/minute (where the reduced time for diastolic filling between beats outweighs the benefit of more beats per minute and cardiac output falls; see Figure 18.1). Thus, treatment for atrial fibrillation in cats is generally reserved for those cats with a ventricular response rate (heart rate) >260 beats/minute, and such treatment consists of administering medications that delay AV nodal conduction.

The signalment of cats with AF reflects the underlying cause: most cats with AF are male (82%) and have underlying myocardial disease (restrictive or unclassified cardiomyopathy: 38%; hypertrophic cardiomyopathy or left ventricular concentric hypertrophy of other origin: 36%; dilated cardiomyopathy: 12%, including cases from the pre-taurine era) (Côté et al. 2004; Boyden et al. 1984). Thirty-three percent of cats with arrhythmogenic right ventricular cardiomyopathy had AF in one case series (Fox et al. 2000). A wide age range through adulthood exists in feline AF patients (mean ± SD: 10.2 ± 3.7 years), and there is no known breed predisposition for AF specifically.

The owners' chief presenting complaints for cats with AF are consistent with cardiac disease (dyspnea, signs of aortic thromboembolism, lethargy) but 22% of cats with AF are found to have the arrhythmia during routine examination, indicating that AF, as an incidental finding, may be considered a marker for underlying structural heart disease in the cat.

The hallmark physical examination finding in AF is an irregularly irregular rhythm. That is, auscultation of the heart reveals that the time between heartbeats varies chaotically, and an inconsistent, patternless rhythm is heard. Given the rapid heart rate (>200 beats/minute) of many cats in the hospital environment, underdiagnosis of AF is likely because at faster heart rates, the irregularity of AF may be difficult to appreciate during auscultation. Pulse deficits, so commonly noted in AF in patients of other species, are possible but less common in cats with AF, perhaps because of the smaller diameter femoral artery and variable pulse quality in this species, and because the difference in diastolic filling time is not substantially different if the ventricular response rate in AF is similar to the rate of sinus tachycardia normally experienced by cats in the exam room. A heart murmur, gallop sound, or both, may be ausculted as a result of underlying structural heart disease (with which AF is commonly associated), but AF itself produces no auscultable abnormalities in the cat other than the irregular rhythm.

On physical exam, the differential diagnosis for AF includes premature atrial complexes and premature ventricular complexes; any of the three arrhythmias may produce an irregularly irregular rhythm and an ECG is required to make the definitive diagnosis. Electrocardiographically, the most important differential diagnosis for AF is motion artifact. Purring (Figure 18.10) and shivering (Figure 18.11) are two common such artifacts, and the rapid, tiny baseline undulations they produce can easily be mistaken for AF if care is not given to noting whether the rhythm is irregular.

The confirmatory test for AF is the ECG. Any cat suspected or confirmed of having AF also should undergo tests to identify underlying heart structure and extracardiac organ function in anticipation of medical treatment (see the section "Evaluating the Arrhythmic Feline Patient," above). The ECG features of AF are absence of P waves in all ECG leads, fine baseline undulations representing atrial fibrillatory activity (often too small to be clearly appreciated in the cat), and an irregularly irregular rhythm, such that R-R intervals vary from one beat to the next (see Figure 18.9). In cats with AF, the mean ventricular response rate is 223 ± 36 beats/minute (Côté et al. 2004), which is increased but still overlaps with the expected heart rate range of healthy cats in a similar setting (Abbott 2005; Hamlin 1989). Of note, the R-R intervals of AF in any species may be trivially variable when the heart rate is high—the QRS complexes are sufficiently close together when the heart rate is fast that variation in R-R interval is difficult to

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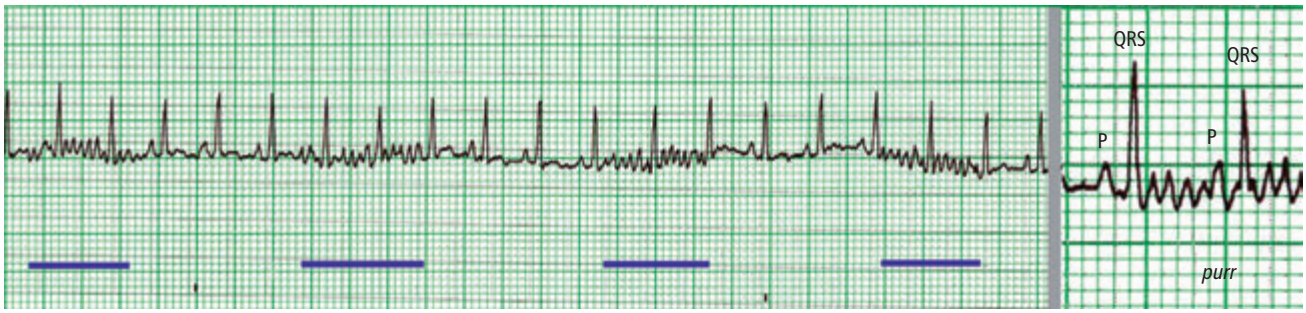


Figure 18.10. Artifact mimicking atrial fibrillation/flutter in a cat: ECG manifestation of purring. Intermittent artifact, rather than supraventricular tachycardia, is diagnosed (during the segments highlighted by the blue bars) because there is no influence on the heart rhythm and in several instances a P wave can be seen at the expected P-R interval during the artifact. A true supraventricular tachycardia producing so many fine deflections due to atrial depolarization instead of these motion artifacts would inevitably conduct on an intermittent, variable basis through the AV node, producing an irregularly irregular R-R interval. The diagnosis is purring artifact in normal sinus rhythm in this adult male cat 24 hours after relief of urethral obstruction. 25 mm/sec, 0.8 cm/mV.

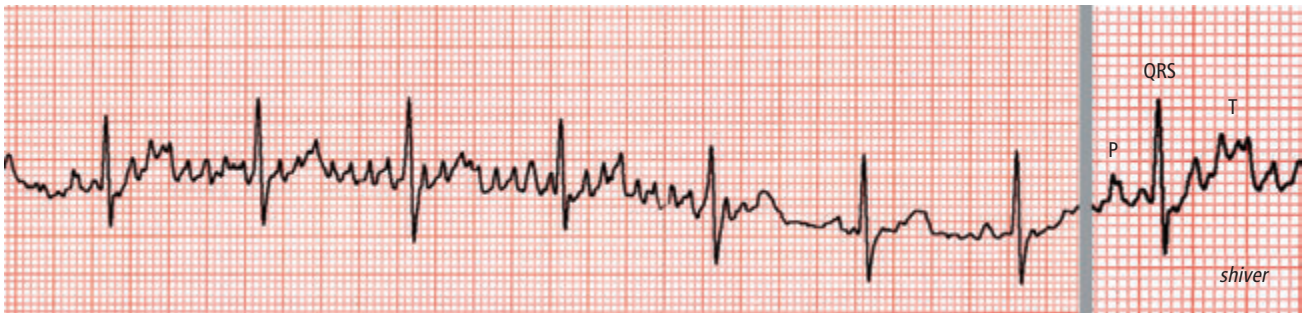


Figure 18.11. Artifact mimicking atrial fibrillation/flutter in a cat: ECG manifestation of shivering. As for Figure 18.9, a supraventricular arrhythmia is essentially ruled out by the perfectly regular R-R intervals. 50 mm/sec, 2 cm = 1 mV.

appreciate. Therefore, a cat suspected of having AF but where uncertainty persists in the ECG diagnosis should have 1) a multiple-lead (10-lead) ECG, to identify P waves and thus rule out AF if the P waves are only visible in some leads and not in lead II, for example; and 2) a vagal maneuver (see above) if the rate is >260 beats/minute and it is not possible to determine whether irregularity exists in the R-R intervals because the beats occur so close together. The paper speed of the ECG should be 50 mm/sec, and accelerating it further rarely helps clarify the diagnosis; the ECG is effectively "stretched" this way but the amount of time between heartbeats is unchanged. Performing a 10-lead ECG and using vagal maneuvers help to identify P waves and a regular rhythm, respectively, and both of these findings are useful for confirming artifact, rather than AF, since organized atrial activity and a regular heart rhythm rule out AF.

The goal of treatment of cats with AF is to limit excessively rapid heart rates, but not usually to convert the AF back to sinus rhythm. Conversion to sinus rhythm is impractical and unlikely to last when substantial atrial enlargement exists (Bright et al. 2005), as it almost always does in cats with AF. Likewise, treatment to suppress AF impulse generation in the atria is not currently available; use of existing medications to accomplish this goal would invariably cause toxicosis before improvement in the rhythm. Therefore, effective treatment in cats with AF, as in the majority of dogs and humans, revolves around rate control: selective modification of the AV node such that the number of impulses transmitted to the ventricles each minute resembles the normal heart rate. A cat with AF whose heart rate (ventricular response rate) is similar to the expected heart rate of a normal cat (e.g., <220 beats/minute in the exam room) does not require treatment for the AF. An "innocent bystander" advantage is sometimes obtained when the underlying heart disease requires treatment and AF is also present; the drug used for treating the structural heart disease (e.g., a beta blocker or calcium channel blocker for HCM, or digoxin for DCM) may have rate-limiting effects on conduction through the AV node, which provides a second benefit by reducing an excessive heart rate. Drugs typically used for treating AF in cats include atenolol (6.25 mg PO q 12h initially; may increase up to 12.5 mg PO q 12h with careful monitoring at higher doses to avoid triggering lethargy, inap-

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petence, recurrence of congestive heart failure, or other signs of beta-blocker excess), diltiazem HCl (7.5 mg PO q8h; avoid sustained-release diltiazem [Dilacor-XL, Cardizem-CD], where pharmacokinetics are unpredictable in the cat (Johnson et al. 1996; Wall et al. 2005) and gastrointestinal/hepatobiliary side effects occur in up to 20% of cats), or digoxin (0.03125 [1/4 of a 0.125 mg tablet] PO q 48 h; never in hypertrophic cardiomyopathy; always with careful monitoring for inappetence, lethargy, vomiting, or diarrhea as signs of digoxin intolerance/toxicosis). The therapeutic target is typically to achieve an exam room heart rate of 240 beats/minute or less. Since this is often already the case for many cats with AF before treatment, the presence of AF in the cat does not automatically require treatment. Without substantiation, cardiologists and clinicians may be more inclined to prescribe treatment for asymptomatic structural heart disease (e.g., HCM) if AF is also present, even at a nonelevated rate, with the intent of using a beta blocker to help both with the cardiomyopathic process and with heart rate limitation related to AF. Holter monitoring, commonly used in dogs and humans with AF to better appreciate heart rate through a 24-hour period (and away from the hospital) is currently little used in feline cardiology for this purpose; ethical concerns about the burden of the monitors' weight being carried by cats with heart disease, monitor availability, and additional expense, are important limitations. The result is likely an underappreciation of the need (or lack thereof) for treatment of AF. Atrial fibrillation is associated with thromboembolic disease in human patients, a result of the loss of atrial contraction and resultant sluggish flow of blood in fibrillating atria, but such an association has not been documented in cats. Nevertheless, since AF in cats is almost invariably associated with atrial enlargement, anticoagulation is warranted on the basis of atrial enlargement alone (see Chapter 20).

Complications of AF and its treatment may include medication intolerance (see description, above) and progression of underlying heart disease leading to congestive heart failure, thromboembolism, and/or sudden cardiac death. The occurrence of such complications is highly variable between cats, and the prognosis for AF in the cat covers a wide range. The median survival in a retrospective study of 24 cats with AF was 165 days, with more than half living >6 months (6–12 months: 21%; 1 year or more: 33%) (Côté et al. 2004). Overall, the survival of cats with AF is longer than that of cats with aortic thromboembolism, shorter than that of cats with asymptomatic/compensated heart disease, and similar to that of cats with congestive heart failure (Atkins et al. 2001).

Premature Ventricular Complexes

Perhaps the most widely recognized, and misinterpreted, ECG abnormality is the premature ventricular complex (PVC; also called *ventricular premature contraction*, *depolarization*, or *extrasystole* [VPC/VPD/VE]). The premature, abnormal-appearing (often wide, bizarre in morphology) QRS complex and T wave of a PVC are the electrocardiographic expression of spontaneous electrical activity originating in the ventricles and serving no useful purpose (Figures 18.12, 18.13).

The mechanisms by which premature ventricular complexes occur are likely the same, at the ventricular level, as those at the atrial level that cause PACs (above): abnormal automaticity, microreentry, and delayed

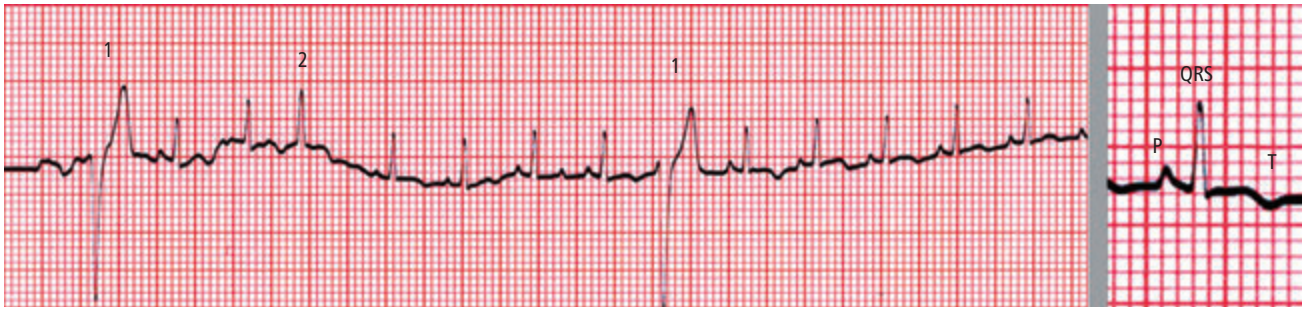


Figure 18.12. Three premature ventricular complexes in a cat with hypertrophic cardiomyopathy. Two populations of PVCs are seen; the background rhythm is normal sinus. "Classic"-appearing, wide, bizarre QRS complexes (with associated bizarre T waves), numbered "1," are considered to be of left ventricular origin. A PVC that is more subtle, numbered "2," is still premature and still has a QRS complex that is different from sinus QRS complexes; thus, the criteria for a PVC are met. PVCs like "2," with a morphology that more closely resembles sinus QRS complexes, are considered to originate from the right ventricle or basal interventricular septum. The hemodynamic consequences of a PVC of this morphology (shape) are just as significant as those of the PVCs marked "1"; neither morphology carries a more or less serious prognosis than the other, and morphology alone does not dictate the prognosis, or need for antiarrhythmic treatment, in patients with PVCs. 25 mm/sec, 1 cm = 1 mV.

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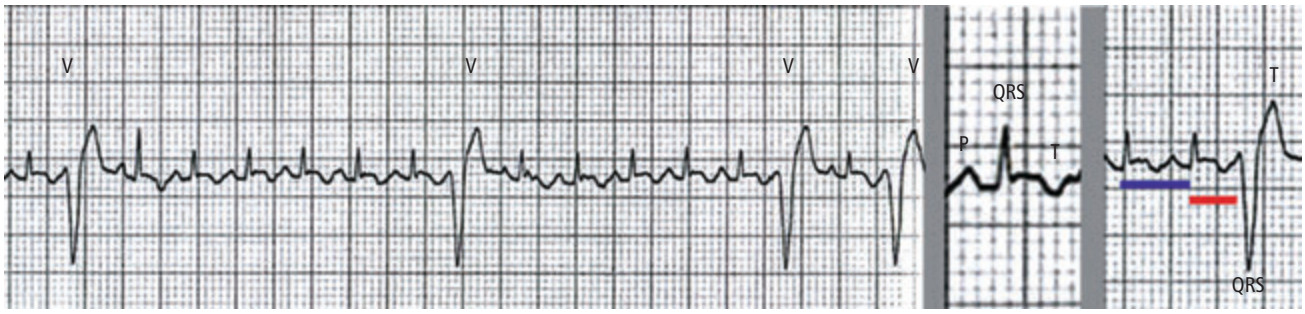


Figure 18.13. Premature ventricular complexes (V) in a cat hospitalized in the intensive care unit due to restrictive cardiomyopathy, congestive heart failure, and hypokalemia. The serum K+ concentration was 3.2 mEq/l. The two insets show a normal sinus heartbeat (inset 1) and a PVC (inset 2); note that, as in Figure 18.12, the PVCs are minimally premature (R-R interval: red bar only slightly shorter than blue bar). Thus, the hemodynamic consequences from these PVCs would be expected to be minimal, and indeed they were an incidental finding. The second inset also shows that like other heartbeats, PVCs consist of a QRS and a T wave. Subjectively, via in-ICU telemetric monitoring, the PVCs decreased substantially in number with correction of hypokalemia and congestive heart failure alone. This sequence suggests that the PVCs may have been caused by a combination of cardiomyopathy, hypokalemia, and pulmonary edema-induced hypoxemia, and that treatment that normalized serum potassium and arterial oxygen levels helped to reduce or abolish the arrhythmia without the need for antiarrhythmic drugs. 25 mm/sec, 1 cm = 1 mV.

afterdepolarizations (Rials et al. 1995). In this manner, PVCs likely represent a catchall term for abnormal electrical activity arising through more than one electrophysiologic substrate, because some may occur via one mechanism whereas others occur through another, but the ECG manifestation remains simply a PVC. For example, PVCs caused by digoxin toxicosis are known to occur as a result of delayed afterdepolarizations, whereas monomorphic ventricular tachycardia (VT; see below) more likely involves microreentry or abnormally enhanced automaticity. In cats, experimentally induced left ventricular concentric hypertrophy caused a higher incidence of inducible VT, decreased ventricular fibrillation threshold, greater dispersion of refractoriness, and prolongation of epicardial monophasic action potential duration—all markers or components of ventricular electrical instability and propensity for ventricular arrhythmia (Rials et al. 1995). These same cats, when hypertrophy was allowed to regress, showed normalization of ventricular electrophysiologic characteristics and had the same low vulnerability to inducible ventricular arrhythmia as sham controls. Thus, concentric hypertrophy alone may be responsible for ventricular arrhythmogenesis, an important observation given the high prevalence of HCM in the cat (Paige et al. 2009). At present, however, the therapeutic implications of these different mechanisms are limited. Current treatment options for ventricular arrhythmias (PVCs, VT) in cats have not been shown to be specific to a particular mechanism in this species. Future investigations are anticipated to clarify whether specific treatments targeted at specific mechanisms of arrhythmogenesis will result in superior rhythm control.

The most meaningful impact of PVCs on the patient relates to diastolic filling. When the ventricles depolarize prematurely, by definition they have not completed their filling phase (diastole) and are driven to eject a suboptimal volume of blood into the circulation. The harm of a PVC therefore lies not in its morphology on the ECG, for example, but rather on the specific impact of the arrhythmia on hemodynamics: did the beat occur so prematurely as to substantially reduce stroke volume, and if so, is this abnormal pattern of cardiac activity occurring often enough to decrease cardiac output? With single PVCs, or PVCs that occur with little prematurity (i.e., where the R-R interval between PVC and preceding beat, the *coupling interval*, is not much shorter than the sinus R-R interval) the hemodynamic impact is minimal: the ventricles have filled to a near-normal volume during diastole, allowing near-normal stroke volume and cardiac output. By contrast, a more substantially negative hemodynamic impact can be expected from PVCs that occur in rapid sequence, especially when persisting at a high rate, because diastolic filling is further compromised the sooner the ventricles are forced to beat. The occurrence of 4 or more PVCs consecutively is defined as *ventricular tachycardia* (VT) and is discussed further below.

With a PVC, the spontaneous depolarization of the ventricles preempts the depolarization of the ventricles that would have been triggered by the normal sequence of SA node and atrial depolarization. However, a PVC, while it depolarizes the ventricles, does not conduct retrograde to the atria. In other words, the endocardial cushion and unidirectional nature of the His bundle isolate a PVC (or any ventricular electrical activity) to

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the ventricles. Thus, the SA node continues to depolarize with perfect regularity despite the occurrence of a PVC. The result is that if a PVC occurs with very little prematurity, the pause that follows the PVC will be only slightly longer than the normal interval between heartbeats. Conversely, if a PVC occurs very prematurely, a comparatively long pause will be present until the next sinus beat. The length of the pause following a PVC is directly related to the degree of prematurity of the PVC because the SA node continues to depolarize unfazed during the PVC. Thus, while the normal beat may be blocked in the AV node during the PVC because the ventricles are in the process of depolarizing from the PVC, the rhythm resumes with perfect regularity thereafter. The P-P interval from the heartbeat preceding a PVC to the heartbeat following a PVC, should be exactly 2 normal P-P intervals. This phenomenon describes a *compensatory pause*, wherein the pause that follows the PVC in some sense "compensates" for the prematurity of the beat and allows the rhythm to return to its previous pattern. By contrast, PACs, which originate in the atria and depolarize the SA node, often produce a *noncompensatory pause*, because the firing pattern of the SA node is reset.

PVCs occur in 78–90% of healthy cats, who experience 0–150 PVCs daily (typically <60/day) (Hanås et al. 2009; Ware 1999). The PVCs are significantly greater in number in healthy older adult cats than healthy young adult cats (Hanås et al. 2009; Ware 1999): in one study, no cat age 1–6 years old experienced more than 9 PVCs/24 h (2 cats: none) compared to all cats age 8–14 years old experiencing at least 1 PVC daily and 40% of cats having >35 PVCs/24 h (Ware 1999).

In dogs and humans, PVCs are associated with virtually any disorder, either cardiac or extracardiac. While this can be true in cats, significantly more cats with PVCs have concurrent structural heart abnormalities compared to dogs. Arrhythmogenic right ventricular cardiomyopathy is increasingly recognized in cats, and its hallmark is ventricular arrhythmia (Fox et al. 2000; Harvey et al. 2005). In another retrospective study, the vast majority (102/106, 96%) of cats with PVCs or ventricular tachycardia (VT) on baseline ECG had an echocardiographic diagnosis of structural heart disease, consisting of left ventricular concentric hypertrophy (n = 66), restrictive or unclassified cardiomyopathy (n = 17), or dilated cardiomyopathy (n = 6). By contrast, a significantly smaller proportion of dogs (95/138; 69%) with PVCs or VT seen at the same time at the same institution had an abnormal echocardiogram, indicating a significantly higher prevalence of structural heart disease in cats with ventricular arrhythmias compared to dogs ($p < 0.001$) (Côté and Jaeger 2008). These results may not reflect the feline population at large, however. For example, when a series of 103 healthy, privately owned cats underwent cardiovascular evaluations, 10 (10%) had arrhythmias on ECG: 7 of the cats did not have evidence of cardiomyopathy on echocardiographic evaluation (4 PVCs, 2 preexcitation, 1 VT), whereas 3 had evidence of cardiomyopathy: either HCM (PVCs in both cats) or arrhythmogenic right ventricular cardiomyopathy (1 cat; VT) (Paige et al. 2009). A higher prevalence here than in previous reports could be explained by the inclusion of ECG abnormalities identified on routine ECG, echocardiography, or both; typically, an echocardiogram affords a period of monitoring the cardiac rhythm that is several times longer than the 30 seconds to 3 minutes of a routine ECG, increasing the likelihood of identifying arrhythmias that occur only intermittently. In practical terms, therefore, the incidental finding of PVCs may be indicative of underlying structural heart disease in some but not all cats, and diagnostic evaluation as described in the initial part of this chapter is appropriate in all cases.

Systemic alterations such as hypokalemia, hypoxemia (classically from pulmonary edema, pleural effusion, or pulmonary thromboembolism), anemia, hyperthyroidism (Peterson et al. 1982; Moïse et al. 1986), or excess circulating catecholamine concentrations (fear, pain, anxiety, anger) may increase the propensity to forming PVCs, and even when an irreversible structural cardiac lesion is present, these correctable factors may be partly or mostly responsible for the cardiac arrhythmia. For example, epinephrine is a documented trigger for ventricular arrhythmias in cats (Hikasa et al. 1996). These contributing or complicating factors represent therapeutic opportunities that should be identified and addressed when a diagnosis of PVCs is made in cats.

The signalment of clinical feline patients with PVCs reflects the signalment of clinical feline patients with the disorder underlying the arrhythmia. For example, hypertrophic cardiomyopathy (HCM) occurs disproportionately more often in male cats, and a higher incidence of PVCs can be expected in male cats for this reason. An unpublished subsample of 23 consecutive cases drawn from a retrospective study (Côté and Jaeger 2008) reveals that cats with PVCs or VT had a 2 : 1 gender distribution (15 males:8 females, all 23 neutered), a mean age of 11.05 ± 4.2 years (median: 10 years), and a breed distribution of 18 domestic shorthairs and 5 domestic longhairs. Outside the patient population, no gender or breed predilection has been noted in healthy cats with PVCs, although they do have more PVCs when they are older, as described above (Hanås et al. 2009; Ware 1999). Overall, information regarding age, gender, and breed appears to be of minimal use in approaching the feline patient that has PVCs, and the usefulness of

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signalment information rather is confined to managing the rest of the case.

The history and physical examination confirm that premature ventricular complexes by definition create a premature heartbeat, which is audible as such on cardiac auscultation. The arrhythmia also may be palpable on the chest surface (*apex beat*). The exact sound of the premature heartbeat is often softer, and only 1 heart sound for the PVC may be heard, rather than the normal 2. The rhythm may be *regularly irregular*, if the premature beats are occurring in a repetitive sequence (e.g., every 4th heartbeat is a PVC), or *irregularly irregular*, if the PVCs occur with no discernable pattern of repetition, as they often do when more than one focus in the ventricles is generating PVCs (*polymorphic* or *multiform* PVCs are seen on the ECG, meaning PVCs of different shapes). PVCs may consist of single premature beats, pairs, or various combinations of premature and normal beats or other arrhythmias such as PACs. An alternating sequence of 1 PVC following 1 sinus beat, repetitively, is referred to as *ventricular bigeminy*, and an alternating sequence of 1 PVC following 2 sinus beats or 2 PVCs following 1 sinus beat is known as *ventricular trigeminy*. When this type of regularity is noted in an arrhythmia on physical examination initially, correlation to respiration should be sought (as would be expected with respiratory sinus arrhythmia), but if no such correlation is clear, or if the heart rate is elevated regardless (since respiratory sinus arrhythmia is vagally mediated and unlikely to occur at a rate >160 beats/minute in the cat), then an ECG is indicated to identify the exact nature of the rhythm. If a PVC occurs with a near-normal coupling interval (i.e., is barely premature), the PVC may be missed on physical examination because the heart rhythm may seem to be regular and pulse strength, maintained by adequate ventricular diastolic filling, is essentially normal. The more prematurely a PVC occurs, the more likely it will be perceived as such, especially when diastolic filling is cut short so that the stroke volume ejected during the PVC fails to generate a palpable pulse. The lack of a single pulse when a premature heartbeat is audible on auscultation is referred to as a *pulse deficit*, a term that should not be confused with a hypotension-induced pulse quality that is consistently poor or simply not palpable. These pulse qualities are termed *weak* or *absent* pulses, respectively.

In cats, PVCs often occur so prematurely, and the normal rhythm (sinus tachycardia) resumes so quickly, that the most common auscultatory finding is not of the premature beat itself but of a missing or "dropped" beat. That is, the PVC occurs but is not heard because heart sounds that were generated by the PVC blend in with the previous beat's heart sounds or simply are too soft to be audible, and only the pause that follows the PVC is heard. Thus, an important physical exam differential diagnosis for PVCs is second-degree AV block, and any instance of a "dropped beat" during a cat's physical examination warrants an ECG to differentiate between the two.

Other historical and physical examination findings in cats with PVCs are nonspecific and generally no different from the findings of patients with the same underlying disorder but no PVCs. That is, PVCs alone do not produce telltale historical or physical examination abnormalities outside an abnormal auscultation and pulse, unless they occur in sustained fashion (see the section "Ventricular Tachycardia," below).

The confirmatory diagnostic test of choice in a patient suspected of having PVCs is an ECG. There are three electrocardiographic features of PVCs: 1) premature occurrence, 2) QRS complex of different morphology than sinus derived beats, and 3) T wave of different morphology (see Figures 18.12, 18.13). Premature occurrence refers to a shorter-than-normal coupling interval: the PVC occurs sooner than a normal sinus QRS would have occurred for that beat. For a PVC to occur, spontaneous firing within the ventricles takes control of ventricular depolarization for that beat, meaning the normal depolarization from the SA node courses normally through the atria (and a P wave is generated) but the impulse is denied access to the ventricles because they are either still in the midst of the PVC's depolarization, or refractory while repolarizing post-PVC. Thus, a P wave exists for a PVC but is not *associated* with the PVC: the normal PR interval is not seen between the PVC and a preceding P wave. Rather, P waves are often hidden by the PVC (and not seen), or they can be identified adjacent to the PVC but separated from it by a shorter distance than the normal PR interval. A QRS complex of different morphology is expected in a PVC because the pattern of ventricular depolarization spreads in a different orientation if it originates from a focus within the ventricles than if it spreads from the His bundle during a normal sinus beat. The electrocardiograph "perceives" the overall pattern of electrical activation of the ventricles as being different from normal and plots a QRS of different shape accordingly. The QRS complex of a PVC is always wider than a normal sinus QRS complex because myocyte-to-myocyte electrical transmission is more time-consuming than the normal rapid conduction through the ventricles' His-Purkinje system. Finally, since the wave of ventricular repolarization follows exactly along the same course as the wave of depolarization that preceded it, the T wave of a PVC is of a different morphology compared to a sinus T wave. The degree of abnormality of these morphologies varies

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according to site of origin: a PVC that begins in the left ventricular free wall spreads toward the right, a very different pattern from normal, resulting in a very wide and different-appearing QRS complex. By contrast, a PVC that originates near the point of entry of the His bundle into the ventricles (e.g., base of the right ventricle) may spread through the ventricles in a manner not substantially different from normal depolarization, and the morphology of such a PVC is only mildly different from the normal QRS complex (see Figure 18.12).

Several electrocardiographic impostors exist that mimic PVCs (Figures 18.14–18.16; see also Figures 18.20a, 18.22, 18.24–18.27, later in this chapter). Therefore it is essential to accurately identify PVCs as such, because misdiagnosis may lead to treatment that worsens rather than helps the patient, convey a grossly inaccurate prognosis, or otherwise bring harm. The differential diagnosis for wide, bizarre QRS complexes on an ECG consists of

- Premature ventricular complex/ventricular tachycardia/AV dissociation with accelerated junctional rhythm
- Ventricular escape rhythm (Figure 18.20)
- Sinus rhythm with right or left bundle branch block or fascicular block (Figure 18.22)
- Right axis deviation due to right ventricular enlargement or displacement of the heart (Figure 18.16)
- Accelerated idioventricular rhythm (Figure 18.15)
- Motion artifact (Figure 18.14)
- Hyperkalemia (Figures 18.24, 18.25)
- Macroreentrant tachycardia (preexcitation) (Figure 18.27)

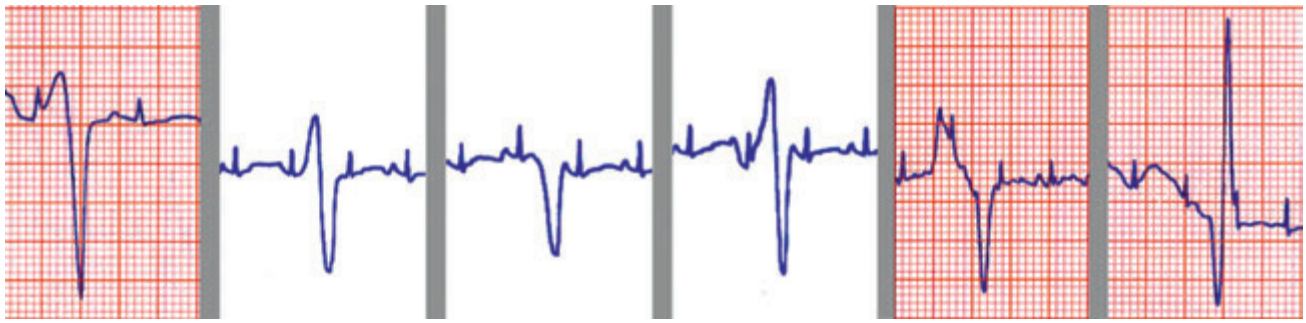


Figure 18.14. Motion artifact mimicking PVCs in 3 cats (cat 1: first panel; cat 2: second through fourth panels; cat 3: fifth and sixth panels). In each case, the ECG deflection occupies a substantial amount of (or more than) an R-R interval and yet does not alter the rhythm—the background R-R interval remains constant despite the wide, bizarre deflection (note 2 heartbeats in the first panel and 4 in each of the others). The unaltered rhythm is in contrast to PVCs, which typically are associated with a pause after they occur (postextrasystolic, compensatory pause). In the uncommon instance of interpolated PVCs, where no pause is seen, the PVC does not encompass the entire duration of the R-R interval.



Figure 18.15. Accelerated idioventricular rhythm in a cat. The first, seventh, eighth, and ninth beats are normal sinus; the others are PVCs. Note that the PVCs occur prematurely (by definition) but with barely any prematurity at all. The result is that the first PVC (second beat on the tracing; arrow on inset), being so minimally premature, allows the P wave to still be visible. Only the short PR interval testifies to the prematurity of the PVC (ventricles depolarized before the normal SA nodal/atrial impulse could cross the AV node and depolarize the ventricles). Also noteworthy: the P wave is engulfed within several of the PVCs, which is typical because the ventricular activity is spontaneous and occurs while atrial depolarization is also occurring. This superimposition of PVC and P wave explains the difference in QRS morphology noted in beats 4 and 5 compared to the other PVCs. Finally, the morphology of the T waves of the PVCs, which is positive, is different from the sinus T waves, which are negative; this finding is typical of the different pattern of repolarization that follows a "different" pattern of depolarization, i.e., a PVC. 25 mm/sec, 1 cm = 1 mV.

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Figure 18.16. Sinus tachycardia mimicking VT in a cat. A quick glance of this monomorphic rhythm with QRS complexes of predominantly negative morphology due to marked axis deviation, might fail to reveal that each QRS complex has a P wave preceding it at a regular PR interval. This is normal sinus rhythm, not VT.

Identifying features that distinguish these impostors from PVCs are

A ventricular escape rhythm always occurs at a slower-than-normal rate for that individual (by definition), such as during third-degree AV block; the QRS complexes are wide and bizarre in shape and occur typically at a rate of 60–120 beats/minute in the cat.

Right bundle branch block and *right axis deviation due to hypertrophy or displacement* (Figure 18.16) represent a deviation in the orientation of intraventricular conduction, with no effect on the rhythm (sequence) of the heartbeats; therefore, consistent R-R and P-R intervals are observed for all beats and the P waves and QRS complexes are of an unchanging morphology (exception: QRS complexes may be of 2 morphologies if bundle branch block is intermittent, but the PR interval remains constant).

Accelerated idioventricular rhythm (AIVR) is the term given to ventricular tachycardia that fails to meet the criterion for rate (i.e., 4 or more PVCs but occurring at a rate >100 but <240 beats/minute). The recognition of AIVR as such, and not VT, is only a matter of correctly identifying the rate, but the clinical significance is essential: the rate of AIVR is sufficiently similar to sinus rates that diastolic filling is not altered from beat to beat, and therefore antiarrhythmic drugs are not warranted to treat AIVR.

With *motion artifact*, the pseudo-PVCs often exceed the range of expected tracing with PVCs, and evidence of normal QRS complexes is superimposed on the pseudo-PVCs; nevertheless, some instances of motion artifact may be extremely deceptive, and careful analysis, ideally of several simultaneously recorded ECG leads, becomes essential for an accurate diagnosis.

Severe *hyperkalemia* may produce consistently wide QRS complexes (see below), and analysis of serum electrolytes is the quickest method for ruling out this possibility.

Finally, *macroreentrant tachycardia* caused by an accessory or bypass tract (see the section "Ventricular Preexcitation and Macroreentry ," below) occurs uncommonly in the cat; when it exists, it may be converted to normal sinus rhythm with a vagal maneuver, and during sinus rhythm a consistently short PR interval (or absent PR segment altogether) is possible.

Treatment of PVCs with antiarrhythmic drugs is generally not undertaken unless the PVCs occur consecutively and for a prolonged duration, meeting the criteria for ventricular tachycardia (VT; see below). Rather, a cat with PVCs should have a complete diagnostic evaluation (see the section "Evaluating the Arrhythmic Feline Patient," above) to identify and address the underlying cause. For example, since PVCs in cats frequently are associated with underlying cardiomyopathy, then identifying the type of cardiomyopathy and degree of structural change may lead to treatment for the cardiomyopathy that is itself also antiarrhythmic. A very common scenario is the cat with PVCs and asymptomatic hypertrophic cardiomyopathy causing PVCs. The presence of PVCs in such a patient adds support for treating with a beta blocker like atenolol, though never at the expense of the patient's tolerance and tractability: the proven arrhythmogenicity of endogenous catecholamines like epinephrine in the cat (Hikasa et al. 1996) signifies that in difficult-to-treat cats, asymptomatic PVCs may best be left untreated beyond identification and control of concurrent inciting causes such as hypokalemia or hyperthyroidism.

The prognosis for PVCs in cats is not known to be different from the prognosis of the concurrent or underlying disorder. Syncope or sudden cardiac death, not gradual deterioration, are the hallmarks of acute arrhythmic decompensation. Sudden cardiac death is a well-recognized occurrence that occurs in a small but

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devastating proportion of feline cardiomyopathy patients, either spontaneously or in association with a stressful episode such as general anesthesia. Stratification of risk of life-threatening episodes such as these is poorly understood in cats at the present time. The presence of clinical signs (dyspnea, lethargy, hiding, or other signs of congestive heart failure; syncope; pulselessness or other signs of aortic thromboembolism) and the degree of ventricular distortion (hypertrophy or other change) probably are negative general prognostic indicators with PVCs, markers that may occur more commonly in arrhythmic cats that have a somewhat worse long-term prognosis. Long-term clinical studies are needed to confirm these suspicions, and currently a markedly worse prognosis (and ensuing decision not to pursue treatment or to euthanize) for PVCs cannot be supported by degree of concurrent echocardiographic change, for example: there are likely too many other variables to pin a prognosis on these parameters alone and a great deal of overlap exists between cats that do well despite these parameters and cats that do poorly.

A likely prelude to syncope or sudden cardiac death is PVCs, and one of the greatest misconceptions in cardiology is that proactive control or elimination of ventricular arrhythmias with antiarrhythmic medications could reduce the risk of sudden death. Indeed, as in human cardiology, "rendering treatment to suppress a risk factor [asymptomatic PVCs] because of the temptation to equate causality with association between the risk factor and a putative clinical outcome has never been more misguided than with nonsustained ventricular tachycardia (Marinchak et al. 1997)." Thus, in feline heart disease, the prognosis associated with PVCs is not conclusively worse than that of normal sinus rhythm given that both can occur with cardiomyopathy, and no study has evaluated the benefit or harm associated with treating ventricular arrhythmias with antiarrhythmic drugs in asymptomatic cats. Certainly, treating incidentally discovered PVCs in asymptomatic humans has been shown conclusively to be harmful with several antiarrhythmic drugs (causing worsening arrhythmias or "proarrhythmia") (Echt et al. 1991; Cardiac Arrythmia Suppression Investigators 1992)). In cats, the prognosis of the concurrent cardiomyopathy is likely the dominant factor rather than the prognosis of the arrhythmia. Cats with PVCs but no associated signs of syncope or collapse should be treated with medications that reverse or correct triggers that exist (e.g., concurrent hyperthyroidism, hypokalemia, or other), and followed up routinely: typically within 1–2 weeks of diagnosis at first, and then as dictated by clinical signs (e.g., every 3–6 months if the arrhythmia is asymptomatic and underlying cause eliminated, or monthly, or even more often if overt clinical signs such as syncope are present). The purpose of follow-up is to update the history (has the client observed a change in clinical signs?) and physical examination; perform an ECG to identify new arrhythmias if present; and perform diagnostic tests (blood or radiographic examinations) as indicated by history of clinical signs, current medications, etc. Subsequent rechecks similarly evaluate these parameters at a minimum and include follow-up telemetry or Holter/event monitoring if done previously.

Accelerated Idioventricular Rhythm

A rhythm that consists of 4 or more PVCs occurring consecutively but where the rate is less than the defined rate for ventricular tachycardia (VT; 240 beats/minute) is called *accelerated idioventricular rhythm (AIVR)* (see Figure 18.15). Initially termed "slow ventricular tachycardia"—a contradiction in terms—AIVR occurs for the same reasons as PVCs and VT. The major difference is that the slower rate of AIVR provides more time for diastolic ventricular filling, and therefore is a more hemodynamically effective rhythm than VT. AIVR and VT likely represent different parts of one continuum, and the lower end of this continuum is approximately 120 beats/minute in the cat; ventricular rhythms lower than this rate are in fact a ventricular escape rhythm, beneficial expressions of spontaneous ventricular activity that save the heart from catastrophic bradycardia or asystole (see the discussion of third-degree AV block, below). AIVR is generally well-tolerated, and treatment is therefore directed at the underlying cause; antiarrhythmic medications are not considered unless management of the underlying cause is ineffective at abolishing the arrhythmia and the rate increases to the point that the criteria for VT are met.

Ventricular Tachycardia

As mentioned earlier, ventricular tachycardia (VT) is the occurrence of 4 or more PVCs consecutively at a rate of 240 beats/minute or greater (Figure 18.17). Accordingly, a major difference between PVCs and VT is that PVCs, since they occur as only 1 or a few at a time, have little or no negative hemodynamic impact. Organ perfusion and oxygen delivery are not affected to a clinically meaningful extent by individual PVCs. Conversely, VT may occur for any length of time and at any rate, including rapid VT (>280 beats/minute) wherein diastolic filling of the ventricles is compromised and a reduced, possibly inadequate, cardiac output occurs.

The causes, mechanisms, associated conditions, signalment, differential diagnoses, and diagnostic evaluation of patients with VT are the same as for PVCs (above)

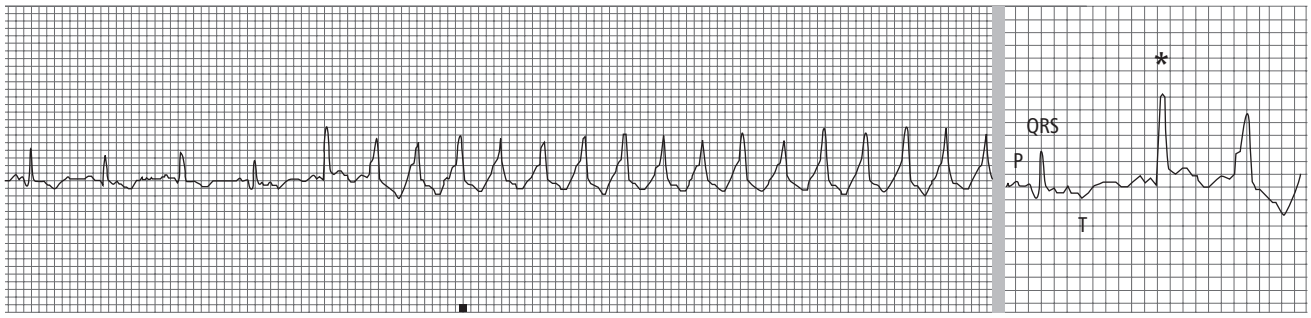


Figure 18.17. Ventricular tachycardia in a cat. A PVC (fifth beat from left; asterisk on inset; note shorter R-R interval than for the first 4, sinus beats) initiates a monomorphic VT at a rate of 300 beats/minute. Macroreentry is less likely but cannot be ruled out. 25 mm/sec, 5 mm/mV.

because both simply represent different magnitudes of the same arrhythmia.

The chief complaint of cats with VT may be nonspecific (unrelated to the arrhythmia; typically an asymptomatic heart murmur or incidental finding of cardiomegaly on radiographs, for example), may suggest arrhythmia in an asymptomatic patient (e.g., irregular heart rhythm ausculted during a routine exam), or may include overt clinical signs such as syncope as a result of tachycardia-associated reduced ventricular filling (see Figure 18.1). Regardless of which of these three contexts applies to a given case, the ECG is the diagnostic test of choice. Extended monitoring (e.g., Holter or event monitor) may be required to demonstrate VT in a patient where it is occurring intermittently, and the decision to proceed with such testing is dependent on the owner's opinion and desire, patient stability and risk to the cat related to carrying the monitor, availability of the monitoring equipment, and cost.

Antiarrhythmic options for addressing VT include lidocaine, propranolol, esmolol, and magnesium sulfate (IV) and procainamide, mexiletine, and sotalol (PO). Except in catastrophic clinical conditions (e.g., collapsed, unconscious cat with ventricular tachycardia at 340 beats/min), antiarrhythmic drugs should only be considered for a patient with VT once all of the following criteria have been met:

- The arrhythmia diagnosis is certain to be VT, not any of its impostors (see Figures 18.14–18.16, 18.20a, 18.22, 18.24–18.27); misdiagnosis can lead to disastrous mistreatment as the "VT" fails to convert to a normal rhythm and medication upon medication is administered with a growing but unjustified sense of urgency.
- An echocardiogram and thoracic radiographs have been performed; the type of myocardial disease, if any, and presence or absence of congestive heart failure, may influence the choice of antiarrhythmics and even whether to withhold treatment for the moment (e.g., if centesis or diuretic administration reestablishes normal oxygen delivery to the myocardium and VT resolves).
- Underlying triggers or potentiating factors that are reversible—classically hypokalemia, anemia, hyperthyroidism, and hypoxemia due to heart failure or severe airway disease—have all been sought with appropriate tests and corrected if present; often, correction of these abnormalities leads to resolution of the arrhythmia without antiarrhythmic drugs.

Cats with VT that are showing overt clinical signs attributable only to the arrhythmia (i.e., syncope or collapse) should be treated with antiarrhythmics, and the cat's mentation, frequency and severity of such signs, and owner perception, desires, and financial considerations should be included as determinants for whether to hospitalize for treatment and monitoring or to discharge and treat as an outpatient.

Cats with VT that is not clearly responsible for clinical signs should be evaluated with portable ECG monitoring. When this is not possible, such cats may be treated with antiarrhythmic drugs if the clinician keeps in mind that treatment may in some cases worsen the patient's status rather than improving it. Common examples of pitfalls, and ways of avoiding them under these circumstances, include

- *Judicious, not excessive, heart rate suppression.* Typically this is a concern with a beta blocker or a calcium-channel blocker, and most often with intravenous use but also possibly with oral use. A rapid change from VT at 260 beats/minute, for example, to sinus rhythm at 150 beats/minute, could be expected in some cats in response to beta-blockade if the dosage is high or the cat is unusually sensitive to the drug. Such a drastic

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lowering of heart rate may trigger congestive heart failure or even hypotension (possibly hypotensive shock) if the improvement in diastolic filling from a lower heart rate is counterbalanced by the large decrease in heart rate, resulting in a lower, not higher, cardiac output. Drugs that can suppress heart rate, like beta blockers or calcium channel blockers, should never be initiated when the patient is in fulminant congestive heart failure, unless extreme tachycardia (HR >280 beats/minute) is present and then only judiciously and with concurrent initiation of intravenous diuretics.

- *Goal of treatment.* Repeated dosing aimed at achieving a perfect ECG should be avoided. The goal is to establish a perfusing rhythm, not permanent sinus rhythm in every case. Thus, success of treatment is judged based on clinical signs (mentation, ability to ambulate), mucous membrane color, pulse strength, blood pressure, and other parameters of cardiovascular stability, not just the ECG.
- *Emphasis on tractability and ease of compliance.* For the small proportion of cats that accept oral medications undisguised, compliance is reasonable. Cats that resist medications should have them hidden in purpose-made treats (e.g., "Pill Pockets") or home-prepared foods (e.g., small quantity of low-salt soft cheese). Forceful medication administration is detrimental on at least three counts: owner's frustration; patient's sympathetic stimulation, with cardiac detriment; and likelihood of tablet fragment remaining in esophagus if not swallowed with food or water. Asymptomatic cats with ventricular arrhythmias should not be treated chronically if treatment involves such noncooperation on the patient's part.

The goal of antiarrhythmic treatment is to reach a rhythm that is hemodynamically stable, providing consistently adequate perfusion/oxygen delivery to organs of the body. Knowing whether antiarrhythmic therapy has worked is a challenge: a spontaneous daily variation in numbers of PVCs of up to 85% is observed in untreated humans and dogs with PVCs, meaning (by extrapolation from these species) that a cat may have 1000 PVCs on a Holter monitor recording one day and 150 PVCs the next day, with no influence from antiarrhythmic treatment. It can be understood from this observation that no conclusions can be drawn regarding success or failure of antiarrhythmic drugs using periodically obtained ECG strips alone. Therefore, in the cat, efficacy of antiarrhythmic treatment is gauged based on improvement in clinical signs (e.g., syncope), if any were occurring, and continuous ECG monitoring, either in-hospital or via portable monitors. Currently, sympathetic stimulation of the clinical environment makes hospitalization of cats solely for ECG monitoring a controversial issue, and Holter monitors may be unwieldy for a cat with severe cardiac disease. As Holter monitor technology leads to further miniaturization, pre- and posttreatment monitoring to assess drug efficacy is likely to increase and bring greater accuracy to antiarrhythmic diagnosis and therapy.

Antiarrhythmic drugs may be administered intravenously or orally. Intravenous antiarrhythmic drugs are indicated in patients with VT that show persistent, severe clinical signs thought possibly to be life-threatening, such as collapse (syncope with poor or only partial recovery), repeated cardiogenic generalized seizures (caused by cerebral hypoperfusion), or obtundation. The advantage of rapid serum levels and fine-tuning of drug administration with IV use must be weighed against the drawbacks of the patient's sympathetic stimulation while in intensive care; the personnel, expertise, and equipment needs required for monitoring; expense; and the lack of proven therapeutic benefit of antiarrhythmic drugs in cats. The pharmacokinetics of intramuscular administration of lidocaine, beta blockers, and other injectables are poorly understood in cats, and the variable perfusion of skeletal muscle in a patient with severe cardiovascular disease makes the intramuscular route a poor choice.

Lidocaine is used as a first-line antiarrhythmic in many species. It is a class Ib compound metabolized principally by the liver; marked first-pass elimination explains its lack of clinically effective oral bioavailability. Lidocaine's effects include sodium channel blockade-mediated slowing of conduction, decrease in dispersion of refractoriness, decrease in action potential duration (reducing triggered activity), increase in effective refractory period, decrease in excitability (more so in diseased myocardium), and reduction in the rate of phase 4 depolarization (Moïse 1999; Muir et al. 1999). It is widely reported that as a species, cats may be especially intolerant to lidocaine (Fox and Harpster 1999; Muir et al. 1999). Interestingly, most clinical references in the current literature pertaining to lidocaine as an antiarrhythmic drug in cats with heart disease stem from a series of 7 cats described qualitatively in 1977; some cats suffered adverse neurologic effects but "the majority of these reactions were cardiovascular, including conduction disturbances, bradyarrhythmias, and hypotension, with sudden death in 4 of the 7 cats (Tilley and Weitz 1977)." The cardiovascular nature of complications, particularly in an era when taurine-deficient dilated cardiomyopathy was widespread, is noteworthy, since high-dose lidocaine (10 mg/kg) produces a negative inotropic effect even in a healthy dog ventricle (Tsuboi and Chiba

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1999). Newer work supports the cardiovascular depressant effects of lidocaine in the cat: administration of lidocaine in anesthetized cats produces a significantly lower heart rate, cardiac index, and stroke index compared to administration of equipotent amounts of inhaled isoflurane (Pypendop and Ilkiw 2005; Pypendop et al. 2006). Therefore, cats with VT and concurrent systolic dysfunction (e.g., dilated cardiomyopathy, terminal hypertrophic cardiomyopathy, possibly congestive heart failure of most/all causes) should probably not be treated with lidocaine as a first choice antiarrhythmic. For cats in whom systolic dysfunction is less of a concern (i.e., the majority of feline cases), lidocaine is dosed at 0.25–1 mg/kg IV as a bolus, which can be repeated twice over a period of 15 minutes. Lethargy, mental depression, ataxia, collapse, or new-onset ECG abnormalities (bundle branch block, AV block, sinus bradycardia) warrant immediate cessation of drug administration. Seizures can respond to diazepam 0.5 mg/kg IV bolus (Muir et al. 1999). If ongoing treatment is necessary (and the drug is tolerated), an intravenous constant-rate infusion may be administered at 10–15 mcg/kg/min.

An alternative to lidocaine for intravenous treatment of VT in cats is a beta blocker. The basis is both the narrow safety margin in cats for some first-line antiarrhythmic drugs used commonly in other species (notably lidocaine) and the observation that beta-receptor stimulation via epinephrine can trigger ventricular arrhythmias even in cats with normal hearts (Hikasa et al. 1996), and likely more so in hypertrophied hearts (Rials et al. 1995). Esmolol and propranolol are routinely available. Both bind beta-1 adrenergic receptors, and therefore their antiarrhythmic effect is not specific to the ventricles but is expected to be relevant when catecholamine stimulation is contributing to, or triggering, VT. Beta blockers must be administered in small, graded doses, with repeat dosing based on noting efficacy. A typical protocol for propranolol in an average-sized cat with sustained, rapid, overtly symptomatic VT would involve administering 0.05–0.1 mg as an IV bolus and monitoring for effect (decrease in sinus heart rate, decrease in VT rate and/or conversion to sinus rhythm) for approximately 1 minute. Failure of any effect would warrant repeat dosing with similar 1- to 5-minute monitoring intervals to a total dose of 0.4 mg; failure to respond at this cumulative dose suggests drug refractoriness or logistical problems (e.g., IV catheter not in the vein). Esmolol would be administered as a constant-rate IV infusion at 25–200 mcg/kg/min.

Magnesium sulfate can be considered for treating ventricular arrhythmias in cats, particularly refractory VT and ventricular fibrillation/cardiac arrest. Magnesium deficiency may explain sodium- and potassium-related derangements that predispose to cardiac arrhythmias. Magnesium sulfate can be administered at a dosage of 30 mg/kg slow IV, with monitoring for mental depression or dullness, weakness, bradycardia, hypotension, or hypocalcemia as signs of excess warranting termination of administration. Magnesium sulfate is a logical choice in a cat with VT requiring antiarrhythmic treatment when hypomagnesemia has been documented or is suspected, such as when electrolyte-wasting drugs [e.g., furosemide] or disorders are present, or hypokalemia exists that is refractory to potassium supplementation.

Oral antiarrhythmics of choice for PVCs/VT include sotalol and atenolol. Both are beta blockers (class II antiarrhythmics) but sotalol (2 mg/kg PO q 12h; nonselective beta blocker) also has class III antiarrhythmic properties that atenolol (1–1.5 mg/kg PO q 12h; beta-1 selective blocker) does not. They are generally well-tolerated by cats but should not be started during acute fulminant congestive heart failure. No proof exists for the long-term benefit of these drugs as antiarrhythmics in cats, and broadly, atenolol might be chosen first, with a change to sotalol if a desired clinical response is not achieved (Ferasin et al. 2002). Like most beta blockers, they should be avoided in dilated cardiomyopathy and similar states of systolic dysfunction (e.g., end-stage mitral regurgitation or VSD) since the mild decrease in systolic function conferred by these drugs may be poorly tolerated by such patients, especially when medications are administered as fractions of tablets resulting in variable doses (Margiocco et al. 2009).

Amiodarone is a broad-spectrum antiarrhythmic, with properties extending into all 4 Vaughn-Williams classes but mainly in class III (prolongation of repolarization as a means of reducing myocardial electrical heterogeneity/disorganization). It remains one of the most widely used antiarrhythmics in human cardiology. In cats, a dosage of 5 mg/kg has been shown in vitro to raise the fibrillation threshold, an important and encouraging finding (Stoliarchuk and Storozhuk 1982). However, inducibility of ventricular arrhythmias in cats with myocardial infarctions does not improve despite amiodarone treatment (Marinchak et al. 1989). This finding, together with the thyroid (amiodarone is approximately 1/3 iodine by weight) and hepatotoxic adverse effects noted in other species, make amiodarone a poor choice for treatment of arrhythmias in cats.

Given this assortment of possible therapeutic interventions, a reasonable starting point for intravenous antiarrhythmic use in cats with rapid, persistent ventricular tachycardia and/or any ventricular arrhythmia causing syncope, after correcting reversible contributors to ventricular arrhythmogenesis, is lidocaine 0.25–1 mg/kg IV once, then repeated up to 2 more times over

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a period of at least 15 minutes if no benefit is observed, and then followed with esmolol or propranolol if 2 doses of lidocaine were ineffective. Refractory VT is the diagnosis of exclusion if no improvement is observed with this approach, and while magnesium sulfate or additional treatment may be considered in such a situation, logistic failure (misdiagnosis of right bundle branch block or right axis deviation as VT [Figure 18.16]; IV catheter is no longer the vein; hypokalemia is present rendering lidocaine ineffective; etc.) must be addressed first and such problems corrected if present.

Ventricular Flutter, Ventricular Fibrillation, Pulseless Electrical Activity, and Asystole

Each of these four entities represents cardiac arrest, and they are discussed in Chapter 5.

Atrioventricular Block

Disorders arising from faulty intracardiac electrical conduction (as opposed to abnormal spontaneous impulse formation) are simply referred to as *blocks*. Blocks are grouped according to anatomic and functional criteria. Anatomic criteria separate them depending on their level of physical location: SA blocks, AV blocks, bundle branch blocks (BBBs), and fascicular blocks. Functional criteria characterize blocks according to their severity. First-degree block produces a delay in conduction without any instance of complete block; second-degree block causes complete but intermittent block; and third-degree block causes complete, sustained block.

In a healthy heart, the AV node serves an important gatekeeper function that prevents excessive supraventricular electrical impulses from reaching the ventricles (see the section "Premature Atrial Complexes," above). This normal and vital function can fail, either in the form of insufficient filtering, which is rare (see "Preexcitation," below), or at the opposite extreme in the form of excessive restriction of conduction to the ventricles, called AV block. AV blocks are defined as delays or stoppages of conduction between the atria and the ventricles.

Recall that f*irst-degree AV block* simply is a delay in AV conduction. Conduction through the AV node is slower than normal, but every impulse crosses the node successfully (Figure 18.18). It may be permanent or transient and may arise from a structural lesion or simply be functional. The ECG diagnosis is based on normal, sinus-appearing QRS complexes and a prolonged PR interval. The clinical manifestations are nil; first-degree AV block is an ECG finding only and neither produces overt clinical signs nor warrants treatment. Its importance is at best diagnostic, drawing the clinician's attention to possible causes of delayed conduction, which include AV nodal damage due to heart disease and iatrogenic problems including excessive administration of such cardiac glycosides as digitalis or other antiarrhythmic therapy. First-degree AV block is uncommon in the cat, likely because it often arises from high vagal tone, which in turn is rare in this species in the clinical setting. First-degree AV block is not known to progress to second- or third-degree AV block except in cases of drug toxicity (e.g., digoxin).

Second-degree AV blocks involve a true interruption of AV conduction that occurs intermittently. Therefore, a P wave exists for every QRS complex, but a QRS complex does not exist for every P wave. Two important subtypes of second-degree AV block exist. The first, *Mobitz type I* second-degree AV block, is characterized by a progressive lengthening of the PR interval until ultimately a P wave is blocked (P wave without QRS complex), an entity known as the *Wenckebach phenomenon*. This gradual lengthening until block typically repeats such that every 3rd, 5th, or any other multiple of P waves is blocked after PR interval lengthening. Anatomically, Mobitz type I second-degree AV block originates high



Figure 18.18. First-degree AV block in a cat. The PR interval (red bar) is 0.12 sec., which is excessively long; the upper limit of normal for the PR interval in the cat is 0.09 sec. (blue bar). This abnormality was an incidental finding in a 12-year-old male domestic shorthaired cat with unexplained right atrial enlargement and no overt clinical signs. Heart rate = 160 beats/min. 50 mm/sec, 1 cm = 1 mV.

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in the AV node and is said to carry a good prognosis because it is closely related to first-degree AV block and virtually never causes clinical signs. This form of second-degree AV block is very uncommon in the cat, perhaps because, like first-degree AV block, it usually arises in states of parasympathetic predominance. The other type of second-degree AV block, Mobitz type II, by contrast demonstrates perfectly regular PR intervals for all QRS complexes, until suddenly one or more P wave(s) is/are blocked. Mobitz type II second-degree AV block arises from the AV bundle and is said to carry a more guarded to poor prognosis because it more closely resembles third-degree AV block. However, objective evidence is lacking to support this extrapolation of severity in Mobitz types I and II from human cardiology to feline patients. In "simple" Mobitz type II second-degree AV block, more conducted P waves occur than blocked P waves, whereas in "advanced" or "high grade" Mobitz type II second-degree AV block (Figure 18.19), more blocked P waves occur than conducted P waves. The presence or absence of clinical signs in second-degree AV block appears to be related to the overall ventricular rate. Therefore Mobitz type I second-degree AV block essentially never produces clinical manifestations such as lethargy or syncope, whereas the more advanced Mobitz type II second-degree AV block cases often have clinical signs that are similar to third-degree AV block, concurrent with a slow ventricular rate (100 beats/minute or less): weakness, lethargy, syncope, and cardiogenic seizures (true convulsions caused by critical, bradycardia-induced cerebral hypoperfusion) even with minimal exertion.

Assessment of the physiologic (generally harmless) versus pathologic (may cause clinical signs such as syncope) nature of second-degree AV block may be undertaken using an atropine response test: an ECG strip is recorded, and 0.04 mg/kg atropine is immediately administered IV. One or both follow-up ECGs recorded 15 and 30 minutes later should show sinus tachycardia when second-degree AV block is vagally mediated and therefore likely harmless; this is more likely with Mobitz type I than II, but either type may respond to atropine. If atropine response is noted, and the cat displayed symptoms consistent with poor arterial perfusion, such as syncope, treatment with terbutaline may be tried (0.625 mg PO q 8–12h); propantheline (0.8–1.6 mg/kg PO q 8h, titrate down or stop if constipation or other extracardiac vagolytic signs occur) is a second choice if terbutaline is not effective or not tolerated. However, many syncopal cats with AV block ultimately may require a pacemaker (see below). In the absence of overt clinical signs such as weakness or syncope, treatment of second-degree AV block generally is not necessary. An exception to this rule is a stable patient that requires general anesthesia, where bradycardia that is unresponsive to anticholinergics may develop intraoperatively. Cats with high-grade second-degree AV block should be instrumented with a temporary pacemaker (Côté and Laste 2000; Petrie 2005) if they require general anesthesia, as they may otherwise arrest or develop severe bradycardia at induction or during maintenance, and drugs that only accelerate SA nodal activity (atropine, glycopyrrolate, epinephrine) are likely to be ineffective because they rarely increase conduction speed through a diseased AV node. In second-degree AV block, drugs with negative chronotropic properties, including beta blockers and calcium-channel blockers, are contraindicated.

Third-degree AV block is a complete and sustained interruption of AV conduction. The only ventricular

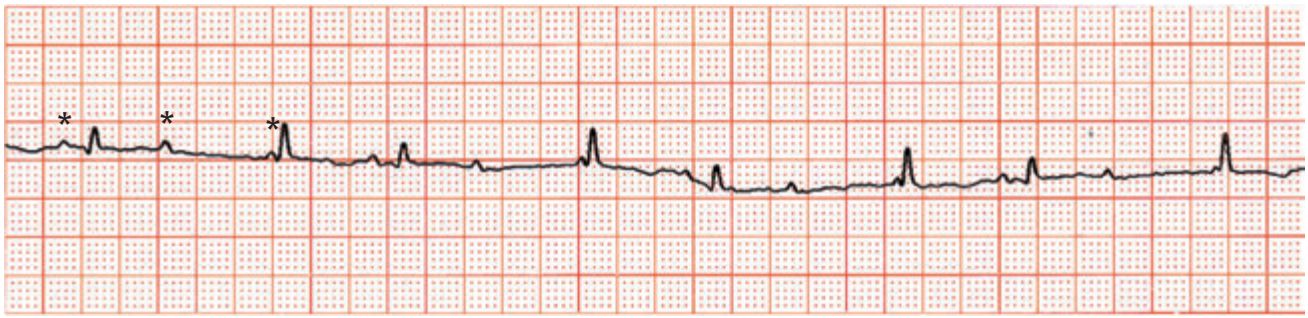


Figure 18.19. Mobitz type II second-degree AV block, 3 : 1, in a cat. The first beat on the left is a sinus beat, with P wave (1st asterisk) followed by a QRS. The second P wave is blocked (2nd asterisk) and no ventricular activity is present. The third P wave (3rd asterisk) is preempted by a ventricular escape beat, which emerges because the ventricles have been inactive for 0.44 sec (the time from the normal sinus beat to the escape beat), an effective ventricular escape rate of 136 beats/minute. This pattern—1 normal sinus beat, then 2 blocked P waves with a ventricular escape beat occurring around the time of the second blocked P wave—repeats for the rest of the tracing. 50 mm/sec, 1 cm = 1 mV.

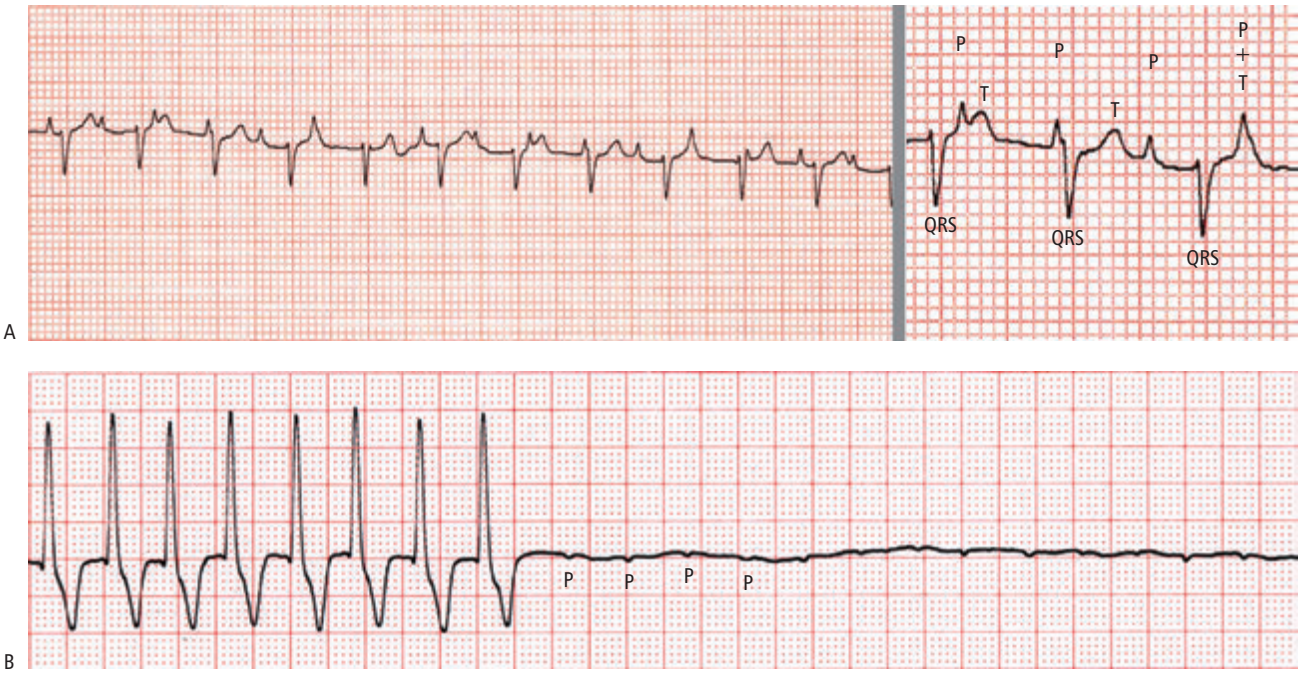


Figure 18.20. Third-degree AV block in 2 cats. **(A)** A 16-year-old female spayed domestic long-haired cat with compensated hypertrophic cardiomyopathy (mild LV thickening) identified echocardiographically based on a heart murmur on routine physical exam. AV block was an incidental finding. The P-P interval is regular (rate: 230/minute), but the P waves are not all followed by QRS complexes at a consistent PR interval; this indicates AV dissociation, and specifically, third-degree AV block since the ventricular rate is slower (150 beats/minute) and the ventricular rhythm is regular, as escape rhythms usually are. This rapid escape rate explains the lack of clinical signs. **(B)** Wide-complex tachycardia (first 1/3 of tracing) is suddenly blocked in a sustained fashion at the AV node, such that atrial activity continues at the same rate (180/minute) but no ventricular activity is triggered. There is also failure of emergence of a ventricular escape mechanism. This 13-year-old male domestic short-haired cat had multiple daily episodes of syncope and underlying hypertrophic cardiomyopathy. This tracing was obtained from a portable event monitor the cat was wearing at the time of syncope. An episode like this one occurred later the same day from which the cat could not be revived. 25 mm/sec, 1 cm = 1 mV.

electrical activity is a slow, regular, independent rhythm, called an *escape rhythm* (junctional or ventricular; see below) (Figure 18.20a). It is important to recognize the life-saving salvage function of a ventricular escape rhythm, because it prevents asystole. Therefore even though ventricular escape QRS complexes may be wide and bizarre, ventricular antiarrhythmic therapy is absolutely contraindicated. Third-degree AV block with failure of escape mechanisms has been documented in the cat and can be fatal (see Figure 18.20b).

In third-degree AV block, electrical communication between the atria and ventricles is nonexistent (complete AV dissociation). Therefore the ECG diagnosis is based on the complete absence of P wave conduction (P waves occur regularly and typically at a normal sinus rate of 140–260/minute, but are not followed immediately and consistently by QRS complexes; there is no consistent PR interval) and the presence of a slow ventricular rhythm, uniform, but wide and bizarre QRS morphology (shape). The P-P interval is usually constant, and the R-R interval (ventricular escape beats) is usually constant, but no connection exists between the two. Despite signifying complete atrioventricular dissociation, third-degree AV blocks may or may not produce overt clinical signs such as exercise intolerance, weakness, or syncope in cats. The occurrence of such signs depends on the ventricular rate. If a cat's ventricular escape rate is sufficiently rapid (>100 beats/minute), cardiac output may not be appreciably reduced compared to normal. Cats routinely appear to develop ventricular escape rhythms that are suitably rapid: in a case series of 21 cats with third-degree AV block, all cats had a ventricular rate between 100 and 140 beats/minute (median 120 beats/minute) (Kellum and Stepien 2006), which may explain the finding that only 3/21 cats (14%) had collapse as the presenting complaint.

Third-degree AV block represents 5.8% (10/170) of recorded ECG abnormalities in cats according to one retrospective analysis (Côté and Harpster 2009). Three retrospective studies and several case reports and textbook chapters describe 37 cats with third-degree AV block and thus provide a useful compilation of clinical

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information (Fox and Harpster 1999; Côté 2010; Kellum and Stepien 2006; Côté and Harpster 2009; Harvey et al. 2005; Ferasin et al. 2002; Fox et al. 1991; Kaneshige et al. 2006; Penning et al. 2009; Côté et al. 1999; Harpster 1987, 1992). In summary, cats with third-degree AV block show no clear gender tendency (18 male, 12 female), a varied breed distribution (20 mixed breed, 4 Siamese, 3 Burmese, 1 each Himalayan, Russian Blue, Persian), and an age range of 4–19 years. Chief complaints are stated for 34 cats; 7 (21%) had chief complaints suggestive of cardiac arrhythmia (e.g., syncope, collapse), 19 (56%) were presented because of nonspecific signs (e.g., lethargy, inappetence, dyspnea), and in 8 (23%), there was no complaint and third-degree AV block was an incidental finding. Heart rate on physical exam ranged from 70–160 beats/minute, and ECG identified third-degree AV block with ventricular escape rates between 55 and 160 beats/minute. There was no appreciable association between ventricular rate and presenting complaint; third-degree AV block was an incidental finding in cats with ventricular escape rates ranging from 80–140 beats/minute (Côté and Harpster 2009; Harpster 1992), for example, and cats with congestive heart failure did not have a significantly different heart rate than cats without congestive heart failure (Kellum and Stepien 2006). The QRS complexes of the ventricular escape rhythm were wide in 5 cats (19%) and narrow in 21 (81%). When echocardiographic or postmortem results were reported (n = 25), many cats had underlying structural heart disease (HCM/DCM/RCM/UCM [n = 7; 28%], mitral valve disease [n = 4; 16%], excessive LV moderator bands/false tendons [n = 2; 8%], ARVC [n = 2; 8%]). The association between cardiomyopathy and AV block is consistent with the finding that cats with third-degree AV block and HCM commonly have fibrosis of the branching portion of the AV bundle and the upper portion of the left bundle branch, extensive fibrosis of the central fibrous body, and endocardial and myocardial fibrosis in the upper border of the ventricular septum (Kaneshige et al. 2006). However, in 10 cats (40%), echocardiographic findings were described as normal or consistent with mild chamber dilation expected due to bradycardia-induced, neurohormonally mediated sodium and water retention.

Pacemaker implantation was performed infrequently (11/36 cases; 31%). Cats with untreated third-degree AV block had a wide range of survival times (median: 386 days in 1 study; range: 1 day–5.7 years postdiagnosis), and third-degree AV block does not automatically confer a poor prognosis in the cat. Congestive heart failure or indeed structural heart disease did not confer a worse prognosis in the largest of these case series (Kellum and Stepien 2006). Survival is likely increased with pacemaker implantation in cats where the arrhythmia is responsible for overt clinical signs, but this intuitive impression remains unproven in the cat. Interestingly, sudden death is not documented in cats with third-degree AV block, perhaps because cats commonly express a more rapid ventricular escape rate (e.g., 100–140 beats/minute) compared to other species, because overt clinical signs become sufficiently dramatic to elicit veterinary attention while a ventricular escape mechanism remains functional, and because retrospective reports often do not provide follow-up information to the time of death.

The causes of AV block are diverse, but in cats an association with cardiomyopathy is common (Kaneshige et al. 2006; Liu et al. 1975). First-degree AV and Mobitz type I second-degree AV blocks often are functional (high vagal tone in healthy individuals, negative dromotropic effects of digitalis, antiarrhythmics, or alpha 2-stimulating anesthetics) and thus are normal physiologic variants or resolve with drug discontinuation. Less commonly, cardiac disease with atrial dilation and AV nodal lesions may be present as a cause of first-degree or Mobitz type I second-degree AV block. Mobitz type II second-degree AV block and third-degree AV block are sometimes functional (hyperkalemia, digitalis toxicity, alpha 2-stimulating anesthetics) but are more commonly associated with a structural lesion: inflammatory (endocarditis, Lyme myocarditis, traumatic myocarditis) or degenerative (physical disruption of the AV node arising from cardiomyopathy with or without degeneration and fibrosis, as indicated above). Treatment is therefore aimed at the underlying cause when possible. In clinically overt, advanced, Mobitz type II second-degree AV blocks or third-degree AV blocks, response to parasympatholytic or sympathomimetic drugs tends to be fairly disappointing and potentially dangerous. Pacemaker implantation is a better choice.

Although spontaneous conversion from third-degree AV block to normal sinus rhythm has been documented in the cat (Kellum and Stepien 2006), in most cases the block is permanent, and treatment is necessary if clinical signs attributable to the bradycardia are present. Medical therapy is usually unrewarding for third-degree AV block but may be attempted in stable patients (see discussion of second-degree AV block, above). Pacemaker implantation is the treatment of choice for third-degree AV block (Figure 18.21). It is performed less frequently than in dogs, and with some important differences. At least 12 cases of therapeutic feline pacemaker implantation have been described (Kellum and Stepien 2006; Ferasin et al. 2002; Fox et al. 1991; Kaneshige et al. 2006; Penning et al. 2009; Stamoulis et al. 1992). For cats, a human pediatric pacemaker generator (the "can") is the implant of choice. It is generally placed in the abdomen

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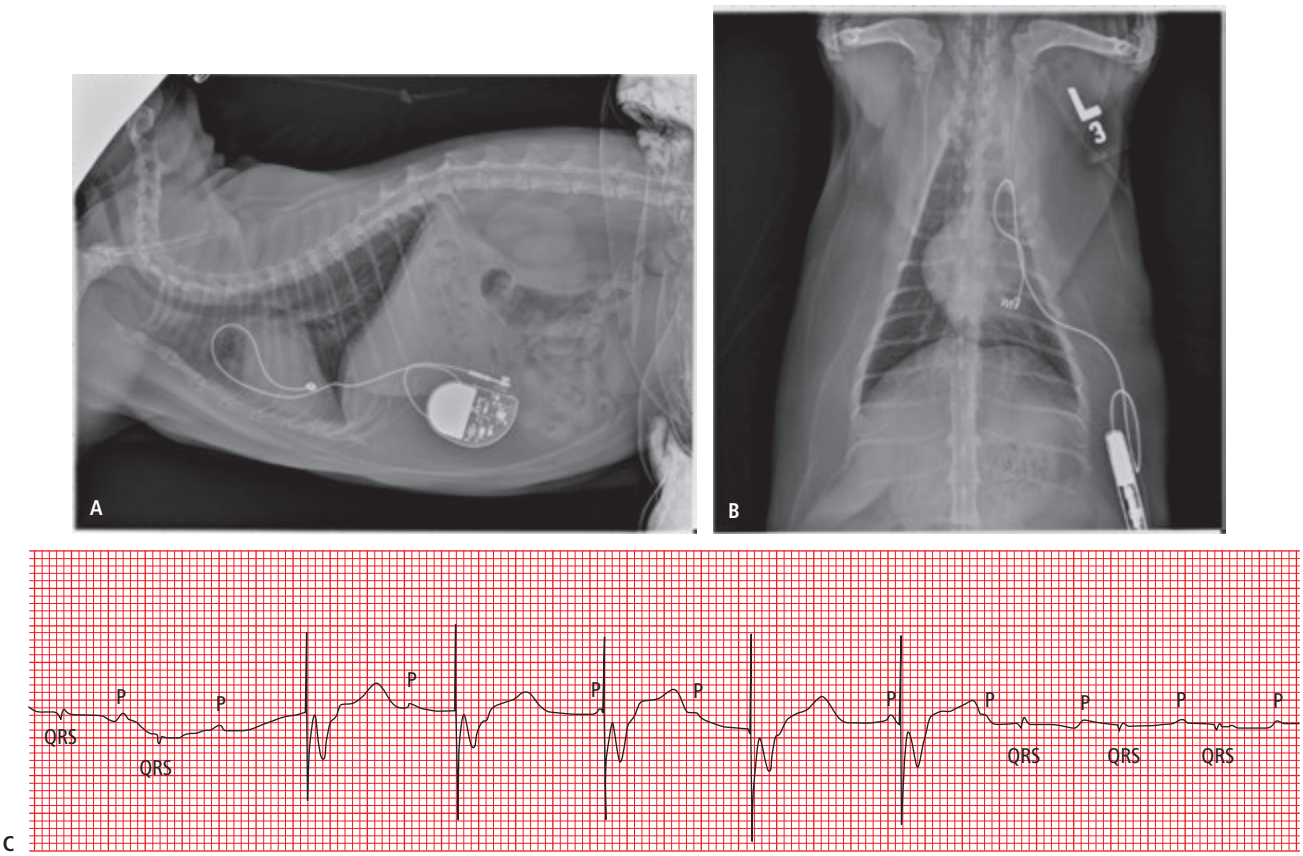


Figure 18.21. Permanent pacemaker therapy in a cat. **(A)** (lateral) and **(B)** (ventrodorsal) are radiographs obtained after pacemaker implantation, demonstrating an active-fixation (corkscrew-type) epicardial lead affixed to the left ventricle, with the generator located in the subcutaneous space of the left lateral thorax. **(C)** is a postoperative ECG that identifies normal sinus rhythm (beginning and end) with 5 paced beats (large deflections in center of tracing). Note that pacing begins in response to AV block: the second P wave from the left is not followed by a QRS complex. 50 mm/sec, 10 mV/cm.

or subcutaneously over the lateral thorax because the cervical location is impractical in the cat compared to the dog. The generator connects to the heart via an epicardial lead that is actively fixed (sutured, with or without corkscrewing/harpooning of the lead tip into the myocardium) to the outer surface of the heart through lateral thoracotomy, midline laparotomy, or combined midline laparotoromy and caudal sternal midline thoracotomy. The much less invasive transvenous jugular approach using an endocardial, passive fixation lead as routinely performed in dogs and humans was advocated initially based on 2 case series (Fox et al. 1991; Stamoulis et al. 1992); currently it has found disfavor due to anecdotal reports and a case description of complications involving venous obstruction, notably chylothorax (Ferasin et al. 2002). However, these choices have been based on very small numbers of cases. The optimal programmed rate is unknown for cats and ranges from 70 to 129 in reported cases. Outcomes are known for 10 cats treated with pacemakers for symptomatic bradycardia (Kellum and Stepien 2006; Ferasin et al. 2002; Fox et al. 1991; Kaneshige et al. 2006; Penning et al. 2009). The long-term prognosis in these cats has been fair to good: 2 cats (20%) have lived at least 4–6 months postoperatively, and 8 (80%) have lived 1 year or more after the onset of clinical signs, including 5/10 with syncope-free survival 18, 22, 34, 41, and 45 months postoperatively. Reported complications include chylothorax (above), seroma formation (Fox et al. 1991; Stamoulis et al. 1992), and generator infection and skin ulceration (Petrie 2005), similar to complications described in dogs and humans.

Bundle Branch Blocks and Fascicular Blocks

BBBs are slowings or interruptions of conduction involving one or more of the ventricular branches of the His bundle. Blocks may be functional (transient interruptions due to the depolarizations occurring during the refractory period) or structural (permanent interruptions due to a physical disturbance). The ECG

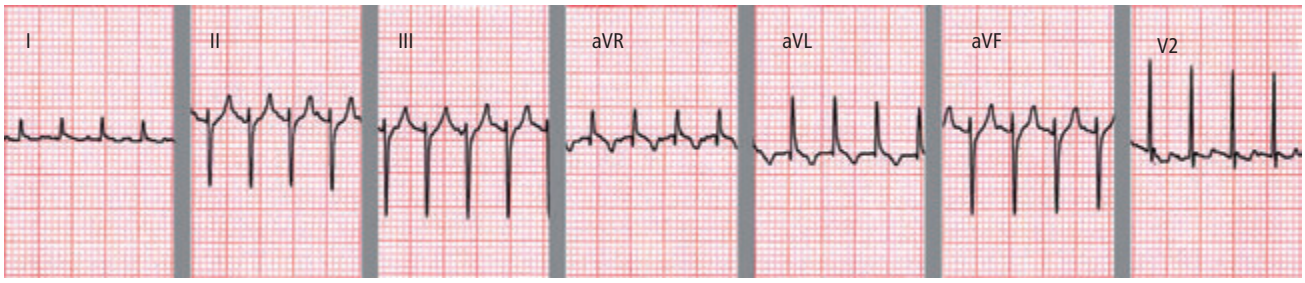


Figure 18.22. Left anterior fascicular (LAF) block pattern in a 13-year-old male domestic short-haired cat with mild symmetrical left ventricular concentric hypertrophy. The marked left axis shift seen here (–75°) suggests LAF block, which has been associated with hypertrophic cardiomyopathy in cats. Sinus tachycardia; heart rate = 230 beats/minute. 25 mm/sec, 1 cm = 1 mV.

diagnosis of BBBs is based on the abnormal shape of the QRS complexes, which become widened due to the desynchronization of the two ventricles. BBBs cannot be considered arrhythmias because they do not alter the rhythm of the heartbeat; therefore, the ECG diagnosis should be stated as "rhythm" (e.g., normal sinus rhythm) "with [right or left] bundle branch block" (or bundle branch block pattern). In cats with BBB, the duration of the QRS complexes is greater than 0.04 second, and the polarity is positive in lead II for left BBBs and negative in lead II for RBB blocks. If BBBs occur during sinus rhythm, the ECG diagnosis is straightforward, because other than the abnormal appearance of the QRS complexes, the P-QRS-T sequence throughout the ECG is normal: a P wave occurs before each QRS and the PR interval is fixed and normal. Still, care must be taken to properly identify the rhythm as normal sinus rhythm and avoid misdiagnosis of VT based on wide, bizarre QRS complexes alone. If the block occurs concurrently with a nonsinus rhythm, such as AF, establishing a diagnosis in BBB can be much more challenging. Important characteristics that allow differentiation are that AF + BBB produce an irregularly irregular rhythm and the heart may slow with application of a vagal maneuver, whereas VT tends to be regular (constant R-R interval) when monomorphic (when the wide, bizarre QRS complexes all look alike) and VT tends to not respond to vagal maneuvers.

Left Anterior Fascicular (LAF) Block

Cats with heart disease, especially cardiomyopathy, are classically described as being prone to developing block in a subdivision of the LBB known as the *left anterior fascicle* (LAF). The LAF, also called the left anterior hemibundle or left anterior arborization, is described as covering the dorsalmost part of the left ventricle, but such anatomic distribution is extrapolated from humans (where it is highly variable). Blockage of the LAF is not appreciably harmful: no hemodynamic impact is noted clinically, and indeed this ECG finding is rather used for increasing the index of suspicion of underlying cardiomyopathy. LAF block produces a tall R wave in leads I and aVL, and a deep S wave in leads II, III, and aVF, and therefore a left-axis deviation (Figure 18.22). The association between LAF block and cardiomyopathy, notably HCM, is a histologically proven but clinically ambiguous one. Histologic observation of fibrosis involving especially the left parts of the His-Purkinje system in cats with HCM supports the link between HCM and LAF block (Kaneshige et al. 2006); a survey of 63 cardiomyopathic feline hearts revealed degeneration, fibrosis, osseous metaplasia, and other lesions in 58 (92%) of cases, with 54 (86%) of left bundles affected compared to only 20 (32%) of right bundles (Liu et al. 1975).

It should be noted that an important artifact could mimic LAF block and it is not routinely addressed in retrospective studies of ECG in cats. Simply altering the position of a cat's limbs may deviate the mean electrical axis in a way that could mimic LAF block on the ECG. Therefore, in some cases, LAF block could be misdiagnosed (see Chapter 9). From a practical standpoint, LAF block may be addressed as follows: if good ECG technique was used when obtaining the tracing and the tracing is consistent with LAF block, then further investigation is warranted (e.g., echocardiogram). If the patient's position at the time the ECG was done is not known or was known to be incorrect, then ECG findings consistent with LAF block should be disregarded until the ECG can be repeated.

The causes of BBB are many, because BBBs may be due to a variety of pathologic changes, including concentric hypertrophy (as seen in hypertrophic cardiomyopathy, above), dilation (as seen in dilated cardiomyopathy), and inflammation (endocarditis, traumatic myocarditis). In many feline cases, RBB block is often a completely normal, unnecessarily worrisome ECG

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finding, especially if the diagnosis was reached partly or entirely in error due to incorrect limb position during restraint for the ECG (see Chapter 9). Clinical manifestations of BBBs alone generally do not occur. These disturbances therefore do not warrant specific treatment beyond that of their underlying cause if one exists. The importance of recognizing BBB lies in the fact that they could be the first indicators of underlying cardiac disease, which itself warrants further diagnosis and treatment, and that they can—and should not—be misinterpreted as ventricular arrhythmias.

Atrial Standstill (Silent Atrium)

This rhythm disturbance is characterized by the total absence of atrial depolarization. The three differential diagnoses for atrial standstill are 1) moderate to marked hyperkalemia (K^+ >7.5 mEq/l; see below), 2) atrial myopathy (Gavaghan et al. 1999; Richig and Tilley 1984), and 3) ECG artifact (P waves too small, or isoelectric, preventing them from being seen properly on a chosen ECG lead). Given the very small size of normal feline P waves, a 10-lead ECG (with reduced or no noise filtration and an increased gain of 20 mm/mv [Schrope et al. 1995]) is always warranted when atrial standstill is suspected (Figure 18.23); the presence of P waves on even 1 lead rules out atrial standstill. While hyperkalemia is the most common cause of atrial standstill (and the only reversible one; see below), atrial standstill may occur due to marked atrial stretch, as occurs in severe feline cardiomyopathies (Gavaghan et al. 1999; Richig and Tilley 1984). Atrial myopathy is not common, and it carries a grave prognosis; severe right-sided CHF is usually responsible for the major clinical signs, and it is worsened by the bradycardia. Regardless of cause, the ECG appearance is of a regular rhythm, usually with QRS complexes that are of a supraventricular appearance, and with a normal rate but without detectable P waves in any lead on the ECG. Differentiating between atrial myopathy and hyperkalemia using the ECG alone is difficult. If P waves are not evident, immediate measurement of serum electrolytes is warranted.

Sinus Node Dysfunction (Sick Sinus Syndrome, Bradycardia-Tachycardia Syndrome)

This polyarrhythmic disorder, which is well-recognized in humans and dogs, has never been reported as such in the cat. An autoimmune disturbance directed at the heart's nodal tissues, or at autonomic receptors, has been shown in humans with this disorder, but such mechanisms have not been evaluated in veterinary medicine (Côté 2010). The hallmark ECG findings are a mixture of sinus pause/sinus arrest with a failure of escape rhythm to emerge (causing asystole of up to several seconds' duration) and AV block, as bradycardias; PVCs and/or PACs as tachycardias; and generally a variety of these arrhythmias occurring unpredictably and sometimes simultaneously on the same ECG strip. Based on cardiac event monitoring in dogs, it is bradycardia that is associated with the clinical signs, and therefore optimal treatment includes pacemaker implantation. The prognosis in cats is unknown, as it has not been reported in this species. Interrestingly, cats with third-degree AV block causing syncope often have a failure of escape mechanism and prolonged periods of ventricular asystole corresponding to the syncopal episodes (see Fig 18.20). This failure of ventricular (or junctional) escape mechanism emergence, together with AV block, could be consistent with the criteria for sinus node dysfunction. However, the underlying cardiomyopathy that often exists in these cats (see discussion of AV blocks, above), and histologic demonstration of segmental degeneration and fibrosis of the intraventricular conduction system with no histologic lesions in the SA or AV nodes (Kaneshige et al. 2006), suggest that a mechanism associated with cardiomyopathy is the cause, rather than multifocal or diffuse lesions affecting the

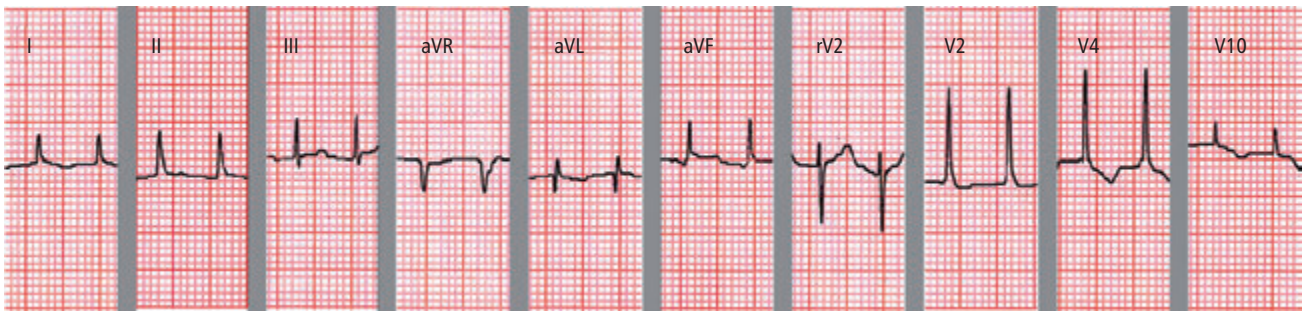


Figure 18.23. Atrial standstill in a young cat with extreme left atrial enlargement (LA : Ao >3 : 1) associated with hypertrophic cardiomyopathy. Two heartbeats are shown for each lead, and no P waves are seen. The serum K^+ level was 4 mEq/l (within normal limits). Because feline P waves are often very small, all 10 ECG leads are needed to identify atrial standstill. T waves (positive in III, aVF, rV2; negative in I, aVL, V4, V10) should not be mistaken for P waves. 25 mm/sec, 1 cm = 1 mV.

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conduction system disease exclusively, as in "true" sinus node dysfunction.

Ventricular Preexcitation and Macroreentry

In preexcitation, the normal impulse originating from the SA node is split at the end of atrial depolarization, with part of the impulse traveling normally through the AV node and another part of the impulse traveling simultaneously through an abnormal shaft of rapidly conductive fibers that links the atria and the ventricles, called an *accessory pathway* or *bypass tract*, thus bypassing the AV node. The result is partial, premature, immediate activation of the ventricles through the bypass tract, without the benefit of a pause in the AV node; hence the term preexcitation. With one major exception (see below), the effect of this abnormal pattern of activation is minimal, because the minor interventricular asynchrony means only a part of the atrial contribution to ventricular filling is lost. The ECG (see Figure 18.26, later in this chapter) demonstrates that the normal delay through the AV node was preempted by conduction through the bypass tract (i.e., the PR interval is reduced, often with the P wave apposed directly against the QRS complex) and that conduction through the bypass tract caused early activation of the ventricles (the bypass tract and the normal AV nodal conduction ultimately each activate their share of the ventricles), resulting in a notched QRS complex. The size and location of the QRS complex's notch, the *delta wave*, depends on the distance that separates the bypass tract and the AV node in the individual's heart (i.e., on the amount of myocardium that the His bundle and the bypass tract can each depolarize before the impulses collide with each other). These are the ECG findings noted in the vast majority of cats with preexcitation (28/29 feline cases; 97%) (Fox and Harpster 1999; Paige et al. 2009; Peterson et al. 1982; Rishniw 2000; Harpster 1992; Tilley et al. 1977; Ogburn 1977; Riesen and Lombard 2005; Roland and Estrada 2006; Meurs and Miller 1993; Goodwin 1990; Berry and Lombard 1986; Hill and Tilley 1985; Flecknell et al. 1979).

When cats with preexcitation are examined, a sinus rhythm with the features noted above is usually apparent on ECG. However, in individuals with preexcitation, a premature atrial complex (PAC) may initiate a type of reentry cycle that can produce extreme tachycardias. Although bypass tracts conduct impulses rapidly, their refractory period typically is longer than that of the AV node. Therefore the timing of a PAC may fail to conduct through the bypass tract but be able to conduct through the AV node, depolarizing the ventricles normally. As the impulse completes the depolarization of the ventricles, the bypass tract has repolarized and is able to conduct. Bypass tracts can often conduct impulses in either direction, such that the ventricular impulse conducts retrograde through the bypass tract to the atria, and then again through the AV node in the normal direction, initiating an endless loop of conduction that activates the ventricles with each turn of the loop. This type of self-perpetuating circuit is a macroreentry circuit, and it may produce a potentially very rapid and clinically overt (apparent discomfort, exercise intolerance, lethargy, syncope) tachycardia called *orthodromic* (the impulse travels in a normal, "normograde" direction through the AV node) AV reentrant tachycardia (OAVRT) (see Figure 18.27) (Roland and Estrada 2006). There are various types of macroreentry tachycardias, named according to the location of the bypass tract fibers. The two most common are the Wolff-Parkinson-White syndrome, where atria are directly linked to ventricles via the Kent fibers, and the Lown-Ganong-Levine syndrome, anecdotally the most common form on the cat, where the atrioventricular bypass tract consists of the James fibers. Initial treatment can involve vagal maneuvers that, through slowing of AV conduction (i.e., negative dromotropic action), break the cycle of reentry. Beta blockers such as atenolol also are useful for reducing the likelihood of recurrent tachycardia, but digoxin is contraindicated because it shortens the refractory period of the bypass tract, facilitating extreme tachycardia. Preexcitation is well-documented in the cat, although its prevalence in the feline population is low as evidenced by identification of 3 cases in 118 cases of feline HCM (2.5%) (Harpster 1987) and 1 case in 65 cumulative cases of hyperthyroidism (0.8%) (Peterson et al. 1982; Moïse et al. 1986). At least 29 cases of ventricular preexcitation have been reported in the cat (Fox and Harpster 1999; Paige et al. 2009; Peterson et al. 1982; Rishniw 2000; Harpster 1992; Tilley et al. 1977; Ogburn 1977; Riesen and Lombard 2005; Roland and Estrada 2006; Meurs and Miller 1993; Goodwin 1990; Berry and Lombard 1986; Hill and Tilley 1985; Flecknell et al. 1979). From these, various data are available for some cases but not others, and the following observations can be compiled: preexcitation is recognized in adult cats (median age 4.5 years; range 1–12 years) with no clear gender predominance (44% male, 56% female) and a varied breed distribution (domestic short-haired [n = 12], Persian [n = 2], Siamese, domestic long-haired, Himalayan [n = 1 each]). In these reports, ventricular preexcitation was often an incidental ECG finding (11/20; 55%) although several cases presented with clinical signs consistent with reciprocating tachycardia (9/20; 45%). In two cases, (one hypovolemia due to GI disease, one hyperthyroidism) preexcitation was noted at presentation during severe illness, and supportive care

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was associated with resolution of preexcitation subsequently (Rishniw 2000; Riesen and Lombard 2005). Structural heart disease was often present concurrently (left ventricular concentric hypertrophy/HCM [n = 12/24; 50%], restrictive/unclassified cardiomyopathy [n = 3/24; 13%], congenital heart disease (unspecified) [n = 2/24; 8%], "myocardial disease—other" [n = 2/24; 8%], dilated cardiomyopathy [n = 1/24; 5%], Ebstein's malformation of the tricuspid valve plus heartworm disease [n = 1/24; 5%]). In 3/24 cases (13%), echocardiographic findings were within normal limits. The association of preexcitation with Ebstein's malformation (Meurs and Miller 1993) is intriguing, because this association is well-recognized in the dog and human. Long-term outcome is explicitly described in only 6 cases, and in these cats preexitation seemed to confer a fair prognosis: 4 cats lived for at least 2–7 months (1 with recurrent syncope and then lost to follow-up) and the remaining 2 were euthanized for other reasons (gastrointestinal lymphoma; donation).

CARDIAC EFFECTS OF SYSTEMIC POTASSIUM AND CALCIUM ABNORMALITIES

Because cardiac activity depends fundamentally on transmembrane movements of ions, pathologically high or low systemic concentrations of potassium and calcium may lead to disturbances in cardiac function, some of which can have important effects on the heart's rhythm.

Hypokalemia

Serum potassium concentrations are most accurate if measured on blood drawn into lithium heparin (green top) tubes. Red top tubes allow coagulation, a process that, during platelet activation and aggregation, releases potassium and may artifactually raise the measurement by small but clinically significant levels, masking hypokalemia or falsely suggesting hyperkalemia.

A low serum potassium concentration produces two major effects in cardiomyocytes. First, it makes the resting membrane potential increasingly negative (see Figure 18.13) (DiBartola and Autran de Morais 2006; Surawicz 1995), which decreases myocyte excitability. This effect is a result of the greater difference between intracellular and extracellular potassium concentrations in hypokalemia compared to normokalemia (hyperpolarization) and in cardiomyocytes is generally mild and transient. Second, hypokalemia prolongs repolarization, increasing action potential duration (DiBartola and Autran de Morais 2006; Surawicz 1995). Myocyte repolarization depends principally on the activity of potassium currents, notably the delayed rectifiers I_{Kr} and I_{Ks}. With hypokalemia, these currents function more slowly. This prolongation of repolarization lengthens the normally very brief period of repolarization during which the diastolic membrane potential is near the threshold potential. Therefore, hypokalemia-induced prolongation of repolarization opens a window of increased excitability during which spontaneous ectopic activity (such as atrial or ventricular extrasystoles) can occur based on the threshold being reached after the absolute refractory period by a slowly repolarizing cell. Clinically, the second (arrhythmogenic) effect predominates over the first (suppressive), and the dominant cardiovascular effect of a serum potassium concentration <3.5 mEq/l in cats is an increased risk of spontaneous depolarizations, notably ventricular extrasystoles (PVCs). Other ECG manifestations of hypokalemia can include evidence of prolonged, abnormal repolarization in the form of U waves (see previous discussion), QT interval prolongation, and AV dissociation (Atkins 1991). Because class I antiarrhythmics (e.g., lidocaine, mexiletine, quinidine) act on sodium channels that require normal serum potassium concentrations to function, hypokalemia is also important as a cause of antiarrhythmic drug refractoriness: in a patient whose PVCs are caused by hypokalemia, a decrease in PVC number, or resolution of the arrhythmia altogether, is expected with potassium supplementation alone, whereas treatment with lidocaine during hypokalemia is unlikely to alter the ventricular arrhythmia, but may still cause lidocaine toxicosis if dosing is readministered repeatedly because of presumed inadequate drug response. This important observation has wide-ranging implications in patients with dilutional hypokalemia (e.g., trauma patient with large-volume fluid resuscitation) or potassium-wasting metabolic illness (e.g., chronic kidney disease) when PVCs/VT occur and the question "When should I treat this arrhythmia with an antiarrhythmic?" arises. An important initial step toward answering this question should always be to ensure that normokalemia is present before considering antiarrhythmic therapy.

Hyperkalemia

ECG changes associated with increasing degrees of hyperkalemia have been clearly categorized and published widely (DiBartola and Autran de Morais 2006; Surawicz 1995; Ettinger et al. 1974; Norman et al. 2006). According to these criteria, the ECG passes through different stages as hyperkalemia becomes more severe, and accordingly, veterinarians have sought to stratify the risks associated with hyperkalemia based on ECG findings. This stratification has not held up well to clinical scrutiny, with some cats having markedly greater serum potassium concentrations than would be expected from the ECG, and others markedly lower, or some cats

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surviving despite life-threatening serum potassium levels and others arresting under seemingly identical or less severe conditions. An important observation to explain this discrepancy is that graded ECG changes reported in the literature are based on infusion of potassium salts (typically potassium chloride) intravenously in experimental animals, with simultaneous ECG monitoring and measurement of serum potassium levels. In contrast, feline patients with urethral obstruction, acute renal failure, reperfusion injury, or any other naturally occurring cause of hyperkalemia, often have one or more concurrent metabolic abnormalities, such as hypovolemia, anemia, acid-base disturbances, serum calcium abnormalities, or hyperlactatemia, any of which may alter cardiomyocyte membrane potential and threshold. Therefore, the distinct, step-by-step approach to ECG changes associated with progressive hyperkalemia are scientifically accurate for experimental studies but not absolute in the clinical setting. The presence or absence of P waves appears to be the most important hyperkalemia-associated finding in cats, and as noted for atrial standstill (above), more than one ECG lead should be evaluated before P waves are considered to be absent because they may normally be small or inapparent in some leads (see Figure 18.23).

Mildly elevated serum potassium levels (5.6–6.5 mEq/l) are associated with greater cell membrane permeability to potassium during repolarization. These repolarization effects predominate over depolarization effects. Thus, mild hyperkalemia in cats may be reflected on the ECG as faster ventricular repolarization, i.e., a shorter than normal QT interval and an abnormally narrow, often peaked or "tented" T wave (DiBartola and Autran de Morais 2006; Surawicz 1995; Ettinger et al. 1974). It is a common but serious mistake to think that tented T waves must always equal hyperkalemia, because cats may have tall or peaked T waves in health, and likewise may be mildly or moderately hyperkalemic with minimal or no observable change in T wave morphology. Serial ECGs in the same patient, obtained under the same conditions, that show progressively taller T waves are probably the most reliable application of this association; obtunded patients in ICU, or patients under general anesthesia, are examples where increasingly tall T waves should prompt serum potassium level measurement.

Mild hyperkalemia (e.g., serum K^+ concentration = 6–6.5 mEq/l) may be considered as slightly antiarrhythmic because myocardial excitability is reduced compared to normokalemia, without adverse effects on contractility. For this reason, cats with PVCs and/or VT should have serum potassium concentrations that are well within the normal range and preferably at the upper end of normal, provided they are able to excrete it if excessive (i.e., urinary tract is patent and renal function is normal). Thus, PVCs/VT may be more likely to occur in a hyperkalemic patient as serum potassium concentrations decrease toward normal (Figure 18.24).

Sinus bradycardia may also occur with hyperkalemia because hyperkalemia decreases the activity of normal pacemaker tissue. Specifically, it decreases the slope of phase 4 of diastolic depolarization (Surawicz 1995), which slows the heart rate. However, naturally occurring hyperkalemia also routinely coexists with abnormalities in acid-base status or other serum electrolytes, pain, fear, sepsis, and other disorders, all of which may increase circulating catecholamine concentrations and cause the opposite—sinus tachycardia. The routine observation that many cats with even severe hyperkalemia have elevated heart rates makes this physical exam or ECG parameter unreliable for inferring a patient's serum (K^+) (Norman et al. 2006; Tag and Day 2008).

Mild to moderate increases in serum potassium (6.6–7.5 mEq/l) may begin to interfere with cell-to-cell transmission velocity in the ventricles, which explains the initial QRS complex widening observed in some patients with serum potassium concentrations in this range.

Moderate to severe hyperkalemia (7.0–8.5 mEq/l) can cause PR interval prolongation and absence of P waves altogether, which are probably the most characteristic ECG findings for hyperkalemia in cats. The atria are more sensitive to hyperkalemia than are the ventricles, and within the atria, the myocardium is more sensitive to the effects of hyperkalemia than are the internodal tracts (three sets of specialized fibers in the atria consisting of the paired ventral [anterior] pathways, which carry electrical activity directly to the AV node, and the dorsal [posterior] pathway called Bachmann's bundle, which is also responsible for left atrial activation). The result when severe hyperkalemia occurs is a sinoventricular rhythm, so named because the heartbeat originates normally in the SA node, crosses the atria through the internodal tracts (but the impulse does not spread outward—no atrial activation, no P wave), and then passes through the AV node and His-Purkinje system in the usual sequence. The ECG appearance is a regular rhythm with normal or slightly widened QRS complexes, and no P waves (Figure 18.25).

Very high serum potassium concentrations (>8.5 mEq/l) can be fatal. So many other factors influence the rhythm in these catastrophically ill patients that an exact cutoff for lethality cannot be established for serum potassium concentration alone. Any cat with a serum potassium concentration >8.5 mEq/l is at risk of death from a combination of hyperkalemia and the inciting disorder. Experimental studies have shown that

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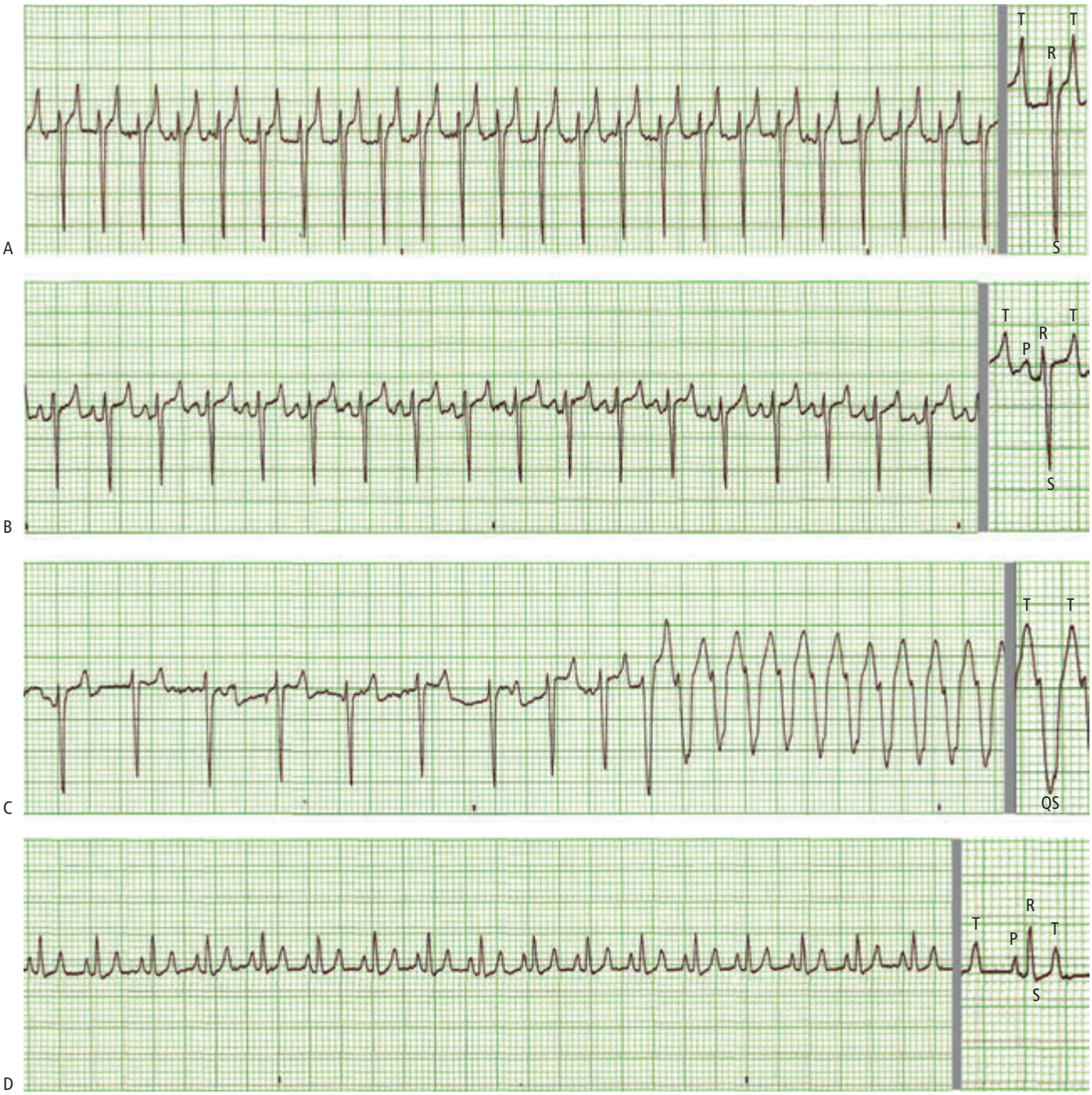


Figure 18.24. Hyperkalemia in a 2-year-old male domestic short-haired cat with urethral obstruction. **(A)** Serum K^+ = 8.1 mEq/l; patient has been induced into general anesthesia for passage of a urethral catheter to relieve the obstruction. The tentative ECG diagnosis was ventricular tachycardia (VT). **(B)** Four minutes later, patient is turned into dorsal recumbency for the procedure, revealing a P wave for each QRS and identifying the ECG diagnosis as sinus tachycardia, not VT. The ability to visualize P waves is attributed to alteration in limb position and position of the heart in the thorax. Treatment of hyperkalemia with K^+-free IV fluids and IV calcium gluconate was continued. **(C)** Twenty minutes after **(B)**, an onset of VT was noted. Small (0.05–0.1 mg) boluses of propranolol were administered IV to a maximum total dose of 0.3 mg in 15 minutes, while pursuing K^+-lowering treatment via dilution (crystalloid fluid administration). **(D)** Twelve hours later, the rhythm is normal sinus. This series demonstrates the shortcoming of single-lead ECGs (where sinus tachycardia may be misinterpreted as VT if P waves are not apparent in one lead) and points to a possible reason for overdiagnosis of VT in cats with hyperkalemia. These tracings may also indicate the antiarrhythmic effects of potassium, wherein a ventricular arrhythmia can be triggered more readily during a period of falling serum K^+ concentrations. All tracings 25 mm/sec, 1 cm = 0.65 mV.

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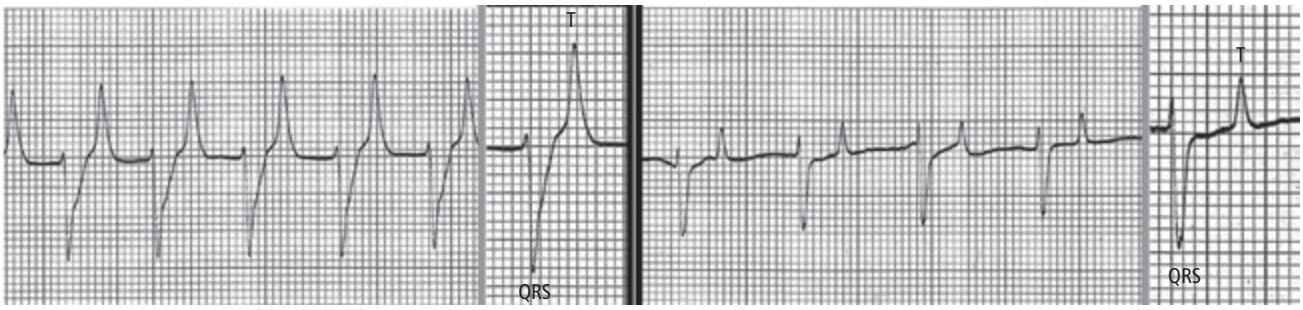


Figure 18.25. Hyperkalemia in 2 male cats with urethral obstruction. Serum K^+ concentration in both cats was 10.5 mEq/l. Similarities include atrial standstill (no P waves), wide QRS complexes, and peaked T waves; differences include degree of QRS widening, intraventricular conduction disturbance (present in tracing on left as evidenced by notched upstroke of S wave, absent in tracing on right), and heart rate (left: 140 beats/minute; right: 90 beats/minute). These tracings show that serum K^+ concentration alone is not fully responsible for all the ECG changes that are seen with in naturally occurring disorders that cause hyperkalemia, because serum K^+ concentrations were the same in both cats. 25 mm/sec, 1 cm = 1 mV. Tracings from the collection of the late Dr. Brian Hill, courtesy of Dr. Sherri Ihle, Atlantic Veterinary College, UPEI, Canada.

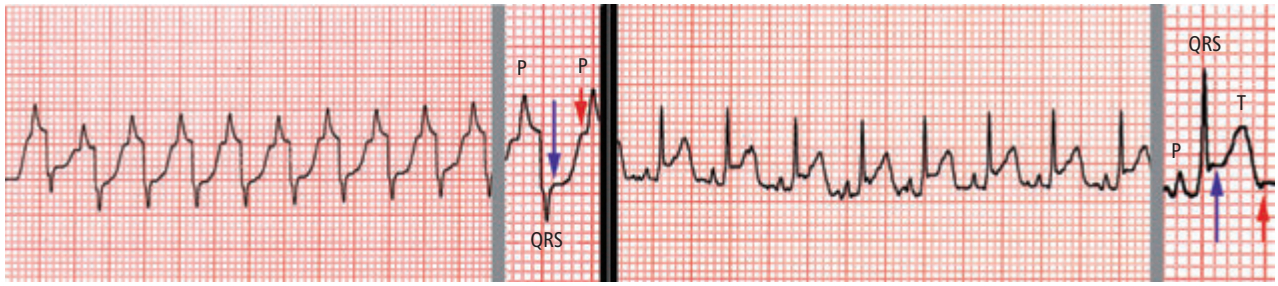


Figure 18.26. ST segment changes. Left panel: sinus tachycardia (heart rate = 220 beats/minute) with extreme ST segment depression in this cat under general anesthesia that had just received intravenous meperidine. The J point (blue arrow; end of the QRS complex) should be at the same vertical level as the tail of the T wave and baseline (red arrow). 25 mm/sec, 1 cm = 1 mV. The changes resolved spontaneously. Right panel: sinus tachycardia (heart rate = 170 beats/minute) with moderate ST segment elevation in this cat with mild, compensated hypertrophic cardiomyopathy. 25 mm/sec, 1 cm = 1 mV.

with further increases in serum potassium concentration comes increasing widening of the QRS complex and the T wave (see Figure 18.25), which may blend into a sine-wave type of regular but poorly functional rhythm, or a ventricular-type of escape rhythm at a very low rate. Either of these can be pre-agonal rhythms. If not corrected immediately, critical hyperkalemia producing these dramatic ECG changes can cause cardiac arrest (ventricular fibrillation, escape rhythm with pulseless electrical activity) at any time.

Hypocalcemia

Low serum calcium concentrations have modest and often clinically insignificant cardiac effects; instead, the skeletal muscle effects dominate the clinical picture. Altered calcium concentrations affect the threshold of a myocyte's action potential, rather than the resting membrane potential as does potassium. Hypocalcemia lowers the threshold, facilitating depolarization. The clinical expression is fine muscle fasciculations progressing to generalized tremors if calcium is not normalized. This effect is minimal in cardiomyocytes. Hypocalcemia also prolongs the initial phase of ventricular repolarization, which can manifest as a prolongation of the QT interval on the ECG.

These effects help explain why intravenous calcium infusions are considered "cardioprotective" in severe hyperkalemia, even though they do not change the serum K^+ concentration. Hyperkalemia raises the resting membrane potential, and providing additional calcium raises the threshold for depolarization, reestablishing a more normal ionic gradient across the cell membrane. Considering that 75% of cats with urethral obstruction concurrently have mild, moderate, or severe hypocalcemia (Drobatz and Hughes 1997), IV calcium gluconate (usually 10% solution [100 mg/ml]; administer 50–200 mg/kg slow IV infusion over several minutes with constant ECG monitoring) appears to be the preferred

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first-line treatment for severe hyperkalemia in these patients. This way, both the hyperkalemia and hypocalcemia are addressed simultaneously. When infusing calcium intravenously, ECG changes attributed to hypercalcemia (notably shortening of the QT interval and sudden slowing of the sinus rate), lip-smacking, or restlessness can be used as markers of excessively rapid infusion, and are grounds for stopping the infusion and resuming later if necessary. Here, as with hyperkalemia, serial ECGs are particularly valuable because baseline ECG recordings obtained at admission can be compared to ECG recording obtained during hospitalization, allowing the clinician to determine whether the patient's parameters are changing during treatment compared to his or her own baseline.

Hypercalcemia

Similarly, hypercalcemia generally is of greater concern for its extracardiac effects than for any alterations in cardiac rhythm. Severe hypercalcemia raises the threshold of the cardiomyocyte, which should hinder depolarization. It also shortens early ventricular repolarization, making the QT interval shorter. These consequences of severe hypercalcemia are of secondary concern compared to dystrophic mineralization of the kidneys and other soft tissues, for example.

MORPHOLOGIC ECG ABNORMALITIES

Axis

The mean electrical axis and its deviations are discussed in Chapter 9.

Electrical Alternans

The pattern of alternating R wave height known as *electrical alternans* is classically associated with pericardial effusion. The alternating short-tall QRS complexes are attributed to the change in mean electrical axis associated with the swinging motion of the heart in a fluid-filled pericardium. Differentials include ECG filtration, intraventricular conduction abnormalities, and the Brody effect(Côté 2010). In the cat, the occurrence of pericardial effusion is less common than in the dog, and the small feline QRS complex means that changes in amplitude need to be substantial to be visible. For these reasons, electrical alternans is rarely documented in cats.

Small QRS Complex Amplitude

A decrease in QRS amplitude may be noted as a result of pleural or pericardial effusion, or in association with obesity, hypothermia, hemorrhage, hypothyroidism, and intrathoracic mass in other species (Côté 2010). QRS complexes may indeed become smaller as a result of such disturbances, but the normally small QRS complexes of many cats makes this finding of little value unless the change is observed in serial ECGs from the same patient. Even then, care must be taken to rule out technical factors, especially limb position and ECG filters, either of which can artifactually reduce R wave amplitude.

P Pulmonale/P Mitrale

P wave enlargement is recognized as an indicator of atrial enlargement. An unusually tall P wave (>0.2 mV in lead II in the cat), termed *P pulmonale*, or an unusually wide P wave (>0.04 sec in the cat), termed *P mitrale*, suggest the presence of right or left atrial enlargement, respectively. The mechanism consists of a larger myocardial mass generating a greater amount of electrical activity toward the positive pole of a lead (P pulmonale), a larger mass of myocardium deviating the atrial axis and requiring a longer period of time to complete depolarization (P mitrale), or a combination of both. In cats, criteria for sensitivity and specificity of these findings are not established, such that the association between such ECG findings and the corresponding change in atrial structure is loosely defined. In clinical practice, the value of excessively tall or wide P waves in cats is that either finding should prompt the suspicion of atrial enlargement, which justifies an echocardiogram.

ST Segment Depression/Elevation

The ST segment refers to the part of the ECG that extends from the end of the QRS complex (the junctional or "J" point) to the beginning of the T wave. It should be horizontal, flat, and at the same height as the baseline and PR segment. A vertical shift of the ST segment of more than 0.1 mV away from baseline levels is referred to as ST segment shift, and specifically as ST elevation or depression depending on the direction of displacement of the ST segment (Figure 18.26).

The basis for ST segment change is myocardial hypoxia, because a hypoxic state causes myocardium to repolarize unevenly. Specifically

> Under normal conditions, the ST segment is usually nearly isoelectric because virtually all healthy myocardial cells attain approximately the same potential during early repolarization—that is, during the plateau phase of the ventricular action potential. Ischemia, however, has complex time-dependent effects on the electrical properties of myocardial cells. Severe acute ischemia can reduce membrane potential, shorten the duration of the action potential in the ischemic area, and decrease the rate of rise and amplitude of phase 0. These changes cause a voltage gradient between normal and ischemic

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Figure 18.27. Ventricular preexcitation. **(A)** In this 6-year-old male domestic short-haired cat, transition from normal atrioventricular conduction (left half of upper panel) to ventricular preexcitation (right half of upper panel) occurred intermittently and without clinical signs. Note the loss of a PR segment, with blending of the P wave directly into the upstroke of the QRS complex, during preexcitation (inset). A delta wave was not apparent in any lead. Normal sinus rhythm, 130 beats/minute. 25 mm/sec, 1 cm = 1 mV. **(B)** Rarely, tachycardia was observed, the ECG features of which are consistent with macro reentry (the Wolff-Parkinson-White syndrome): the tracing shows this cat's long PR, short RP tachycardia at a rate of 320 beats/minute (note paper speed doubled compared to upper tracing: 50 mm/sec, 1 cm = 1 mV). No clinical signs were observed, and although mild left atrial and ventricular dilation were observed echocardiographically, this cat was free of clinical signs for at least 3 years until lost to follow-up. Tracings courtesy of Dr. Stephen Ettinger, California Animal Hospital Veterinary Specialty Group, Los Angeles, CA.

zones that leads to current flow between these regions. These currents of injury are represented on the surface ECG by deviation of the ST segment (Mirvis and Goldberger 2008).

This principle is based on regional or uneven zones of ischemia, which is likely to occur even in the absence of coronary artery disease according to several mechanisms, including coronary vasospasm, regional variations in myocardial blood flow, and heterogeneity of myocardial thickness.

In feline practice, ST segment changes are important because they can constitute a marker for myocardial hypoxia. ST segment changes in cats may be an expression of a systemic state (e.g., hypoxemia due to airway disease, anemia, methemoglobinemia) or of a localized myocardial hypoxia due to cardiomyopathy, secondary cardiac hypertrophy, myocardial toxicity, or other cardiac disturbance. ST segment changes may be present at rest if there is an ongoing hypoxia-inducing disorder, or they may develop during states of greater myocardial oxygen demand such as anxiety, exercise, or general anesthesia. In the latter case, ST segment changes may be the first marker of iatrogenic hypoxemia, and this valuable ECG clue must lead to immediate troubleshooting of the anesthetic circuit: assurance that the pop-off valve is open; assurance that oxygen is flowing (assess flow meter, ensure that oxygen remains present in oxygen tanks and an oxygen tank valve is open and flowing); and assurance that the endotracheal tube is not obstructed by respiratory secretions (especially common and hazardous in cats with endotracheal tube diameter <4.0 mm), kinked, or inserted an excessive distance such that a bronchus is cannulated. ST segment changes—and the attendant myocardial hypoxia—are reversible if the inciting cause is identified and corrected with appropriate speed.

J Wave/Osborn Wave

Abnormal ventricular repolarization may distort the shape of the second half of the QRS complex (Côté 2010). This finding, called a *J wave* or *Osborn wave*, is typically associated with hypothermia in other species but not in the cat. Hypothermia may cause T wave alter-

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nans (Maisenbacher and Adin 2006) or transient third-degree AV block (Kellum and Stepien 2006) in cats, but J/Osborn waves have not been described.

U Wave

A very small wave following the T wave, notably in cases of severe hypokalemia, is called the U wave. It is noted very infrequently in cats (Atkins 1991) even with severe hypokalemia, perhaps at least in part due to the small amplitude of feline ECG deflections in general. Aberrant repolarization of Purkinje fibers, the long action potential of midmyocardial (M) cells, or delayed repolarization in areas of the ventricle that undergo late mechanical relaxation are mechanisms that have been proposed to explain its existence (Mirvis and Goldberger 2008). Clinically in the cat, identification of U waves should simply prompt confirmation of hypokalemia and appropriate treatment of the electrolyte deficit.

T Wave Alternans

Abnormal ventricular repolarization may manifest as an alteration in the appearance of the T wave. In one cat, profound hypothermia (32°C [91°F]) produced marked prolongation of the QT interval (320 msec, compared to 200 msec when the cat was subsequently normothermic) and T wave alternans—a pattern of alternating tall and wide versus narrow and short T waves (Maisenbacher and Adin 2006). These ECG abnormalities resolved with correction of hypothermia. T wave alternans also has been documented in experimental cats undergoing electrical stimulation of the stellate ganglion (Schwartz and Malliani 1975). T wave alternans, and more recently, microvolt T wave alternans, is a negative prognostic indicator in humans with coronary artery disease (greater risk of sudden cardiac death), but such an association is not recognized in the cat.

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SECTION G

Congestive Heart Failure

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19

Congestive Heart Failure

DEFINITIONS

Key Points

- Congestive heart failure is a clinical syndrome that occurs secondary to severe heart disease of many causes, including those that cause severe diastolic dysfunction (e.g., hypertrophic cardiomyopathy or restrictive cardiomyopathy), systolic myocardial failure (e.g., dilated cardiomyopathy), or volume overload secondary to valvular insufficiency or left to right shunting congenital heart diseases (e.g., ventricular septal defect).
- Backward heart failure consists of congestion and edema.
- Forward heart failure (i.e., low output heart failure) consists of low cardiac output, arterial hypotension, and poor peripheral perfusion.
- Left heart failure in cats is characterized by pulmonary edema and/or pleural effusion.
- Right heart failure is characterized by pleural effusion with or without ascites or mild pericardial effusion.

INTRODUCTION

Heart failure is a clinical syndrome caused by the inability of the heart to function within normal diastolic filling pressures, which leads to congestion/edema (i.e., backward failure) or poor peripheral perfusion (i.e., forward heart failure) at rest or with exercise (Kittleson 1994). Previous definitions focused on the inability of the heart to pump, which is only one small fraction of the causes of heart failure in animals. Heart failure may be a result of severe diastolic dysfunction, systolic myocardial failure, or volume overload from valvular insufficiency or left to right shunting congenital heart diseases. Most heart failure in cats is clinically identified as backward failure (i.e., "wet"; congestive), versus forward "low output" failure (i.e., "cold"), because the body prioritizes maintenance of normal systolic blood pressure over maintenance of normal capillary pressure. Since an overwhelming majority of cats with heart failure present with clinical signs of congestive heart failure (CHF) rather than low output heart failure, the majority of the chapter will refer to CHF unless specifically stated as low output heart failure. CHF may be left-sided (pulmonary edema ± pleural effusion), right-sided (pleural effusion ± ascites), or a combination of both (Figure 19.1). Low output heart failure occurs when cardiac output is so severely decreased that there is poor tissue perfusion and arterial hypotension. It is uncommon in cats and is often seen as a terminal event, unless precipitated by an acute transient tachycardia or bradycardia.

CHF is the end result of severe cardiac disease; however, many cats may have heart disease and never develop heart failure. There are many diseases that can lead to CHF in cats, and the majority cause diastolic heart failure (Figure 19.2). Diastolic heart failure is caused by impaired diastolic filling that leads to elevated diastolic filling pressure, in the face of normal systolic function. The ventricles are able to contract normally, but they cannot normally accept the diastolic inflow of blood within normal pressures (i.e., the heart is stiff or cannot relax), which leads to a backward transmission of elevated venous pressure to the capillary bed and ultimately leakage of fluid through the capillary wall to cause edema or effusion. Hypertrophic cardiomyopathy (HCM), unclassified cardiomyopathy (UCM), and restrictive cardiomyopathy (RCM) are all diseases that cause diastolic dysfunction that may lead to CHF.

Systolic myocardial failure may lead to "pump" failure and subsequent increases in diastolic filling pressure. Diseases causing systolic myocardial failure are less

Feline Cardiology, First Edition. Etienne Côté, Kristin A. MacDonald, Kathryn M. Meurs, Meg M. Sleeper.
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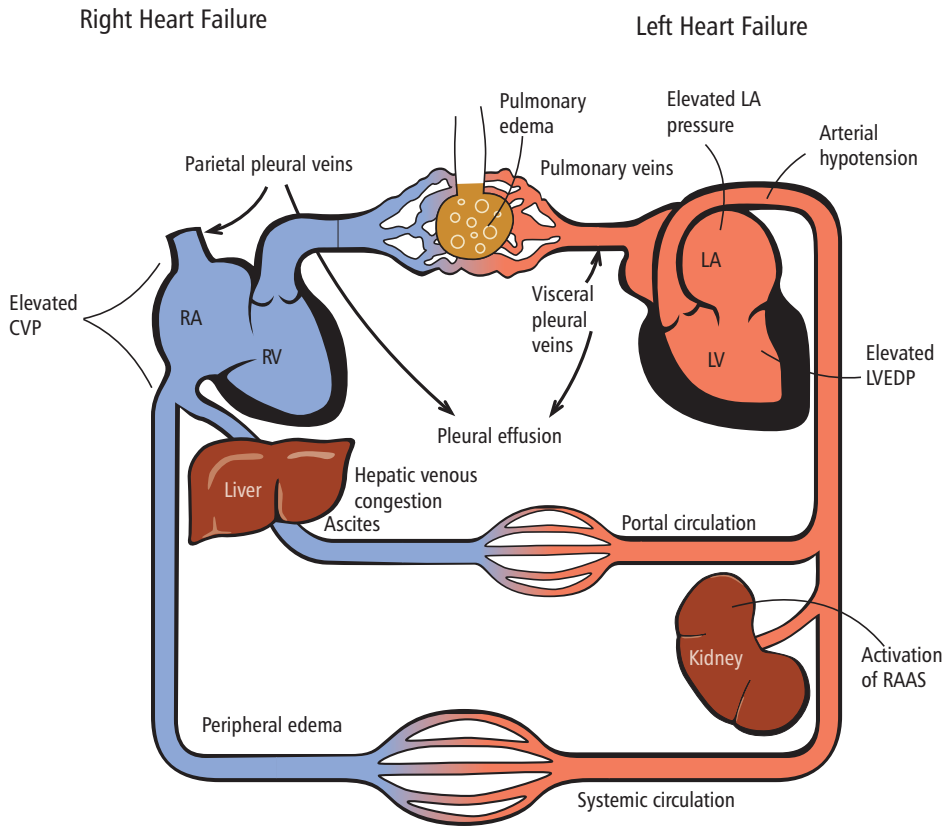


Figure 19.1. Pathophysiology of left and right heart failure. Left heart failure is the end result of severe left heart disease of many etiologies. Pulmonary edema forms when the left ventricular end-diastolic pressure (LVEDP) exceeds 25 mm Hg, and ascites or pleural effusion develops when right ventricular end-diastolic pressure exceeds 10–15 mm Hg. In cats, pleural effusion may develop secondary to left heart failure, likely because visceral pleural veins drain into the pulmonary veins, or secondary to right heart failure since the thoracic duct and parietal pleural veins empty into the cranial vena cava. In addition to elevated diastolic pressure, cardiac output decreases, which causes arterial hypotension and activation of the sympathetic nervous system and the renin angiotensin aldosterone system (RAAS).

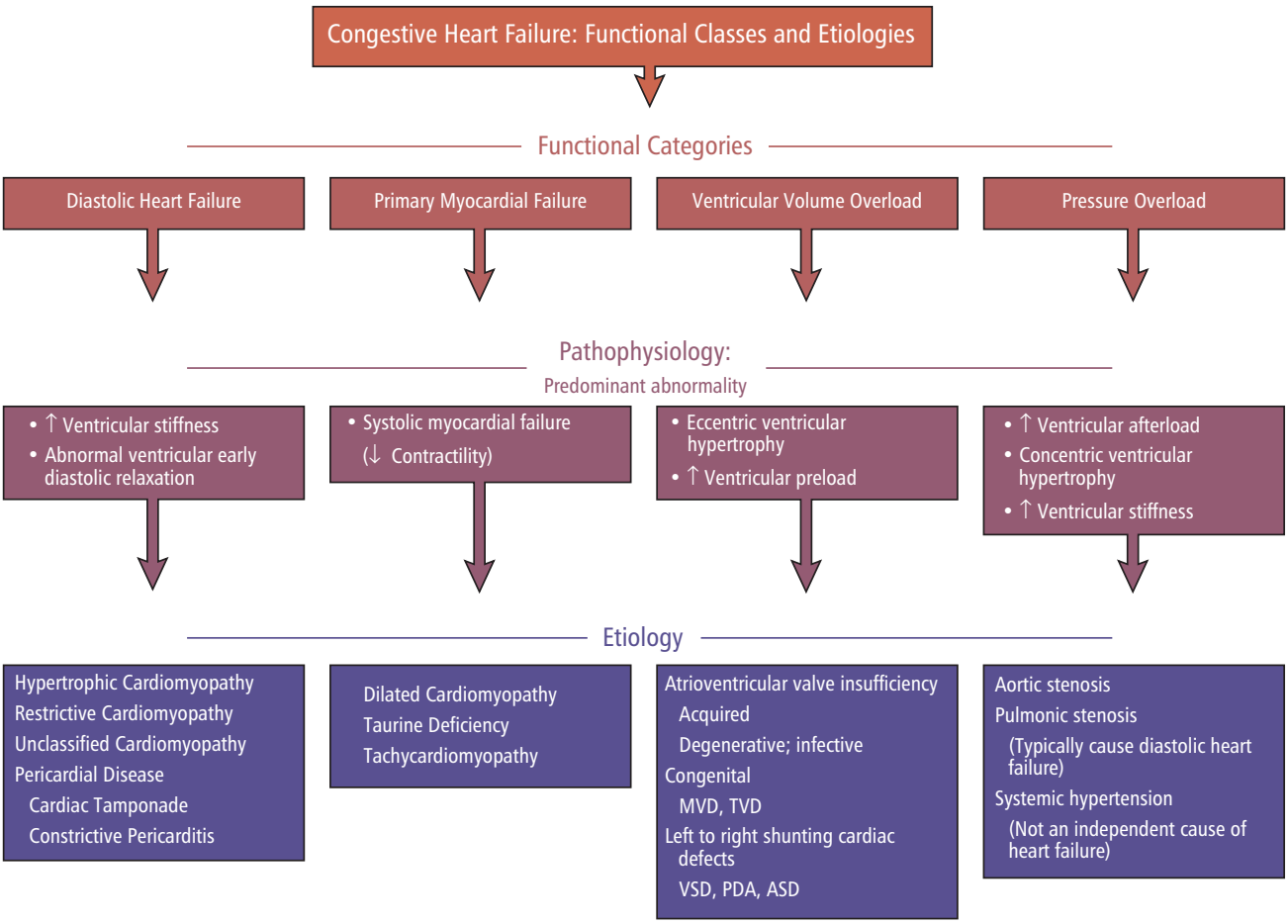
common in cats and include dilated cardiomyopathy (DCM) or arrhythmogenic right ventricular cardiomyopathy (ARVC) (see Figure 19.2). Ventricular volume overload caused by valvular insufficiency or left to right shunting congenital heart defects (e.g., ventricular septal defect) may also lead to elevated diastolic filling pressure and development of CHF (see Figure 19.2).

Incidence/Prevalence of the Disorder

Key Points

- HCM is the most common cause of heart disease and heart failure in cats. CHF occurs in one-third to one-half of cats with HCM. Pulmonary edema is the most common cause of dyspnea in cats with HCM and CHF.
- Biventricular (left- and right-sided) heart failure is present in nearly all cats diagnosed with DCM and consists of pleural effusion (91%), ascites (55%), and pulmonary edema (36%).
- Heart failure is present in slightly over half of cats with unclassified or restrictive cardiomyopathy. Pleural effusion is more common than pulmonary edema in these patients.

The vast majority of information about congestive heart failure in cats has been derived from retrospective case series that have described CHF in hundreds of cats with naturally occurring heart disease, although prevalence in the overall feline population is unknown. HCM is the most common heart disease in cats, and CHF occurs in one-third to one-half of these cats (Rush et al. 2002; Ferasin et al. 2003). Conversely, approximately one-half to two-thirds of affected cats will not develop congestive heart failure. Half of cats diagnosed with CHF second-



MVD, mitral valve dysplasia; TVD, tricuspid valve dysplasia; VSD, ventricular septal defect; PDA, patent ductus arteriosus; ASD, atrial septal defect

Figure 19.2. Algorithm of Functional Categories and Etiologies of Congestive Heart Failure in Cats.

ary to HCM have identifiable precipitating events, including fluid administration, anesthesia and surgery, or recent corticosteroid administration (Depo-medrol or long-acting triamcinolone) 1–2 weeks prior to heart failure development (Rush et al. 2002). Pulmonary edema is more common than pleural effusion in cats with CHF due to HCM, and is seen in 32–66% of cats diagnosed with HCM, although longitudinal studies of the incidence of CHF in cats with HCM over time have not been conducted (Rush et al. 2002; Atkins et al. 1992). Dyspnea is attributed to pulmonary edema in 80% of cats with CHF due to HCM, compared to only 14% of cats that are dyspneic from pleural effusion (Rush et al. 2002). All cats (11/11) diagnosed with idiopathic DCM present with clinical signs of CHF, which consist of pleural effusion (91%), ascites (55%), and pulmonary edema (36%) (Ferasin et al. 2003). Similarly, 84% (31/37) of cats diagnosed with taurine deficiency induced myocardial failure have clinical evidence of heart failure (Pion et al. 1992). Over half (55%) of cats diagnosed with RCM present with clinical signs of CHF, characterized mostly by pleural effusion (55%), followed by pulmonary edema (41%) and ascites (23%). Similarly, a majority (64%) of cats diagnosed with unclassified cardiomyopathy present with clinical signs of CHF, including pleural effusion (50%) and pulmonary edema (9%)l (Ferasin et al. 2003). The prototypical disease of right heart failure is ARVC. A majority of cats with ARVC present with clinical evidence of right-sided heart failure (67%), including pleural effusion (67%) and ascites (33%) and dilated caudal vena cava (17%). It is interesting to note that pleural effusion was much more common than ascites in cats with right heart failure secondary to ARVC. It is possible that there is a contribution of left-sided heart failure, because cats often have concurrent left atrial dilation in this disease (5/8 cats with mild left atrial dilation, 3/8 cats with severe left atrial dilation) (Fox et al. 2000).

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PATHOPHYSIOLOGY AND GROSS PATHOLOGY

Key Points

- Left heart failure is caused by elevated left ventricular diastolic pressure and subsequent increased pulmonary capillary pressure, typically over 25 mm Hg.
- Radiographically, pulmonary edema initially develops as patchy interstitial infiltrates and progresses to alveolar flooding.
- Pleural effusion can develop in cats secondary to elevated pulmonary capillary pressure in left heart failure and may be due to increased hydrostatic pressure in the visceral pleural veins that drain into the pulmonary veins.
- Right heart failure develops when the right ventricular diastolic pressure, right atrial pressure, and central venous pressure exceed 10–15 mm Hg. Right heart failure consists of pleural effusion, jugular venous distension, and often ascites or mild pericardial effusion not severe enough to cause cardiac tamponade.
- Low output heart failure is caused by severely reduced cardiac output. Clinical sequelae include signs of poor tissue perfusion and arterial hypotension.
- Diastolic heart failure is caused by many cardiac diseases that impair diastolic relaxation and increase left ventricular stiffness, which increase left ventricular diastolic filling pressure.
- Systolic heart failure is caused by a decrease in myocardial contractility, which decreases stroke volume and cardiac output. The most important cause of myocardial failure in cats is idiopathic DCM.
- Diseases that cause left ventricular volume overload include abnormalities of the mitral valve, left to right shunting congenital heart diseases, or aortic valve insufficiency. In response to decreased effective stroke volume, renin-angiotensin-aldosterone system (RAAS) activation increases circulatory blood volume, which increases preload (i.e., diastolic wall stress) of the left ventricle.
- Activation of the sympathetic nervous system is an acute compensatory mechanism in heart failure, which increases heart rate and contractility via beta receptor stimulation, and increases blood pressure by alpha receptor stimulation and arteriolar vasoconstriction. This response is short-lived (2–3 days) due to beta receptor uncoupling and down-regulation.
- Activation of RAAS is an important chronic compensatory mechanism in heart failure, which increases sodium and water retention via aldosterone and antidiuretic hormone, and causes arteriolar vasoconstriction through increasing circulating levels of angiotensin II, antidiuretic hormone (vasopressin), and endothelin-I. In animals with ventricular volume overload (e.g., as a result of mitral regurgitation), left ventricular eccentric hypertrophy develops in response to increased diastolic wall stress, which further worsens myocardial failure.
- Chronic deleterious effects of sympathetic stimulation include tachycardia, increased afterload, increased myocardial oxygen demand, and potentially toxic myocardial effects such as apoptosis and fibrosis.
- Chronic activation of the renin-angiotensin-aldosterone system promotes ventricular volume overload and progressive backward heart failure, excessive vasoconstriction, and adverse myocardial remodeling including hypertrophy and fibrosis.
- Pharmacologic antagonists of RAAS and the adrenergic nervous system may be used to lessen their chronic deleterious effects on the circulatory system.

Congestive Heart Failure

Left heart failure

CHF develops when there is increased capillary hydrostatic pressure that overwhelms the lymphatic system's removal capability. Pulmonary edema develops due to an imbalance of hydrostatic and osmotic forces between the capillaries and the interstitium. The Starling equation defines the factors of fluid filtration as follows:

$$J_V = K_f \ [\Pi_\chi - \Pi_{\iota\Phi} - \delta(\Pi_\chi - \Pi_{\iota\Phi})]$$

where J_v is the fluid filtration, K_f is the membrane fluid filtration coefficient, Π_χ is capillary pressure, $\Pi_{\iota\Phi}$ is interstitial pressure, δ is the membrane reflection coefficient to protein, Π_χ is oncotic capillary pressure, and $\Pi_{\iota\Phi}$ is interstitial fluid oncotic pressure (Guyton and Lindsey 1959). There is normally a slow fluid filtration (J_v) from the pulmonary capillaries into the interstitium, that is removed by lymphatic drainage into the thoracic duct. During left heart failure, the left ventricular diastolic pressure, left atrial pressure, pulmonary venous pressure, and pulmonary capillary pressure increase, which leads to increased accumulation of fluid in the pulmonary interstitium (see Figure 19.1). Lymphatic drainage compensates to remove the excessive interstitial fluid, and can increase lymphatic flow by tenfold above baseline. Lymphatic flow increases over the first 4 hours of elevated pulmonary capillary pressure to achieve a new steady state of fluid balance. This provides an "edema safety factor" so pulmonary edema does not occur until the pulmonary capillary pressure increases to ~25 mm Hg. Pulmonary edema initially develops as interstitial fluid accumulation that progresses to alveolar flooding and alveolar edema when there is severe fluid accumulation.

When there is chronically elevated left atrial pressure and chronic interstitial edema, connective tissue is

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deposited into the interstitial space. This connective tissue absorbs some of the excess fluid and reduces $\Pi_{i\Phi}$, which favors increased fluid filtration into the interstitium. Lung mechanics are adversely affected by increased lung fluid weight as well as decreased compliance due to fibrosis (Drake and Doursout 2002). In response to chronic left heart failure, the pulmonary venules, arterioles, and alveolar membrane hypertrophy, which reduces diffusion capacity and impairs oxygenation (Guazzi 2000).

Contrary to dogs, cats may develop pleural effusion secondary to elevated left atrial pressure. Similar to man, the visceral pleural veins in cats drain into the pulmonary veins, and the parietal pleural veins drain into the cranial vena cava (McLaughlin et al. 1961). Therefore, elevated pulmonary venous pressure from left heart failure may impair visceral pleural venous drainage and lead to accumulation of pleural effusion. Most often, there is accumulation of pulmonary edema as well as pleural effusion in cats with left heart failure. Pulmonary arterial hypertension and right atrial hypertension are not necessary for development of pleural effusion in people, but elevated pulmonary capillary wedge pressure is strongly associated with development of pleural effusion (Wiener-Kronish et al. 1987). This is likely the same in cats.

Right heart failure

Ascites and pleural effusion are sequelae to increased right ventricular diastolic pressure, right atrial pressure and right heart failure (see Figure 19.1). Compared to the pulmonary capillaries, the hepatic sinusoids have larger gaps that promote fluid filtration at less severe elevations in pressure. Right heart failure develops once the right atrial and central venous pressures exceed 10–15 mm Hg (Gookin and Atkins 1999). Hepatic venous distension is a consistent abnormality seen in cats with ascites secondary to right heart failure, and may be visualized on ultrasound of the liver. Isolated right heart failure is uncommon in cats, since they often develop concurrent left- and right-sided heart disease. In a large case series of cats with ascites, 29% had right heart failure as a cause of the effusion (Wright et al. 1999). Concurrent pleural effusion is present in a majority of cats (89%) with ascites from right heart failure (Wright et al. 1999).

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine that may contribute to cardiac cachexia, ventricular dysfunction, myocarditis, myocardial fibrosis, and heart failure. TNF-α concentration was elevated in nine of 20 cats with right heart failure, and one of six cats with left heart failure (Meurs et al. 2002). Right heart failure often leads to significant cardiac cachexia, and the mechanism may involve elevated TNF-α concentration. Future areas of interest may involve investigating potential pathophysiologic mechanisms of TNF-α in feline heart failure, and the potential for pharmacologic therapeutic intervention.

Low output heart failure

Low output heart failure (forward heart failure) occurs when there is severely decreased cardiac output and poor tissue perfusion. Usually the diagnosis is made once there is severe end-stage cardiac disease. Presenting complaints often include exercise intolerance, lethargy, and fatigue. Severe weakness, cold extremities, pale mucous membranes, delayed capillary refill time, hypothermia, and hypotension are all clinical features of low output heart failure. Low cardiac output decreases tissue oxygen delivery, yet tissue extraction remains the same, leading to decreased venous oxygen tension (PvO_2). Anaerobic metabolism occurs when the PvO_2 is critically low (<24 mm Hg), and results in hyperlactatemia and acidosis. Cardiogenic shock is rare, and consists of severe arterial hypotension related to a dramatic reduction in cardiac output, and is most often seen in cases of acute heart failure such as infective endocarditis.

Diastolic heart failure

Diastolic heart failure occurs when there is normal systolic function and concurrently increased ventricular diastolic filling pressure. It is diagnosed when there are clinical signs of heart failure in the absence of significant myocardial failure, diseases causing ventricular volume overload such as valvular insufficiency or left to right shunting congenital defects, or pericardial disease. Given the high prevalence of feline cardiomyopathies that impair diastolic function (e.g., hypertrophic cardiomyopathy and restrictive cardiomyopathy), diastolic heart failure is the most common cause of heart failure in cats.

Diastole is divided into an active phase of isovolumic relaxation, early rapid filling, passive filling (diastasis), and atrial contraction (Figure 19.3). Rapid early filling accounts for approximately 80% of the end-diastolic left ventricular volume. Impaired diastolic function can be divided into two main categories: impaired active diastolic relaxation and decreased ventricular compliance. Although discussed as two separate categories, there are interplays and links in the pathophysiologic processes that lead to global diastolic dysfunction and elevated diastolic filling pressures.

Active relaxation occurs when calcium dissociates from troponin C and is sequestered by the sarcoplasmic reticulum-calcium ATPase pump (SERCA) into the sarcoplasmic reticulum. Altered levels or activity of

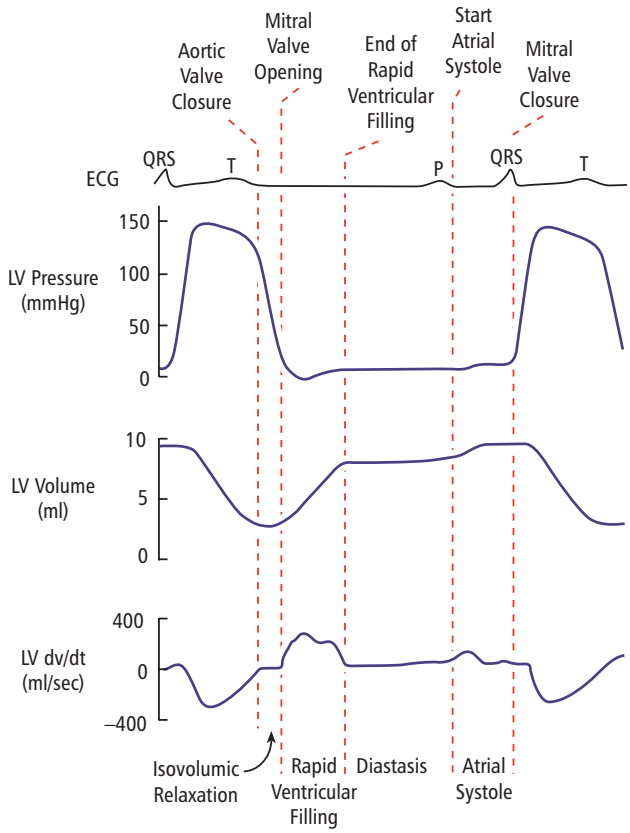


Figure 19.3. Phases of diastole defined by the Wiggers diagram of left ventricular pressure, volume, and rate of change of volume. The four phases of diastole include isovolumic relaxation, rapid ventricular filling, diastasis (passive ventricular filling), and atrial systole. Isovolumic relaxation is an active process, where the left ventricular pressure exponentially declines. The majority of left ventricular filling occurs during the early rapid filling phase. Diastasis occurs when the left atrial and ventricular pressures equilibrate. Atrial systole contributes the remaining 10% of filling to the left ventricle. dv/dt = time derivative of volume (i.e., rate of change of volume); ECG = electrocardiogram ; LV = left ventricular.

SERCA or increased SERCA inhibitory protein (phospholamban) leads to increased cytosolic calcium and inhibition of relaxation due to the continued actin-myosin bond. Abnormalities of SERCA and calcium handling have been demonstrated in cardiac hypertrophy and myocardial ischemia. Enhanced calcium sensitivity of the myofilaments may also impair diastolic relaxation and has been demonstrated in models of familial HCM (Marian et al. 2001). Tachycardia in the face of defective calcium handling leads to marked calcium overload because there is less time for SERCA-mediated sequestration of calcium. Calcium overload perpetuates this vicious circle of diastolic dysfunction. Myocardial ischemia also impairs calcium handling and relaxation. Subendocardial ischemia occurs in HCM and many other heart diseases and may be due to intramural coronary arteriosclerosis or compression of small coronary arteries by concentric hypertrophy and/or increased left ventricular filling pressure (Shyu et al. 2002; Kyriakidis et al. 1997; Cannon et al. 1985). ATP hydrolysis is required for several stages of the relaxation process, including dissociation of actin and myosin, calcium dissociation from troponin C, and sequestration of calcium by SERCA into the sarcoplasmic reticulum. Ischemia leads to greater cytosolic ADP and less ATP, which prolongs relaxation (as well as impairs systolic function). In summary, impaired relaxation is caused by altered calcium handling due to abnormal SERCA activity or level, enhanced myofilament sensitivity to calcium, or myocardial ischemia. Impaired or delayed relaxation not only negatively impacts early diastole, but increases myocardial stiffness through the continuing interaction of contractile elements and persistent development of myocardial tension (Grossman and Barry 1980).

Ventricular compliance is determined by extent of ventricular mass and myocardial composition. Stiffness is the inverse of compliance. Myocardial determinants of stiffness include changes in the extracellular matrix composition or isoform switches in cytoskeletal proteins (titin) and myofilaments. The main component of the cardiac extracellular matrix is collagen (Types I and III). Type I collagen has the tensile strength of steel and is more abundant than type III collagen in the normal heart (7.4:1 ratio). Myocardial fibrosis occurs due to increased synthesis of collagen and decreased degradation of collagen caused by up-regulation of tissue inhibitor of matrix metalloproteinase. Collagen synthesis is stimulated by profibrotic signals from the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, inflammatory cytokines (i.e., transforming growth factor and tumor necrosis factor), and growth factors such as insulinlike growth factor (Ouzounian et al. 2008). Angiotensin II and aldosterone have been shown to induce myocardial hypertrophy and fibrosis in vitro and in vivo (Sadoshima and Izumo 1993; Brilla et al. 1993; Tsybouleva et al. 2004). Both angiotensin II and aldosterone increase collagen synthesis in cultured adult cardiac fibroblasts, which is prevented by treatment with an angiotensin II type I receptor antagonist or aldosterone receptor antagonist (Brilla et al. 1994). Likewise, aldosterone increases hypertrophy in rat myocytes, and increases collagen and transforming growth factor–β1 expression in rat cardiac fibroblasts (Tsybouleva et al. 2004). Titin is a gigantic sarcomeric protein that functions as a molecular spring and is responsible for the majority of diastolic tension. Isoform switches from the larger more compliant titin form (N2BA) to the smaller and stiffer form (N2B) have been found in people with diastolic heart failure (van Heerebeek et al. 2006). It is unknown whether there are

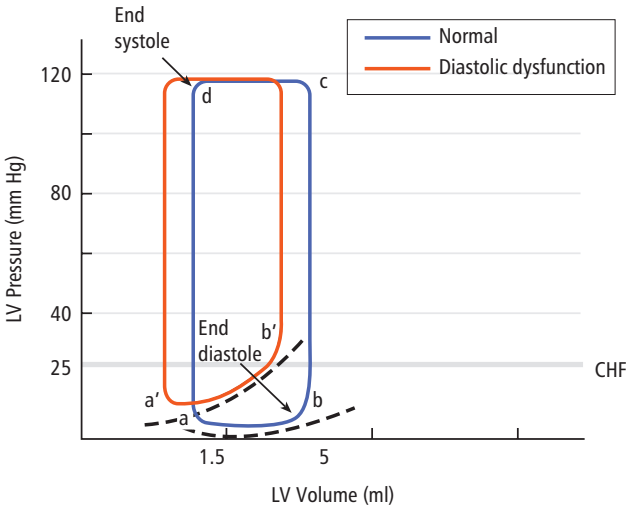


Figure 19.4. Left ventricular pressure volume curve of a normal cat and a cat with hypertrophic cardiomyopathy and diastolic dysfunction.
The pressure volume curve of a normal cat begins at end-systole (a [blue curve]). The left ventricle is compliant, with low pressure at end-diastole (b). Isovolumetric contraction is represented from points b to c, systole occurs from c to d, and isovolumetric relaxation occurs from points d to a. The left ventricle of a cat with HCM or other disease causing severe diastolic dysfunction is stiff, and the end-diastolic pressure volume relation is shifted upward and to the left (dashed line: a′ to b′) with a high end-diastolic pressure. End-systolic volume is decreased due to reduction in left ventricular wall stress, and end-diastolic volume (b′) is decreased due to left ventricular concentric hypertrophy encroaching on the chamber lumen. The grey line represents the threshold for congestive heart failure (CHF); if the end-diastolic pressure (b′) is above this threshold, CHF is likely.

isoform switches in sarcomeric proteins in cats with diastolic heart failure.

Myocardial hypertrophy, fibrosis, and myocyte disarray (all hallmark histopathologic abnormalities in HCM) increase myocardial stiffness, which shifts the LV end-diastolic pressure volume relationship upward (i.e., increases the slope of the diastolic filling curve). For any given diastolic volume, the diastolic pressure in a stiff ventricle is greater (Figure 19.4). Once left ventricular diastolic pressure exceeds 25 mm Hg, left heart failure develops. Left ventricular concentric hypertrophy decreases systolic wall stress, which decreases end-systolic volume and shifts the left ventricular pressure volume curve to the left (Figure 19.4). Left ventricular end-diastolic diameter is also decreased due to the encroachment of the chamber by the thickened ventricular wall (Figure 19.4).

Systolic heart failure

Myocardial failure is defined as a decrease in myocardial contractility and is either primary (i.e., idiopathic dilated cardiomyopathy) or secondary. Idiopathic DCM is an inherent defect within the myocardium that leads to myocardial failure. Causative defects may occur within various regions of the cardiomyocyte, including the contractile sarcomeric proteins (affecting actin-myosin cross-bridge cycling), mitochondria (impairing energy production), cytoskeleton (disrupting the intracellular and intercellular scaffold and impairing force transmission), nuclear envelope, and transcriptional coactivator proteins (Maron et al. 2006). Secondary causes of myocardial failure include nutritional causes (taurine or carnitine deficiency), and diseases that lead to chronic pressure or volume overload of the ventricle (e.g., severe aortic stenosis or ventricular septal defect, respectively), and end-stages of other cardiomyopathies (e.g., HCM). In cats, the only recognized cause of primary myocardial failure is idiopathic DCM.

Systolic myocardial failure is characterized by reduced myocardial contractility, which decreases stroke volume and cardiac output. Myocardial failure causes the tangent (Ees) of the left ventricular end-systolic pressure-volume relation to flatten and increases end-systolic volume (Figure 19.5). Initially, end-diastolic volume is normal and end-systolic volume is increased, decreasing stroke volume. Cardiac output decreases, which leads to arterial hypotension and activates the sympathetic nervous system. Beta receptor stimulation increases heart rate and contractility, which increases cardiac output for a short time. Sympathetic nervous system activation increases arteriolar vasoconstrictor mediators, which normalize blood pressure, at the expense of increased afterload on the failing heart. After 24–72 hours of adrenergic activation, the cardiac beta receptors undergo down-regulation and uncoupling, and contractility decreases. A more sustained compensatory mechanism is needed to increase cardiac output. Theoretically, vasodilation and afterload reduction would allow the failing heart to increase stroke volume and cardiac output, but the top cardiovascular priority is to maintain normal blood pressure. Instead, chronic compensation in myocardial failure occurs by increasing circulating blood volume and preload through activation of RAAS. In response to increased preload, the left ventricle develops eccentric hypertrophy, which markedly increases end-diastolic volume and dramatically shifts the left ventricular pressure volume curve to the right (Figure 19.5). Stroke volume and cardiac output increase to near normal at the expense of a marked increase in diastolic wall stress. End-systolic volume and end-systolic wall stress are increased due to the myocardial failure and systemic arteriolar vasoconstriction. The final result is progressive myocardial failure (progressive flattening of Ees slope) and pathologic

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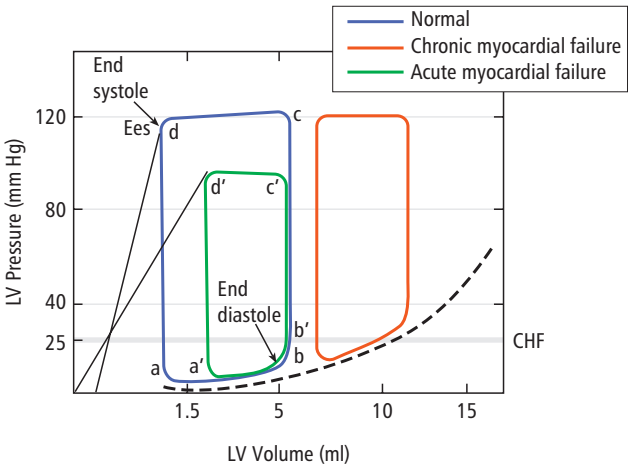


Figure 19.5. Left ventricular pressure volume curve of a normal cat and a cat with dilated cardiomyopathy. The pressure volume curve of a normal cat (blue line) is contrasted with the pressure volume curve of a cat with acute myocardial failure (green line). The slope of the end-systolic pressure volume relation line (Ees) represents contractility, and it is decreased with myocardial failure, which initially shifts the pressure volume curve downward and to the right. Acute myocardial failure causes a decrease in systolic pressure (c′) and hypotension, as well as increased end-systolic volume (d′) since less blood is ejected out during systole. Stroke volume is decreased (a′ to b′) and cardiac output falls, leading to arterial hypotension. Due to chronic compensatory mechanisms of heart failure, chronic myocardial failure (red line) is illustrated by marked chamber enlargement (eccentric hypertrophy and increased end-diastolic volume), marked increase in end-systolic volume, decreased Ees, and normalized stroke volume. The left ventricular pressure volume curve is shifted rightward, on the steeper slope of the normal end-diastolic pressure volume relation (dashed line); elevated end-diastolic pressures are above threshold (grey line) and consistent with congestive heart failure.

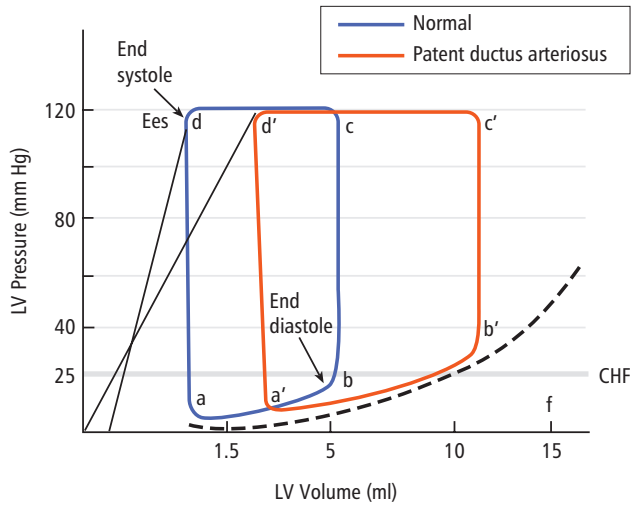


Figure 19.6. The pressure volume curve of a normal cat (blue line) is contrasted with the curve of a cat with a large left to right shunting patent ductus arteriosus (red line). The large left to right shunt causes severe left ventricular volume overload (increased end-diastolic volume, b′). There is secondary myocardial failure, which decreases Ees and increases the end-systolic volume (d′). The stroke volume (a′ to b′) remains high due to the marked volume overload and only mild myocardial failure. The left ventricular pressure volume curve is shifted rightward, on the steeper slope of the normal end-diastolic pressure volume relation (dashed line), leading to congestive heart failure.

ventricular remodeling with progressive ventricular enlargement.

Left ventricular volume overload and heart failure

Diseases that cause left ventricular volume overload include abnormalities of the mitral valve (mitral valve dysplasia, myxomatous degeneration, infective endocarditis, or systolic anterior motion of the mitral valve), left to right shunting congenital heart diseases (e.g., patent ductus arteriosus or ventricular septal defect), or aortic valve insufficiency. A quantity of total stroke volume is lost either backward into the left atrium (regurgitant volume), or in left to right shunting cardiac defects such as a PDA it is lost into the pulmonary artery, which decreases effective forward stroke volume. That is, the full volume of blood that leaves the ventricle does not reach the arterial circulation in its entirety. The reduced cardiac output triggers RAAS to increase sodium and water reabsorption, which increases circulating blood volume and ventricular preload (i.e., diastolic wall stress). The left ventricular response to increased diastolic wall stress is to replicate sarcomeres end-to-end and grow a larger left ventricular chamber. End-diastolic volume greatly increases, and forward stroke volume normalizes (Figure 19.6). Total stroke volume is very high, because systolic function is normal and the end-systolic volume is normal. This creates a high ejection fraction, and wall motion appears hyperdynamic. Left ventricular diastolic pressure increases secondary to the volume overload, and pulmonary edema (±pleural effusion in cats) develops once the diastolic pressure exceeds 25 mm Hg. Secondary myocardial failure may develop when there is chronically increased wall stress from severe volume overload of the left ventricle, especially in animals with a patent ductus arteriosus or aortic insufficiency (Figure 19.6). Myocardial failure causes an increase in end-systolic volume, which normalizes the previously high ejection fraction and decreases stroke volume. Myocardial failure is evidenced as a rightward shift of the left ventricular pressure volume curve and flattening of the Ees slope of the left ventricular end-

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systolic pressure volume relation (Figure 19.6). The systolic wall stress in mitral regurgitation may be less than in other causes of volume overload to the left ventricle such as a patent ductus arteriosus or aortic insufficiency, because blood leaks back into the low pressure left atrium prior to opening of the aortic valve and essentially "unloads" the left ventricle. This likely helps to preserve systolic function until end-stage heart failure occurs in animals with mitral regurgitation.

Compensatory Mechanisms in Heart Failure

Acute compensatory mechanisms in heart failure

Immediately following a cardiac insult, cardiac output and arterial blood pressure are reduced. Since the most important priority of the cardiovascular system is to maintain adequate arterial blood pressure, the high pressure baroreceptors are immediately activated and cause a reflex neuroendocrine feedback to activate the sympathetic adrenergic system. Stimulation of cardiac beta receptors increases heart rate (positive chronotropic effect) and contractility (positive inotropic effect) to immediately increase cardiac output. Alpha adrenergic receptors in the arterial vascular bed are stimulated to cause vasoconstriction, and blood volume is shunted from the periphery to the central compartment. This acute response is necessary to increase cardiac output and maintain perfusion to the critical organ beds of the heart, kidney, and brain. However, this immediate response is not able to compensate for more than a few days, and more chronic compensatory mechanisms are necessary for the animal to survive. After approximately 2–3 days of adrenergic activation, the beta receptors become down-regulated and uncoupled, which blunts the positive inotropic and lusitropic (i.e., relaxation) response of beta adrenergic stimulation.

Chronic compensatory mechanisms in heart failure

Activation of the renin angiotensin aldosterone system occurs when there is reduced renal blood flow, reduced delivery of sodium to the macula densa, and beta adrenergic stimulation of the juxtaglomerular apparatus. The classical system includes renin release from the juxtaglomerular apparatus, which cleaves angiotensinogen in the liver to angiotensin I, which is further cleaved by angiotensin converting enzyme (ACE) in the lungs or other tissues to form the active hormone angiotensin II (ATII). ACE also inactivates vasodilators such as bradykinin. ATII binds to the angiotensin II type 1 receptor (AT1R) to exert powerful effects of vasoconstriction, increases aldosterone synthesis from the adrenal gland, stimulates thirst, elicits vasopressin release from the pituitary, induces endothelin I synthesis, and increases sympathetic tone. Systemic vascular resistance is increased by imbalance of increased vasoconstrictors (ATII, vasopressin, endothelin-I, norepinephrine) and decreased vasodilators including nitric oxide, natriuretic peptides, and prostaglandins. The net effect of RAAS activation is maintenance of systemic organ perfusion by increased systemic vascular resistance and increased blood volume through sodium and water retention, which occur within several days of activation.

Increased blood volume (i.e., increased preload) stretches the cardiomyocytes, which stimulates them to replicate their sarcomeres end to end and elongate in a process called *eccentric hypertrophy*. The left ventricle chamber grows larger (i.e., increased end-diastolic diameter and volume), which increases stroke volume and cardiac output. In chronic diseases of ventricular volume overload (i.e., myocardial failure, valvular insufficiency, and left to right shunts), end-diastolic volume can be increased by as much as 200%, but at the expense of increased diastolic filling pressure and the development of congestive heart failure. Volume overload also leads to altered chamber geometry with increased sphericity, increased systolic wall stress, and annular dilation, which worsen ventricular systolic function and exacerbate valvular insufficiency.

Except for the generation of renin by the kidney, all components of RAAS are present at the myocardial level as well as in many other organs, and are capable of generating high levels of ATII and aldosterone locally. Aside from cardiac ACE, other alternative pathways including chymase, ACE-2, cathepsins, and tonin convert ATI to ATII. In fact, in dogs, cats, and humans, chymase is responsible for 90% of myocardial ATII formation (Balcells et al. 1997; Aramaki et al. 2003). Tissue RAAS appears to be activated earlier in the course of cardiac disease than circulating RAAS. This means that detection of RAAS activation based on plasma neurohormone measurements may not reflect activation of RAAS on a myocardial level. ATII and aldosterone induce myocardial hypertrophy and fibrosis, which appear to be mediated by activation of the angiotensin II type 1 receptor (AT1R) leading to increased transforming growth factor–β.

Chronic deleterious effects of compensatory mechanisms

Although the initial effects of the sympathetic nervous system activation are positive and life saving, chronically there are deleterious effects that worsen cardiac dysfunction and perpetuate progressive deleterious ventricular remodeling. An autonomic imbalance occurs due to

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arterial baroreceptor dysfunction, which increases heart rate due to increased sympathetic tone and decreased parasympathetic tone. Tachycardia and increased afterload (from alpha receptor mediated vasoconstriction) lead to increased myocardial oxygen consumption, which worsens myocardial hypoxia and mechanical dysfunction. High concentrations of norepinephrine at the level of the myocardium also cause toxic changes to the cardiomyocytes, including apoptosis, myofibrillar degradation, and increased collagen synthesis. Chronic catecholamine stimulation may also induce malignant ventricular arrhythmias.

Chronic activation of the renin-angiotensin-aldosterone system promote volume overload (ADH, aldosterone, increased thirst), excess vasoconstriction (ATII and endothelin I), and adverse myocardial remodeling including hypertrophy and fibrosis. Overall, the deleterious effects of increased afterload, tachycardia, increased myocardial oxygen consumption, increased preload, and adverse myocardial remodeling leads to a vicious circle of progressive systolic and diastolic failure, where heart failure begets heart failure. Pharmacologic inhibitors target the neurohormonal systems responsible for the chronic deterioration of cardiac function and include beta blockers, ACE inhibitors, angiotensin II receptor blockers, aldosterone receptor blockers, endothelin I antagonists, and antidiuretic hormone antagonists.

This sequence describes uncontrolled progression of cardiac disease, producing heart failure. It is worth remembering that a majority of cats with heart disease remain asymptomatic and never reach this end point, but rather live normal lives (Rush et al. 2002; Atkins et al. 1992; Paige et al. 2009). This compensated state may be due to reaching a plateau in the above-mentioned mechanisms, or to a very slow rate of disease progression.

Pathology

Key Points

- Pulmonary edema develops in several stages, starting with excess interstitial fluid that is removed by a compensatory increase in lymphatic flow. Interstitial pulmonary edema first develops around vessels and small airways, and progresses to alveolar flooding once the interstitial pressure exceeds the alveolar pressure.
- Gross abnormalities of pulmonary edema include dark, heavy lungs that exude fluid on cut surface and sink when placed in water. Microscopic abnormalities include engorged tortuous pulmonary capillaries and lymphatics, edema fluid within the interstitium and alveoli, and alveolar macrophages containing erythrocytes or hemosiderin (i.e., heart failure cells) throughout the lungs.
- Pulmonary hemorrhage and infarction are commonly seen in cats with left heart failure.
- Gross abnormalities of right heart failure include passive hepatic congestion, where the liver is heavy, firm, and has swollen rounded margins of the lobes. Chronic passive hepatic congestion leads to appearance of a nutmeg liver, characterized by red congested centers of the liver lobes and periacinar necrosis, surrounded by pale, slightly raised periportal regions containing fatty hepatocytes.
- Antemortem arterial thromboemboli are common in cats dying of heart failure. Thromboemboli may be found in the distal abdominal aorta, renal arteries, iliac arteries, carotid arteries, left and right atria, and pulmonary and hepatic vessels.
- Acute or chronic renal infarctions are commonly seen in cats dying of heart failure.

Pulmonary pathology of left-sided congestive heart failure

Hydrostatic pulmonary edema (i.e., left-sided congestive heart failure) is caused by elevated pulmonary venous and capillary pressures secondary to many heart diseases. The initial stage of heart failure consists of a compensatory increase in lymphatic flow, which removes excess interstitial fluid, and the interstitial volume is normal (Stage 1). Once the lymphatic drainage capacity is exceeded, fluid and colloid accumulate in the interstitial areas surrounding bronchioles, arterioles, and venules. Early interstitial fluid often accumulates in the perihilar region, which has "looser" regions of the pulmonary interstitium. Interstitial fluid cuffs develop around small airways and vessels (Stage 2). As the lung fluid increases, lung compliance decreases and premature expiratory closure of small airways may occur (West 1982). Once interstitial pressure exceeds alveolar pressure, fluid enters into the alveoli and initially accumulates in the corners (Stage 3A) and then progresses to alveolar flooding (Stage 3B).

Edematous lungs are brown to dark brown, wet, heavy (~50–70 grams), and sink when placed in water (SK Liu 1970). They do not collapse when the thorax is opened. Chronic pulmonary edema leads to fibrosis and thickening of alveolar walls, which leads to the gross appearance of firm and brown lungs (i.e., brown induration). Pink to reddish, foamy edema fluid oozes from the cut surface. In fulminant heart failure, the trachea may contain pinkish foamy fluid. In Stage 2 edema, interstitial fluid may appear clear or slight yellow. Once alveolar flooding

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has occurred, often there is pinkish fluid secondary to capillary hemorrhage. Microscopically, edema fluid appears acidophilic or faintly granular, and fills the alveoli, interstitium, and lymphatics (Liu and Fox 1999). Lymphatics and pulmonary capillaries appear engorged and tortuous. Alveolar macrophages containing erythrocytes or hemosiderin (i.e., heart failure cells) are present throughout the lungs and increase in number with chronicity of heart failure (Liu and Fox 1999). There are often regions of red, well-demarcated, firm tissue in the lung periphery, consisting of pulmonary hemorrhage and infarction (SK Liu 1970). Muscular hypertrophy of small pulmonary arteries and fibrous thickening of pulmonary capillary walls is seen in cats with pulmonary hypertension (uncommon).

Pleural effusion occurs secondary to left or right heart failure. Grossly, it may appear clear to tan, or chylous. The mechanism of true chylous effusion occurring secondary to isolated left-sided cardiac disease is unknown. True chylous effusion occurring secondary to right-sided heart disease may occur due to increased hydrostatic pressures in the thoracic duct, since the thoracic duct empties into the cranial vena cava which has elevated hydrostatic pressure. The pleura typically appear thickened in cases of chronic pleural effusion, and lung lobe edges may be fibrotic. Lung lobe collapse is also often seen (Figure 19.7).

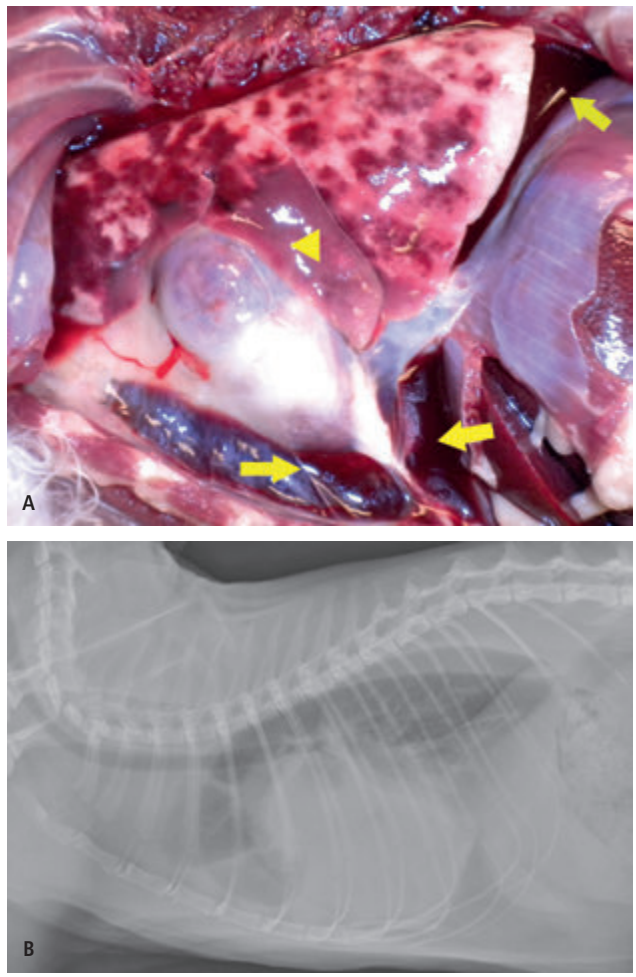


Figure 19.7. Gross pathology and radiograph of a cat with severe HCM and pleural effusion. Gross pathology **(A)** of a cat euthanized due to refractory congestive heart failure depicts serosanguineous pleural effusion (arrows) which was classified as a modified transudate, atelectic ventral portions of the left lung lobe (arrow head), and cardiomegaly. The heart weighs 30 grams, which is massively increased due to the severe left ventricular concentric hypertrophy and severe left atrial dilation. An antemortem lateral thoracic radiograph **(B)** of this cat provides a clinical correlate, and shows severe pleural effusion that obscures the cardiac silhouette and pulmonary vasculature.

Pathology of right-sided congestive heart failure

Ascites may develop in cats with isolated right heart failure and is most often seen in conjunction with pleural effusion. In passive hepatic congestion (i.e., right heart failure), the liver is heavy (~115–133 grams), firm, and swollen with rounded edges of the central lobes. Acute passive hepatic congestion results in a swollen, dark liver that oozes blood when sectioned. The capsule appears opaque and is often covered with a sheet of yellowish-gray fibrin accumulating from extruded hepatic lymph. Initial histopathologic abnormalities include hepatic sinusoidal engorgement, and with chronicity, the capsule develops a fine nodular appearance, and a reticulated acinar pattern is seen on sliced sections (i.e., nutmeg liver). This nutmeg appearance is caused by red congested centers of the liver lobes and periacinar necrosis, surrounded by pale, slightly raised periportal regions containing fatty hepatocytes. Chronic passive congestion also causes the spleen to be congested and heavy, as well as congestion of other abdominal organs including the stomach, intestines, and pancreas. Microscopically, there is usually marked sinusoidal dilation of the spleen.

Other pathologic abnormalities

The kidneys of cats diagnosed with CHF often appear irregular, with regions of firm, pale depressed scars or dark red, elevated, well-demarcated, wedge- or cone-shaped areas, consistent with previous or recent renal infarctions, respectively (SK Liu 1970).

Antemortem arterial thromboemboli are commonly seen in cats dying of heart failure. In a case series of 112 cats with CHF due to acquired heart disease, "red" thromboemboli were found in the abdominal aorta

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(46/112 cats: 41%), left or right atrium (12/112 cats: 11%), and less frequently in renal arteries, iliac arteries, carotid arteries, and pulmonary and hepatic vessels (SK Liu 1970). These "red" thromboemboli consist of fibrin meshes that entrap red blood cells and leukocytes.

Pathologic abnormalities of the heart depend on the etiology of the heart failure and are discussed in specific chapters.

SIGNALMENT

Key Points

- There is a wide age distribution of cats with heart failure, ranging from less than 1 year to geriatric, which reflects the wide age distribution of the underlying cardiac disorders.
- The domestic shorthair is the most common breed of cat diagnosed with heart failure, likely because it represents a greater proportion of the feline population.

Because both congenital and developmental heart diseases may lead to heart failure, there is a wide distribution of ages ranging from kitten to geriatric. According to a sentinel study in the 1960s, 43% of cats dying from heart failure were less than 1 year of age and less than 1% were over 16 years of age (Liu et al. 1970). Seventeen percent of the cats in this study had congenital heart disease, and a majority (77%) of them died of heart failure by 1 year of age. The most common breed diagnosed was the domestic shorthair (63%) followed by Siamese (32%), which were overrepresented in both congenital and acquired disease categories. There was no sex predisposition for congenital or acquired disease leading to heart failure. Another study reported that the most common cause of ascites in cats less than 1 year of age was congenital heart disease (Wright et al. 1999). However, when analyzing all cats diagnosed with ascites secondary to right heart failure, there was even distribution of age and sex (Wright et al. 1999). Similar to the previous study, the domestic shorthair was the most common breed diagnosed with ascites and right heart failure (63%) (Wright et al. 1999). In cats with HCM, there was no difference in age, sex, or breed among clinical groups of heart failure, arterial thromboembolism, syncope, or subclinical disease (Rush et al. 2002). In summary, heart failure is evenly distributed among all age groups of cats, with no sex predilection beyond that of the underlying cardiac disorder. The domestic shorthair is overrepresented for development of heart failure.

HISTORY AND CHIEF COMPLAINT

Key Points

- Nonspecific abnormalities noted on history of cats diagnosed with heart failure include: weight loss, inappetence, and lethargy.
- Dyspnea and tachypnea are the most common chief complaints of cats presenting with heart failure.

Typical abnormalities noted by the owners of cats with heart failure include weight loss, lethargy, and hyporexia or anorexia. A majority of cats (72% in one study) with heart failure have a history of inappetence (Torin et al. 2007). Cats may be more reclusive and less interactive with other pets or family members. Dyspnea and tachypnea are the most common complaints, and owners may describe abnormalities including coughing, vomiting (owners may confuse with coughing), open mouth breathing, tachypnea, or dyspnea. Episodic weakness or collapse may be noted by obtaining a careful history. Some cats may have had a chronic history of a heart murmur, especially cats with congenital heart disease or hypertrophic cardiomyopathy. Cats with congenital heart disease may have a history of poor growth (Liu et al. 1970). History of a previous thromboembolic event may include an episode of pain and lameness/paresis and is relatively common in cats with severe heart disease. Sometimes the first clinical sign is sudden cardiac death, which was the presenting complaint in 25% of cats dying of heart failure (Liu et al. 1970).

PRECIPITATING FACTORS THAT MAY CONTRIBUTE TO CONGESTIVE HEART FAILURE

Key Points

- A precipitating event is common in cats presenting with heart failure. Recent fluid administration, general anesthesia, or repositol corticosteroid administration are the most common antecedent events.
- Diseases that increase circulating blood volume, such as significant anemia, may precipitate heart failure in cats with underlying heart disease.
- Hyperthyroidism is another cause of high output heart disease, and may contribute to development of heart failure, especially in cats with underlying heart disease.
- Isolated systemic hypertension does not typically lead to heart failure, but may contribute to diastolic dysfunction in cats with underlying heart disease.

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- There is no clear relationship defined at this time linking diabetes mellitus and congestive heart failure in cats, but studies are lacking.

An antecedent event is common in cats with heart failure. Recent fluid administration (intravenous or large volume [>100 ml] subcutaneous) is a common clinical scenario preceding the clinical presentation of congestive heart failure. Cats often have significant heart disease without overt clinical abnormalities, but they may be precariously "on the edge" of developing heart failure by expansion of the blood volume. Standard volumes and rates of fluid resuscitation may not be tolerated in patients with noncompliant hearts due to concentric hypertrophy or fibrosis. In a retrospective study of cats with HCM (Rush et al. 2002), half of the cats presenting with heart failure had an antecedent event, including in order of occurrence: intravenous fluid administration (17/61), recent anesthesia or surgery (15/61, within a mean of 5 days), recent corticosteroid administration (13/61), trauma (7/61), upper respiratory tract infection (3/61), or miscellaneous causes. Methylprednisolone was the most common corticosteroid administered (70%) followed by a parenteral form of triamcinolone (30%). Ketamine hydrochloride was the most common anesthetic agent administered (8/9 cats with known anesthetic protocol) followed by tiletamine-zolazepam (1/9). Possible mechanisms of methylprednisolone contributing to heart failure were further studied in 12 normal cats (Ployngam et al. 2006). Methylprednisolone was shown to increase plasma volume by 13.4 % (>40% in 25% of cats) and reduce red blood cell count, hematocrit, hemoglobin concentration, as well as serum sodium and chloride concentrations in normal cats (Ployngam et al. 2006). However, echocardiographic variables and blood pressure did not change after methylprednisolone administration in these normal cats. In cats with marked diastolic or systolic dysfunction, the increased plasma volume may further elevate diastolic filling pressures and lead to development of heart failure. In a subgroup analysis of cats presenting for heart failure after methylprednisolone administration, 58% (7/12) of cats recovered without requirement of long-term medical therapy and lived for ≥1432 days without recurrence of heart failure (Smith et al. 2009). In addition to the main effects of regulation of carbohydrate and protein metabolism, negative feedback on the hypothalamic pituitary axis, anti-inflammatory effects, and immunosuppressive effects, glucocorticoids also mediate body water and electrolyte balance through the low affinity corticosteroid receptors (Hadoke et al. 2009). Therefore, even in the absence of significant mineralocorticoid activity, methylprednisolone and triamcinolone may still promote sodium and water retention.

Diseases that increase circulating blood volume and lead to a high output state, such as anemia, may precipitate development of congestive heart failure in patients with underlying heart disease (Yaphe et al. 1993). Anemia is a common comorbidity in humans with heart failure, but prevalence is not documented in cats with heart failure. Anemia is associated with a twofold increase in 1-year mortality in people with systolic or diastolic heart failure and was shown to be an independent predictor of cardiovascular mortality in heart failure patients (Groenveld et al. 2008). Anemia is associated with a high cardiac output when the hemoglobin is <7 g/dl. Arteriolar vasodilation and hypoviscosity of the blood lead to low systemic vascular resistance. Tissue hypoxia and enhanced tissue production of endothelium-derived nitric oxide may be responsible for arteriolar vasodilation in anemia. Elevated circulating catecholamine levels lead to tachycardia and increased myocardial contractility. Chronic increases in blood volume from anemia lead to eccentric hypertrophy of the ventricular myocardium (i.e., volume overload hypertrophy) and elevated diastolic filling pressure (since the ventricle is operating on the rightward aspect of the pressure volume curve). Increased plasma volume and increased diastolic filling pressure in cats with significant systolic or diastolic dysfunction may precipitate heart failure. The cardio-renal-anemia syndrome has been recently described in people, whereby heart failure precipitates renal failure because of poor cardiac output and renal perfusion. Renal failure leads to decreased endogenous production of erythropoietin and subsequent development of anemia. Anemia increases the cardiac workload, which continues the vicious circle. This syndrome has not been well characterized in cats with heart failure.

Pregnancy may be associated with high output cardiac disease and although rare, it may precipitate congestive heart failure. CHF was described in a Himalayan queen, which resolved after cesarean section and did not recur for the life of the cat (Stoneham et al. 2006). Plasma volume and cardiac output may increase up to 50% in pregnancy, which may increase diastolic filling pressures and exacerbate heart failure in cats with underlying diastolic dysfunction (i.e., compensated hypertrophic, restrictive, or unclassified cardiomyopathies) (Schrier et al. 1994).

Although diabetes mellitus is associated with a specific cardiomyopathy, hypertension, and coronary artery disease in people, there is no clear evidence of this relationship in cats. Diabetic cardiomyopathy in

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people consists of diastolic and systolic dysfunction, and pathologic abnormalities include ventricular hypertrophy, myocardial fibrosis, and small coronary artery disease. Coexistence of hypertension and diabetes mellitus accentuate myocardial fibrosis and diastolic dysfunction. Hyperinsulinemia increases salt reabsorption by the kidney and also exerts a direct growth-stimulating effect on myocardial cells. There are few studies evaluating cardiovascular effects of diabetes mellitus in cats. Unlike people, cats do not appear to develop hypertension secondary to diabetes mellitus, as evidenced by the small clinical study demonstrating that systemic hypertension was not present in 14 cats with diabetes mellitus (Sennello et al. 2003). In a retrospective case-control study of 20 cats with diabetes mellitus and 57 matched controls, 30% (n = 6) of diabetic cats died of heart failure, with a relative risk of heart failure in diabetic cats 10.4 times that of control cats (Little and Gettinby 2008). Of the cats diagnosed with heart failure, echocardiography revealed HCM as the underling disease in 3 of the 6 cats, 1 cat had left atrial dilation but normal ventricular size and function (possibly unclassified or restrictive cardiomyopathy), 1 cat had an incomplete echocardiogram with no atrial measurements and normal ventricular size and function, and 1 cat was not evaluated by an echocardiogram (Little et al. 2008). Therefore, it is unlikely that diabetes mellitus caused heart disease in these cats, but it may have precipitated or worsened underlying heart disease.

Hyperthyroidism may contribute to development of congestive heart failure in cats, but at present it is an unusual primary cause of heart failure. The incidence of congestive heart failure in hyperthyroid cats dramatically fell from 20% in 1979–1982 to only 8% in 1992–1993, likely due to early detection and more widespread screening of cats (Fox et al. 1999). Like anemia, hyperthyroidism causes high output heart disease, characterized by increased plasma volume, cardiac filling pressures, heart rate, contractility, and blood pressure. Concentric hypertrophy occurs due to direct stimulation of myocardial protein synthesis and may decrease myocardial compliance. Hyperthyroid cats that develop heart failure often have another underlying primary cardiac disease, and the combination precipitates heart failure. Although rare, severe and chronic hyperthyroidism may lead to an end-stage dilated form of myocardial disease characterized by severe myocardial failure and congestive heart failure (Jacobs et al. 1986).

Systemic hypertension is not associated with heart failure unless significant underlying heart disease is present. Compensatory (secondary) concentric hypertrophy develops in response to increased systemic vascular resistance and is typically mild in severity. The additive deleterious myocardial effects of concentric hypertrophy and fibrosis in cats with concurrent systemic hypertension and hypertrophic cardiomyopathy may result in the development of diastolic heart failure.

Bradycardia due to second- or third-degree atrioventricular block may contribute volume overload of the heart and development of congestive heart failure. Cardiac output is decreased from bradycardia and activates RAAS to increase blood volume. Eccentric hypertrophy of the ventricle develops in response to increased preload, which increases stroke volume and normalizes cardiac output. Besides a slow ventricular rate, the hemodynamic impact of third-degree AV block is worsened by the asynchronous atrioventricular contraction, where the atria intermittently contract against a closed atrioventricular valve, which further elevates right and left atrial pressures. In a study of 21 cats with third-degree AV block, 38% had congestive heart failure, but a majority (61%) had underlying primary cardiac disease (Kellum and Stepien 2006). Sinus bradycardia is rare in the cat but appears to be a factor facilitating overt heart failure in people (Alboni et al. 1999). Chronic severe bradycardia leads to volume overload of the left ventricle, compensatory eccentric hypertrophy, and elevated filling pressures.

PHYSICAL EXAMINATION

Key Points

- Respiratory abnormalities including dyspnea, tachypnea, adventitious lung sounds, or muffled lung sounds, are the most common abnormalities on physical examination of cats with heart failure.
- A murmur, gallop, or arrhythmia is variably present in cats with heart failure. A systolic murmur is most commonly ausculted in cats with HCM.
- Clinical signs of low output heart failure include pale mucous membranes with slow capillary refill time, weak femoral pulses, hypothermia, weakness, or collapse.
- Jugular venous distension and pulsation, muffled lung sounds, hepatomegaly, and abdominal distension are commonly identified in cats with right heart failure.

The most common physical examination findings in cats with heart failure are respiratory abnormalities including dyspnea, tachypnea, and orthopnea. Cats with severe dyspnea may have open mouth breathing and

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cyanosis and should be quickly triaged for emergency care. Muffled lung and heart sounds are commonly present with significant pleural effusion, and often patients have shallow, rapid respirations. Palpation of a noncompliant cranioventral thorax may raise the suspicion of a cranial mediastinal mass as the cause of pleural effusion. Adventitious lung sounds may be present in cats with pulmonary edema and may overshadow detection of a murmur.

Abnormal cardiac auscultation including a murmur, gallop heart sound, or arrhythmia is variably present. Only 20% of cats dying of heart failure in one study had an abnormal cardiac auscultation (Liu et al. 1970). Factors involved with such a low occurrence of abnormal cardiac auscultation may include muffled heart sounds from pleural effusion, adventitious lung sounds masking a murmur, or at the time of that publication in the 1960s the high prevalence of dilated cardiomyopathy, which less commonly causes a murmur. A systolic murmur may be more commonly present in cats with HCM (64–72%) than in cats with restrictive cardiomyopathy (36%) or dilated cardiomyopathy (9%) (Rush et al. 2002; Ferasin et al. 2003). Likewise, the murmur intensity is typically loudest in cats with hypertrophic obstructive cardiomyopathy compared to other cardiac diseases. A gallop heart sound (i.e., extra S_3 or S_4 heart sound) is more common in cats with DCM (45%) compared to HCM (12–33%) and RCM (23%) (see Chapter 1) (Rush et al. 2002; Ferasin et al. 2003). Tachycardia is commonly present and is a result of sympathetic activation (i.e., sinus tachycardia) or a tachyarrhythmia (i.e., supraventricular tachycardia, ventricular tachycardia, or atrial fibrillation).

Lethargy, weakness, collapse, or poor femoral arterial pulse quality may be present in cats with low output heart failure, which is more common in cats with DCM than other cardiac diseases. Slow capillary refill time and pale mucous membranes occur when there is low cardiac output and peripheral hypoperfusion. Absence of femoral arterial pulses, cold extremeties, and cyanotic nail beds may be present in cats with arterial thromboembolism. Cats may have poor body condition and cachexia, especially if they have suffered from chronic congestive heart failure. One study confirmed this observation and found that cats with congestive heart failure had significantly lower body condition score (4 ± 1) compared to cats with compensated heart disease (6 ± 1), and cats with congenital heart disease had lower body condition score than cats with acquired heart disease (Torin et al. 2007).

Clinical abnormalities seen with right heart failure include jugular venous distension, ascites, hepatomegaly, and pleural effusion (Figure 19.8). Jugular venous distension is often overlooked in the physical examination, but it is a key tool for evaluation of elevated right atrial pressure. Unlike large animals and people, cats do not develop peripheral subcutaneous edema with right heart failure.

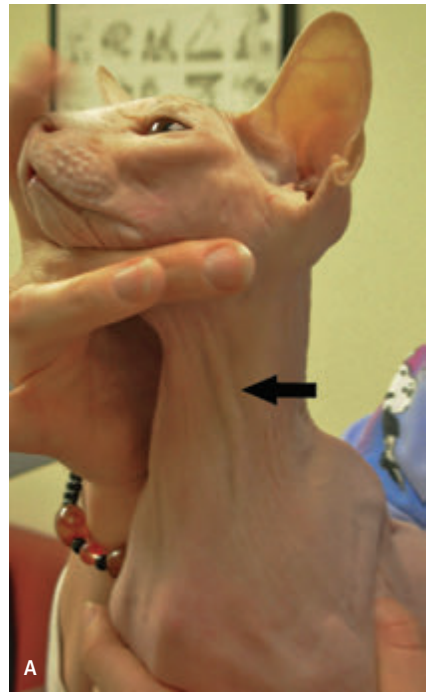




Figure 19.8. Physical examination abnormalities seen in a cat with right heart failure. This Sphynx suffers from right-sided congestive heart failure secondary to severe tricuspid regurgitation and tricuspid valve dysplasia. Examination of the jugular veins reveals severe jugular venous distension and pulsation **(A)**, and there is obvious abdominal distension and a ballotable fluid wave indicative of ascites **(B)**.

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DIFFERENTIAL DIAGNOSIS

Key Points

- The most common causes of pleural effusion aside from heart failure are neoplasia, pyothorax, and feline infectious peritonitis. Fluid analysis helps distinguish pyothorax and feline infectious peritonitis from heart failure.
- Common differentials for pulmonary infiltrates aside from cardiogenic pulmonary edema include pneumonia, neoplasia, acute respiratory distress syndrome, inflammatory lung disease, or neurogenic (noncardiogenic) pulmonary edema.
- Right heart failure, neoplasia, and liver disease are the most common differential diagnoses of ascites in cats. Concurrent pleural effusion is almost always present in addition to ascites in cats with right heart failure.

Pleural Effusion

Pleural effusion is the abnormal accumulation of fluid within the pleural space secondary to any of a wide variety of pathologic processes, which include increased systemic and pleural capillary hydrostatic pressures (congestive heart failure), decreased plasma oncotic pressure (hypoalbuminemia <1.5 g/dl), increased capillary permeability (inflammation, vasculitis), lymphatic obstruction or dysfunction, infectious causes, trauma, coagulopathy, parasitic (heartworm or *Aleurostrongylus*), and intrathoracic neoplasia. According to a case series of 82 cats with pleural effusion, the most common etiologies aside from congestive heart failure (9/82 cats, 11%) were pyothorax (18%), mediastinal lymphoma (17%), and feline infectious peritonitis (18%) (Davies et al. 1996). Pleural fluid analysis and cytology help eliminate many of the differentials for congestive heart failure (infectious, hemorrhagic, feline infectious peritonitis), with neoplasia and idiopathic chylous effusion remaining as the highest differentials.

Pulmonary Edema

Distinguishing cardiogenic pulmonary edema from other causes of pulmonary infiltrates can be very challenging in cats. Unlike dogs, there is no consistent radiographic pattern of pulmonary edema accumulation in cats with heart failure. The main differentials for pulmonary infiltrates aside from heart failure include: infectious (bacterial, fungal disease, toxoplasmosis), inflammatory (eosinophilic lung disease), parasitic lung disease, primary neoplastic disease (bronchoalveolar carcinoma), metastatic pulmonary disease, acute respiratory distress syndrome, pulmonary contusions, or noncardiogenic (neurogenic) pulmonary edema. An echocardiogram can help to eliminate heart failure from the differential list of diseases causing pulmonary infiltrates. Echocardiographic assessment of a normal left atrial size eliminates cardiogenic pulmonary edema from the differential list, in the absence of an acute precipitating factor such as intravenous fluid administration. Serum cardiac biomarker assay may also be very sensitive and specific (see Chapter 8).

Ascites

Cardiovascular and neoplastic disorders are the most common causes of ascites in cats and account for over 50% of the cases in a retrospective case series (Wright et al. 1999). Ascites is almost always seen in conjunction with pleural effusion in cats with congestive heart failure, and concurrent mild pericardial effusion (not causing cardiac tamponade) is also common (37%). In order of occurrence, the most common to least common causes of ascites in a case series of 65 cats included congestive heart failure (29%), neoplasia (28%), hepatic disease (17%), renal disease (9%), feline infectious peritonitis (6%), peritonitis (6%), and urinary tract trauma (5%) (Wright et al. 1999). Abdominal fluid analysis and cytology may be helpful in narrowing the differential diagnosis list. Ascites due to heart failure may be classified as a transudate, modified transudate (most common), or chylous. Aside from heart failure, the main differentials for a transudate include portal hypertension or hypoalbuminemia (<1.5 g/dl) secondary to liver failure, protein-losing enteropathy, protein-losing nephropathy, or glomerulonephropathy. Modified transudate ascitic fluid may be consistent with postsinusoidal portal hypertension, liver disease/failure, neoplasia, congestive heart failure, or obstruction of the caudal vena cava (i.e., from a thrombus or invasive adrenal mass). In a study of 45 cats with peritoneal effusion, only ~7% of ascites was classified as chylous (Wright et al. 1999). There are many etiologies that can cause chylous peritoneal effusion, including congestive heart failure, neoplasia, peritonitis, or trauma (Wright et al. 1999). In summary, the index of suspicion of congestive heart failure as the cause of ascites is greater when there is concurrent pleural and/or pericardial effusion. Fluid analysis may help discriminate between heart failure and the many other etiologies of ascites, with neoplasia and liver failure remaining the highest differentials.

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DIAGNOSTIC TESTING

Key Points

- A minimum data base including complete blood count, chemistry, urinalysis, and thyroxine level (if age appropriate) should be done as a baseline evaluation of overall organ function and metabolic status.
- Routine cardiovascular tests include thoracic radiographs, electrocardiogram, systemic blood pressure measurement, and an echocardiogram.
- Thoracic radiographs are essential for diagnosis of congestive heart failure. Pulmonary edema and/or pleural effusion develop secondary to left heart failure, and pleural effusion and/or ascites develop secondary to right heart failure.
- Cardiogenic pulmonary edema has a variable appearance in cats, without a classic distribution pattern. Common radiographic characteristics include patchy to diffuse, interstitial to alveolar pulmonary infiltrates that are often asymmetrical and almost always involve more than one lung lobe. Cardiomegaly and atrial dilation are often, but not always, identified, and pulmonary vascular distension may be present.
- Radiographic appearance of pleural effusion includes radiopaque fluid accumulation outside the pulmonary parenchyma, pleural fissure lines, scalloping (rounding) of the lung lobes, retraction of the lung lobes from the thoracic wall, and obscured diaphragmatic and cardiac silhouettes. A dilated caudal vena cava is often present in cats with right heart failure. Dorsal deviation of the trachea in the presence of significant pleural effusion is not specific for cardiomegaly.
- An electrocardiogram is the test of choice for evaluation of an arrhythmia. The most common arrhythmias diagnosed in cats with heart failure are: supraventricular tachycardia, atrial fibrillation, ventricular premature complexes, and ventricular tachycardia. A left axis deviation (or left anterior fascicular block pattern) is often seen in cats with hypertrophic cardiomyopathy but it is nonspecific and may also occur in normal cats.
- A "triage" echocardiogram is a valuable tool to determine initially whether there is significant enough cardiac disease to cause congestive heart failure in the dyspneic cat. Goals of the "triage" echocardiogram include evaluation of presence and severity of pleural effusion or pericardial effusion, assessment of atrial size, and assessment of myocardial function.
- A comprehensive echocardiogram should follow the triage echocardiogram once the patient is stable. The comprehensive echocardiogram provides detailed evaluation of cardiac structure and function to help guide optimal treatment and prognosis.
- Measurement of systolic blood pressure is important and may identify systemic hypertension or hypotension.
- Elevated central venous pressure (CVP) greater than 10 mm Hg is consistent with right heart failure. Measurement of CVP should be done after removal of pleural effusion, since significant pleural effusion may increase central venous pressure in the absence of right heart failure.
- Pleural effusion analysis and cytology results often are nonspecific and cardiogenic pleural effusion is characterized as a transudate, modified transudate, chylous, or pseudochylous fluid.

General Diagnostic Tests

Comprehensive blood work including a complete blood count (CBC), serum chemistry, urinalysis, and total thyroxine level (if age appropriate) should be done on all cats if clinically feasible. It may be necessary to emergency triage and stabilize overtly dyspneic cats prior to obtaining the minimum database, because these patients are very fragile. The CBC may reveal mild leukocytosis with a stress leukogram or may be unremarkable. Serum chemistry may reveal mild azotemia (prerenal or renal), mild hyperglycemia (likely stress-induced), and mildly elevated liver enzymes. In a large study of 260 cats with HCM including 120 cats with CHF, 68% of cats had elevated liver enzymes (alanine aminotransferase or aspartate aminotransferase) (Rush et al. 2002). Urinalysis may identify hyposthenuria in cats with concurrent renal insufficiency or urinary tract infection/pyelonephritis in azotemic cats. It is important to identify cats with underlying renal insufficiency or renal failure, because these cats may be less tolerant of aggressive diuretic therapy and may require more frequent monitoring of renal values during treatment. Total thyroxine level is important to evaluate for concurrent hyperthyroidism, because this provides a target for treatment. Free thyroxine concentration by equilibrium dialysis may be done in cats with a thyroxine level in the equivocal range to confirm whether there is early hyperthyroidism, which may be a complicating factor in heart failure. Overall, the minimum database is not useful to confirm heart failure, but it is essential to assess the metabolic status of the cat and to determine baseline renal and electrolyte values prior to diuretic therapy.

Routine Cardiovascular Diagnostic Tests

Thoracic radiography

Thoracic radiographs are an essential diagnostic tool for confirmation of congestive heart failure. Along with

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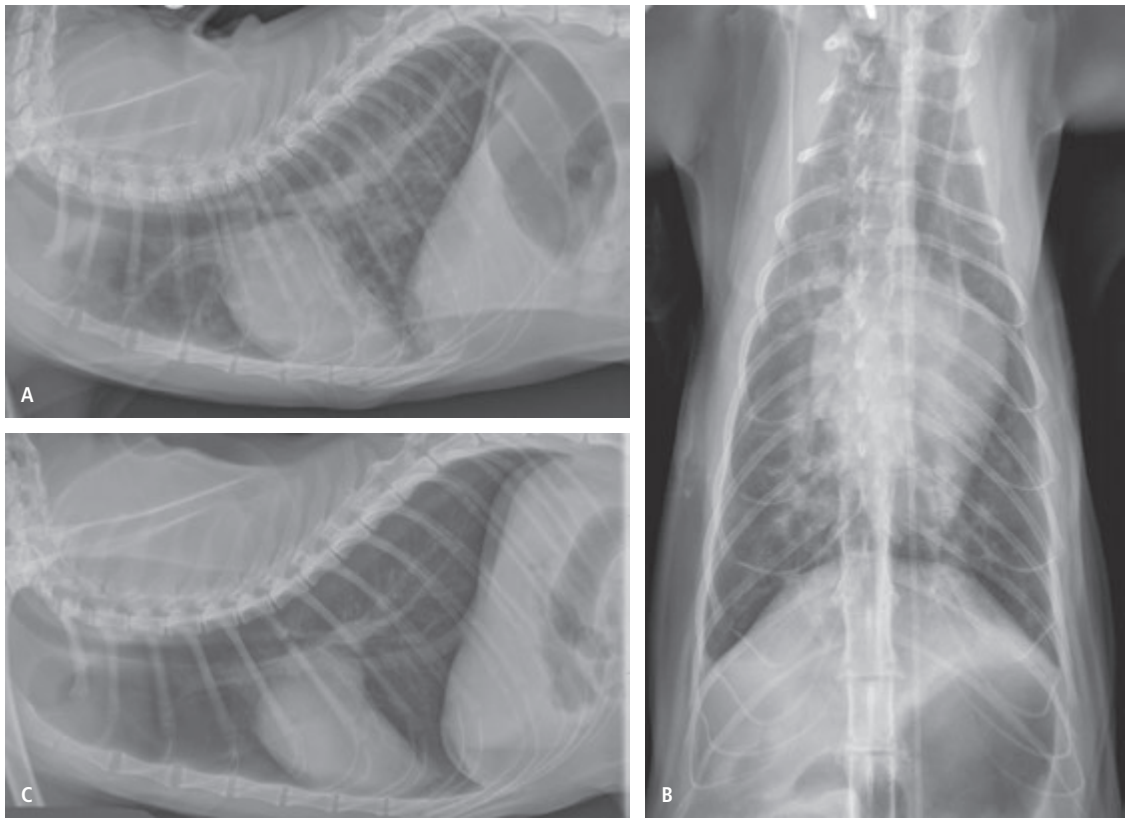


Figure 19.9. Thoracic radiographs of a cat with severe hypertrophic cardiomyopathy and mild left heart failure before and after medical therapy. Thoracic radiographs including right lateral **(A)** and ventrodorsal **(B)** projections of this cat show cardiomegaly with severe left atrial dilation. Radiographic abnormalities include mild, patchy to diffuse interstitial pulmonary infiltrates and pulmonary venous distension. The combination of these abnormalities is consistent with mild pulmonary edema and left heart failure. A week after medical therapy with furosemide and enalapril, a recheck right lateral radiograph reveals resolved pulmonary edema and resolved pulmonary venous distension, but persistent cardiomegaly and left atrial dilation **(C)**.

history and physical examination, radiographs may be the only other test necessary to make the diagnosis of heart failure in some cases. However, thoracic radiographs should never be a terminal event in the fragile, dyspneic cat. Cats should be handled as carefully as possible to minimize stress, with the least possible restraint. A dorsoventral radiograph (sternal recumbency) is the least stressful view to obtain and may provide enough information to assess whether there is severe cardiac disease and heart failure in the unstable patient. Ideally, both a lateral and dorsoventral (or ventrodorsal) views should be obtained if possible, or may be obtained once the cat is more stable. Another option for evaluation of severe pleural effusion in the unstable, dyspneic cat is a brief "triage" echocardiogram. Two-view radiographs should be obtained after thoracocentesis to assess cardiac size and evaluate the pulmonary parenchyma and pulmonary vasculature.

Cardiogenic pulmonary edema in cats can be a perplexing diagnosis to make. Classic thoracic radiographic abnormalities include cardiomegaly and atrial dilation, pulmonary venous distension, and interstitial to alveolar pulmonary infiltrates often in the perihilar region and the caudal or accessory lung lobes (Figure 19.9). However, radiographic appearance of congestive heart failure in cats is highly variable and may pose a diagnostic dilemma for distinguishing primary respiratory disease from congestive heart failure (Figures 19.10—19.12). Unlike dogs who develop the typical perihilar to caudodorsal distribution of cardiogenic pulmonary edema, cats do not develop a particular distribution pattern of edema. In a study of 23 cats with cardiogenic pulmonary edema, all cats had interstitial infiltrates, and most had alveolar infiltrates (83%) in a diffuse pattern (78%) (Figures 19.9, 19.10) (Benigni et al. 2009). Interstitial infiltrates are caused by pulmonary edema accumulating in the interlobular septa and consist of a reticular or granular hazy pattern (Figures 19.9, 19.10). Almost 40% of cats had a regional distribution of pulmonary edema, with ventral distribution the most common (22%), followed by caudal distribution (13%) and lastly hilar distribution (4%) (Benigni et al. 2009). Mild edema initially accu-

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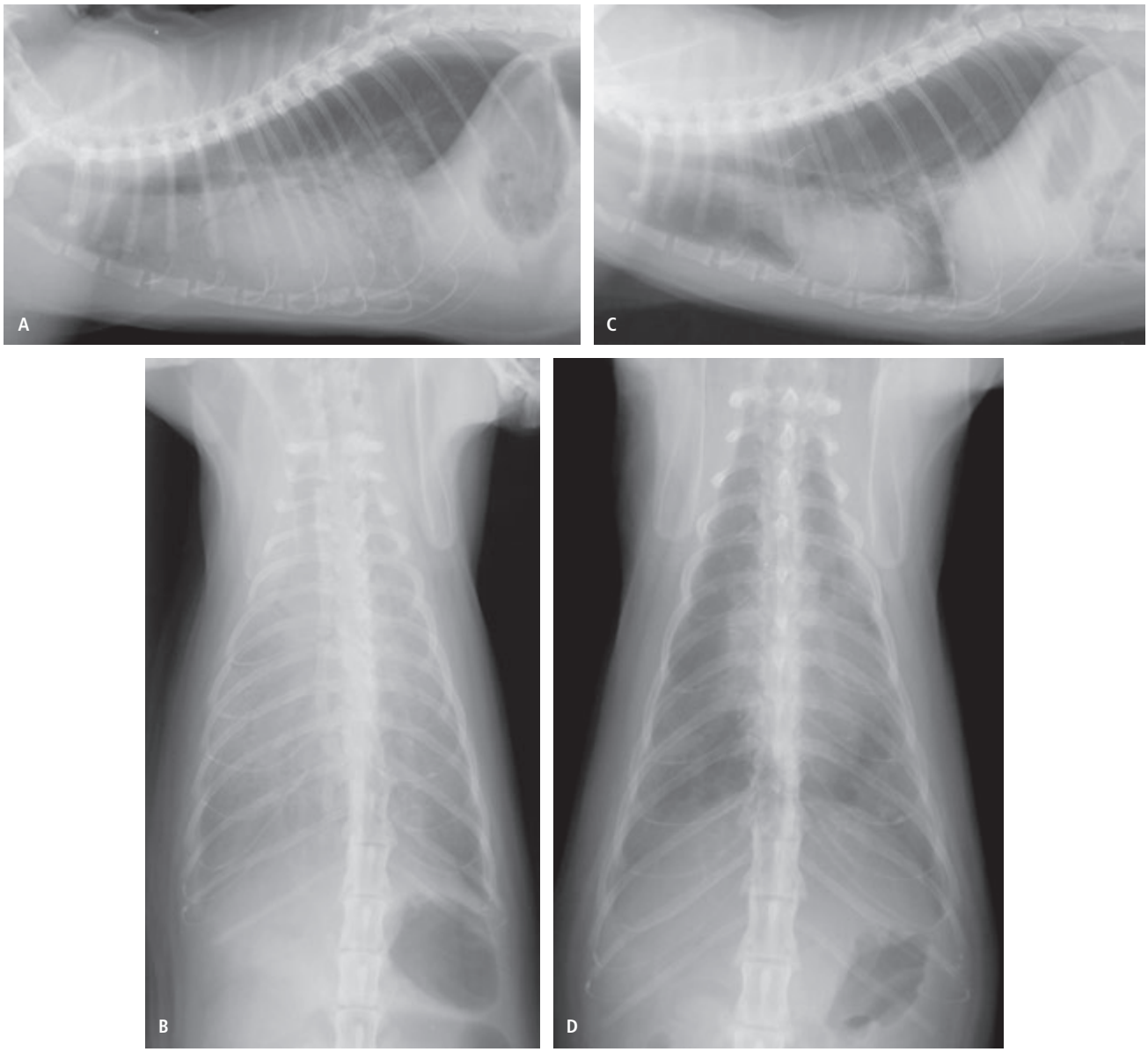


Figure 19.10. Thoracic radiographs of a cat with severe restrictive cardiomyopathy and concurrent severe pulmonary edema and pleural effusion. Thoracic radiographs including right lateral **(A)** and dorsoventral **(B)** projections of this severely dyspneic cat show heavy alveolar pulmonary infiltrates and mild pleural effusion that obscure the cardiac silhouette. Repeat thoracic radiographs one day after aggressive diuretic therapy show improved and mild to moderate pulmonary edema and nearly resolved pleural effusion **(C)** and **(D)**. Cardiomegaly and left atrial dilation are now visible.

mulates in the perihilar region, which may be obscured by superimposed structures including pulmonary vasculature and the left atrium. Pulmonary edema is often asymmetrical (78%) rather than bilaterally symmetrical (22%) (Benigni et al. 2009). Because there is greater pulmonary mass and blood flow to the right lung lobes, there may be greater edema formation in the right lung lobes. To further obscure the differentiation of heart failure versus primary respiratory disease, 61% of cats with cardiogenic pulmonary edema also had a bronchial pulmonary pattern (Benigni et al. 2009). Cardiogenic pulmonary edema was never present in just a single lung lobe, which may help distinguish heart failure from some cases of bronchopneumonia or aspiration pneumonia. Although often present in heart failure (71% of cats in 1 study), pulmonary venous distension may not be present in cats that are dehydrated or receiving diuretics (Benigni et al. 2009). Often both pulmonary arteries and pulmonary veins are distended in congestive heart failure. Heart failure should never be ruled out based on

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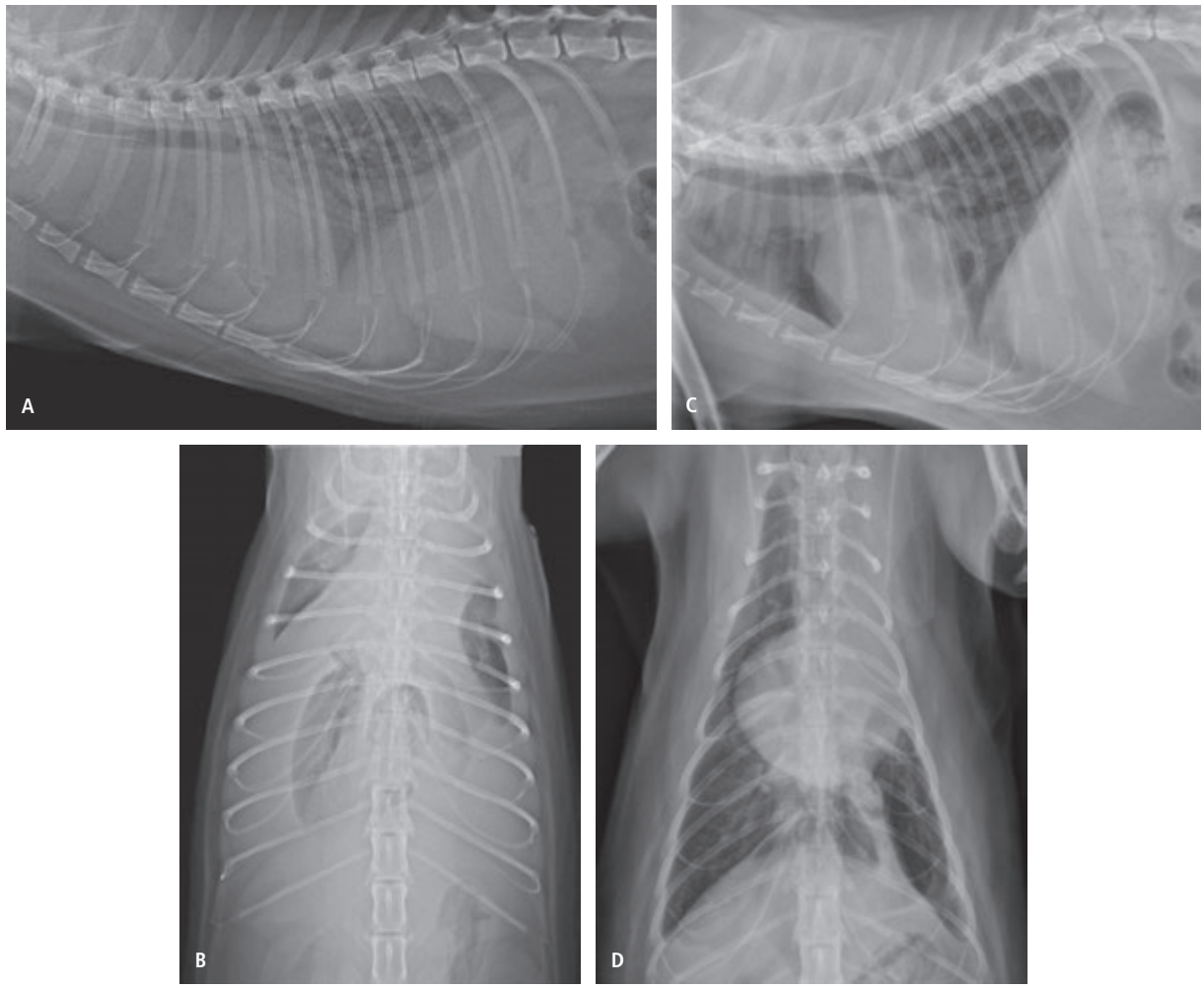


Figure 19.11. Thoracic radiographs of a cat with severe pleural effusion and severe unclassified cardiomyopathy.

Thoracic radiographs including right lateral **(A)** and dorsoventral **(B)** projections of this severely dyspneic cat, show marked pleural effusion that obscures the cardiac silhouette. The lung lobes are scalloped and retracted from the thoracic wall, with rounded edges suggesting chronicity of pleural effusion. There is dorsal deviation of the trachea, which is not specific for cardiomegaly in the face of severe pleural effusion. Immediately after thoracocentesis, right lateral and ventrodorsal projections show mild residual pleural effusion **(C)** and **(D)**. Biatrial dilation and severe cardiomegaly are present, as well as moderate, patchy to diffuse pulmonary infiltrates consistent with pulmonary edema.

absence of pulmonary venous distension, but its presence increases the suspicion of CHF. There is often a mixed pattern of pulmonary edema and pleural effusion in feline congestive heart failure (Figure 19.10). In a large study of cats diagnosed with HCM, pulmonary edema was present in 66% of cats and was the cause of dyspnea in 86% of cats with heart failure, as opposed to only 14% of cats that were dyspneic due to severe pleural effusion (Rush 2002).

Pleural effusion is easily identified by thoracic radiographs, with radiographic characteristics that include: radiopaque fluid accumulation outside the pulmonary parenchyma, pleural fissure lines, scalloping (rounding) of the lung lobes, retraction of the lung lobes from the thoracic wall, and obscured diaphragmatic and cardiac silhouettes (see Figures 19.10–19.12). It is often impossible to visualize the cardiac silhouette and pulmonary vasculature due to the presence of significant pleural effusion and/or pulmonary edema. Dorsal displacement of the trachea may be present in cats with moderate or severe pleural effusion regardless of cardiac size and is not an indicator of cardiomegaly in cats with significant pleural effusion (Snyder 1990).

As long as the cardiac silhouette is not obscured by pulmonary edema or pleural effusion, cardiomegaly is almost always detected in cats with congestive heart failure. Measurement of vertebral heart size may be useful to quantify cardiac size and determine whether

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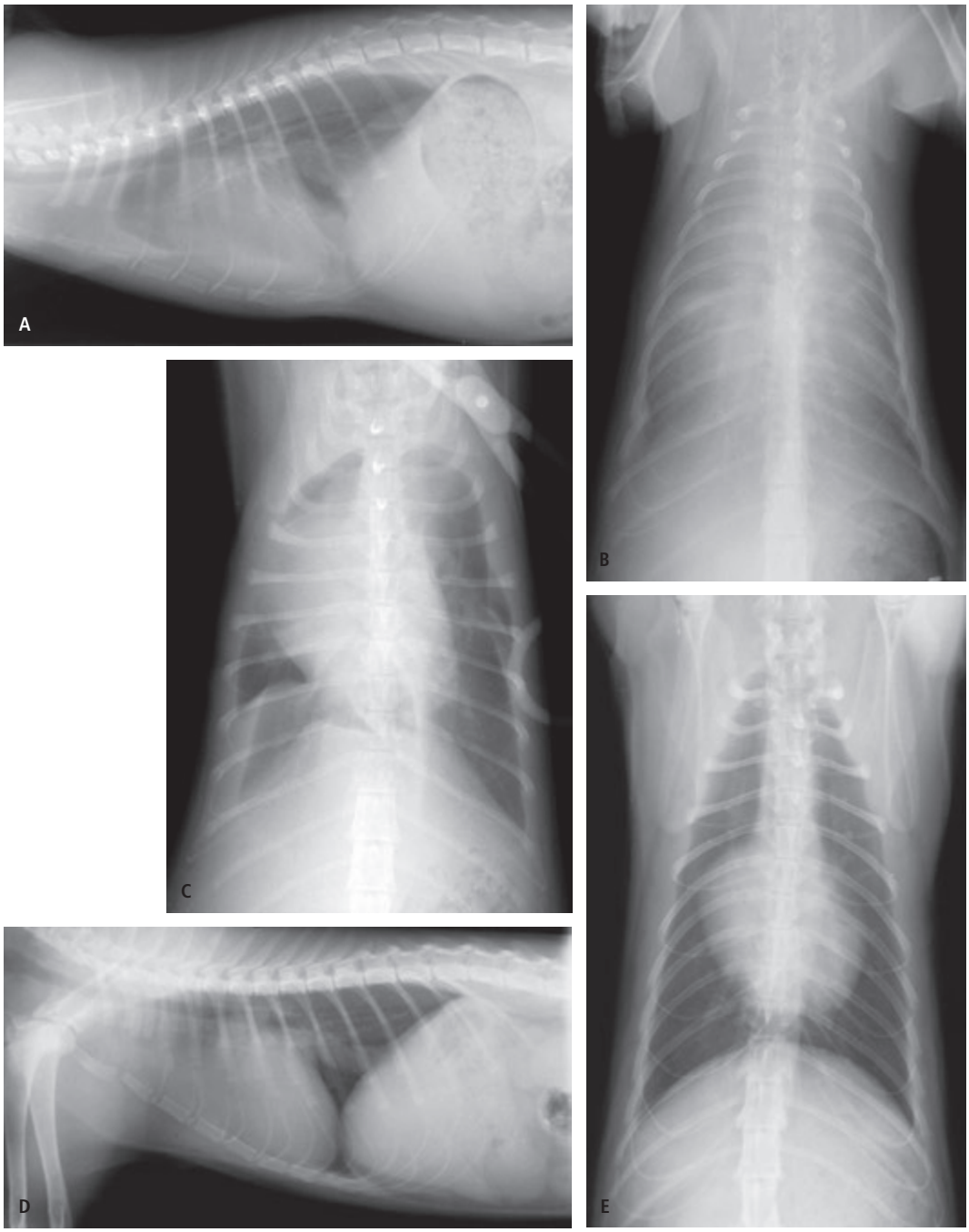


Figure 19.12. Thoracic radiographs of a cat with pleural effusion secondary to severe tricuspid valve dysplasia.

Right lateral **(A)**, dorsoventral **(B)**, and ventrodorsal **(C)** projections of thoracic radiographs of this dyspneic 6-month old domestic short-haired cat show severe pleural effusion. The ventrodorsal view (with the patient in dorsal recumbency) allows partial visualization of the cardiac silhouette due to the pooling of the pleural effusion dorsally above the heart and shows severe right-sided cardiomegaly. Radiographs after thoracocentesis and medical treatment with furosemide and enalapril show resolved pleural effusion and persistent severe right heart enlargement **(D)** and **(E)**. The caudal vena cava is severely dilated, indicating markedly elevated right atrial pressure (D).

there is cardiomegaly (normal range is 6.9–8.1, mean 7.5 ± 0.3 vertebrae) (Litster and Buchanan 2000; see Chapter 6). Using subjective assessment, left atrial dilation was only identified in 48% of cats with cardiogenic pulmonary edema in one study (Benigni et al. 2009). Conversely, another study found a much higher percentage (72%) of cats with subjective assessment of left atrial dilation on thoracic radiographs that had confirmed left atrial dilation by echocardiography (Schober et al. 2007). In that study, subjective assessment of left atrial size was

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moderately sensitive (72%) and specific (74%) for left atrial dilation.

Cats with right heart failure often have a dilated caudal vena cava, right heart enlargement, pleural effusion, and possibly loss of abdominal detail suggestive of ascites (see Figure 19.12). Assessment of a dilated caudal vena cava in cats is subjective, since there are no studies assessing caudal vena cava size in cats. Often the caudal vena cava is dilated and tortuous when there is severe right heart disease. In dogs, the ratio of the diameter of the caudal vena cava to the diameter of the descending aorta measured on a lateral thoracic radiograph >1.5 was strongly suggestive of right heart disease (Lehmkuhl et al. 1997). Caudal vena caval diameters may be indexed to the diameter of the T5 or T6 vertebra, and the mean normal CVC:V ratio is 0.75 ± 0.13, so a caudal vena caval diameter equal to or greater than the diameter of T5 or T6 may indicate dilation (Buchanan and Bucheler 1995). A globoid-shaped cardiac silhouette and cardiomegaly may be seen in cats with pericardial effusion.

There is a variable rate of resolution of cardiogenic pulmonary edema and pleural effusion in response to diuretic therapy. Although diuretics have an acute onset of action following intravenous administration and with repeated doses for treatment of dyspnea, radiographic improvement still lags behind clinical improvement by as much as 12–24 hours. Convincing early signs of radiographic improvement may occur within 12 hours, but overt decrease in respiratory effort is almost always apparent earlier, and often within 1 to a few hours after diuretic administration. Complete resolution of interstitial or alveolar infiltrates may take 24 hours or longer. Pleural effusion typically requires many days to resolve with diuretic treatment alone, which explains the need for thoracocentesis rather than diuretics in the acute stabilization stage when large-volume effusion is responsible for dyspnea.

Electrocardiogram

The electrocardiogram (ECG) is the diagnostic test of choice to evaluate a cardiac arrhythmia. It is insensitive for detection of chamber enlargement, but it is relatively specific. Common arrhythmias in cats with heart failure include atrial fibrillation, supraventricular tachycardia, ventricular premature complexes, and ventricular tachycardia. In a large retrospective study of cats diagnosed with atrial fibrillation, a large percentage of cats had heart failure consisting of pleural effusion (61% of cats) or pulmonary edema (22%). Cats with heart failure may have sinus tachycardia due to increased sympathetic tone. However, presence of sinus tachycardia does not discriminate between cats with heart failure and asymptomatic cats. In a large study of cats diagnosed with HCM, sinus tachycardia was not more frequent in cats with heart failure compared to cats without symptoms (Atkins et al. 1992). A left axis deviation (or left anterior fascicular block pattern) is commonly seen in cats with HCM (or in normal cats). Other arrhythmias that may be present in cats with heart failure include third-degree atrioventricular block, atrial standstill, ventricular tachycardia, or atrial premature complexes.

Echocardiogram

Basic "triage" echocardiogram

A "triage" echocardiogram is useful in emergency situations to define whether dyspnea is due to heart failure or primary respiratory disease. The purpose of the triage echocardiogram is to establish whether there is significant enough cardiac disease to cause the patient's clinical signs and help define whether emergency cardiac treatments are needed, which may include thoracocentesis, pericardiocentesis, diuretic therapy, anticoagulant therapy, and inotropic therapy. The essentials of the triage echocardiogram are to identify whether there is significant pleural effusion that would require immediate thoracocentesis, to evaluate for pericardial effusion and/or cardiac tamponade, to identify significant left or right atrial dilation, and to evaluate myocardial structure and function (subjectively or quantitatively). If there is no atrial dilation, the cranial mediastinum should be imaged for presence of a mediastinal mass in cats with pleural effusion.

A brief thoracic ultrasound is a useful and minimally stressful diagnostic technique for evaluation of significant pleural effusion in the unstable dyspneic cat. It is often a safer choice than thoracic radiographs in the unstable patient, because minimal restraint is needed for the ultrasound. The cat can be maintained in sternal recumbency and supplemented with oxygen if it is tolerated. The left and right sides of the thorax should be evaluated for significant pleural effusion, and the optimal location is identified for palliative thoracocentesis (see Chapter 3). Thoracocentesis is an immediately life-saving procedure in cats with severe pleural effusion and should be done quickly once the diagnosis has been made. After the cat stabilizes, a more thorough echocardiographic examination should be done to evaluate whether the pleural effusion is cardiogenic in origin.

Evaluation of pericardial effusion should also be done on a triage basis in cats with pleural effusion and/or ascites. Although it is uncommon for cats to develop moderate to severe pericardial effusion and cardiac tamponade, mild pericardial effusion not requiring pericar-

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diocentesis is common in cats with congestive heart failure. Moderate or severe pericardial effusion can cause cardiac tamponade and right heart failure. Careful distinction of pleural and pericardial effusion is necessary. The pericardium should be identified at its attachment to the heart base and is helpful to distinguish pleural from pericardial effusion. Cardiac tamponade is subjectively assessed by visualization of diastolic collapse of the right atrium and/or right ventricle. The left ventricle often appears underloaded when there is cardiac tamponade. This appears as a small ventricular internal diameter during diastolic and systole, and possibly mildly thickened left ventricular wall and septum (pseudohypertrophy). Accurate left ventricular measurements are only possible once the cardiac tamponade has been relieved. If there is life-threatening cardiac tamponade, immediate pericardiocentesis should be done prior to a comprehensive echocardiogram. However, if the patient is reasonably stable, a detailed echocardiogram should be done to evaluate for cardiac or pericardial masses, which are better visualized in the presence of pericardial effusion.

Identification of significant left and/or right atrial dilation is essential to establish the diagnosis of congestive heart failure versus primary respiratory disease, which has immediate treatment implications. Left atrial dilation suggests that the left atrial pressure is elevated, which occurs secondary to systolic myocardial failure, diastolic dysfunction, valvular insufficiency, or left to right shunting congenital heart diseases. Presence of significant left atrial enlargement indicates severe cardiac disease and implies a poorer long-term prognosis, although there is tremendous individual variation regarding disease progression, response to therapy, and survival. Left atrial enlargement is an independent predictor for serious adverse cardiac events in people with HCM and was associated with more severe diastolic dysfunction and higher filling pressures (Yang et al. 2005). Likewise, increased left atrial size is negatively correlated with survival time in cats with HCM (Rush et al. 2002). The left atrial size is measured from a right parasternal cross-sectional view at the level of the aortic valve (see Chapter 7). The left atrium and aortic diameters are measured either from a two-dimensional image or by using M-mode with the cursor placed through the body of the left atrium and the aorta. The ratio of left atrial diameter to aortic diameter (LA:Ao) is used to eliminate the influence of body size on left atrial size, and provides a dimensionless index of atrial size. Two-dimensional echocardiography is recommended for measurement of left atrial size, since it is not limited by the location and alignment of the cursor when using M-mode. The right parasternal short-axis basilar view at the level of the aortic cusps is obtained, and the first diastolic frame in which closure of the aortic valve is evident is selected. The aortic diameter (Ao) is measured by a line parallel to the commissures of the right coronary and noncoronary cusps, using the inner edge method (the internal diameter of the structure is measured not including the wall thickness) (see Chapter 7). The left atrial diameter (LA) is measured by a line parallel to the commissure of the left coronary and noncoronary cusp, with care to avoid the pulmonary vein insertion into the left atrium. An LA:Ao >1.5 indicates left atrial dilation. Although the degree of left atrial dilation is subjective, suggested criteria for mild, moderate, and severe left atrial dilation are LA:Ao 1.51–1.79, 1.79–1.99, and ≥2.0, respectively. Left atrial dilation is usually moderate to severe in cats with heart failure. Sometimes the left atrial size decreases to be only mildly dilated after acute aggressive diuretic therapy. If left atrial size is normal, it is highly unlikely that congestive heart failure is the cause of pulmonary infiltrates, and the cat should be evaluated for primary respiratory diseases. One exception is the cat that has undergone an acute exacerbating event, such as intravenous fluids, acute tachycardia, anesthesia in the preceding 48 hours, or Depo-Medrol® or other long-acting glucocorticoid injection in the preceding 7 days, where the left atrial size may not be markedly dilated in the face of congestive heart failure. Extremely rare causes of cardiogenic pleural effusion in the face of normal atrial size are constrictive pericarditis or a mass or an intraluminal cranial vena caval thrombus or mass. Pulmonary edema and/or pleural effusion may be seen in cats with significant left atrial dilation and left heart failure, whereas right atrial dilation and right heart failure lead to pleural effusion and/or ascites and pericardial effusion. Right atrial size is subjectively evaluated from the right parasternal long-axis 4-chamber view and the right parasternal cross-sectional view at the heart base. The right atrium is normally smaller than the left atrium and is dilated when it is subjectively larger than the left atrium. In cats with atrial dilation, it is essential to carefully evaluate for spontaneous echocardiographic contrast or a thrombus within the dilated atrium (see Chapter 20).

Myocardial structure and function are assessed from the right parasternal cross-sectional view at the level of the left ventricular papillary muscles. The fundamental objectives for the triage echocardiogram are to (briefly) assess myocardial structure and function and identify whether there is markedly reduced myocardial systolic function (e.g., dilated cardiomyopathy), overt concentric hypertrophy of the left ventricular wall and septum, or the ventricle appears relatively normal in structure and function. Cats with an overtly thickened

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left ventricle do not necessarily have congestive heart failure, but combined with left atrial dilation or an acute triggering event, this finding suggests a diagnosis of congestive heart failure. In cats with severe dilated cardiomyopathy, the myocardial failure is often obvious by subjective assessment. Left ventricular measurements obtained by two-dimensional measurements or M-mode measurements of the left ventricle at the level of the papillary muscles at end-diastole and end-systole (see Chapter 7). Increased end-systolic diameter over 11 mm and decreased fractional shortening <28% together indicate myocardial failure. Cats with dilated cardiomyopathy do not develop congestive heart failure until there is moderate to severe myocardial failure, with a fractional shortening <20% (usually <15%) (K. MacDonald, personal observation). Right ventricular eccentric hypertrophy (i.e., increased right ventricular diastolic diameter) is also present in cats with DCM and is subjectively evaluated. Cats with severe mitral regurgitation may develop secondary myocardial failure, especially of the left ventricular free wall, but fractional shortening is usually >28%. Marked or extreme enlargement of one or both atria, with echocardiographically normal-appearing ventricles, suggests restrictive or unclassified cardiomyopathy as the cause of congestive heart failure.

Comprehensive echocardiogram

A comprehensive echocardiogram is warranted in all cats with suspected or confirmed congestive heart failure since accurate determination of the underlying heart disease leads to optimal treatment and prognostication. End-diastolic interventricular septal thickness and left ventricular free wall thickness are measured using two-dimensional or M-mode echocardiography. Concentric hypertrophy is defined as interventricular septal and/or left ventricular wall thickness of 6 mm or greater, and may be present in cats with hypertrophic cardiomyopathy or secondary causes of concentric hypertrophy (i.e., systemic hypertension and hyperthyroidism) (see Chapter 11). Cats with secondary causes of concentric hypertrophy (i.e., hyperthyroidism or systemic hypertension) do not usually develop heart failure without additional underlying heart disease (i.e., concurrent hypertrophic cardiomyopathy or unclassified cardiomyopathy). Systolic anterior motion (SAM) of the mitral valve is visualized by two-dimensional Doppler and color-flow Doppler, and the severity is quantified by continuous-wave Doppler measurement of aortic blood flow velocity. SAM of the mitral valve adds weight to the suspicion of primary myocardial disease (hypertrophic cardiomyopathy) but is not absolutely specific for HCM. Abnormalities that may be identified in cats with heart failure from restrictive cardiomyopathy include marked, diffusely thickened and hyperechoic endocardium and hyperechoic subendocardium possibly obliterating the papillary muscles; fibromuscular bridging band tethering the left ventricle and the septum; restrictive filling pattern on pulsed-wave Doppler interrogation of the mitral inflow; and moderate to severe left atrial dilation. Typical abnormalities seen cats with congestive heart failure secondary to unclassified cardiomyopathy include moderate to severe left atrial dilation and/or right atrial dilation in the absence of significant myocardial failure or concentric hypertrophy. Color-flow Doppler may identify mild centrally arising atrioventricular valvular insufficiency.

Evaluation of congenital heart disease also requires a detailed comprehensive echocardiogram. A thorough assessment of the hemodynamic effects of the congenital heart malformation is essential to form an appropriate treatment plan and to identify patients that may be suitable for surgical correction. Difficulties in assessment of congenital heart disease may arise when there are multiple congenital abnormalities present, requiring a high level of expertise for accurate diagnosis. A combination of two dimensional echocardiography, color-flow Doppler, pulsed-wave Doppler, and continuous-wave Doppler is needed for adequate evaluation of congenital heart diseases. A positive contrast echocardiogram (using agitated saline) is often necessary to identify the presence and location of right to left shunting defects. Two-dimensional echocardiography is used to assess for chamber enlargement, concentric hypertrophy, morphologic defects of the cardiac valves, myocardial failure (in addition to M-mode echocardiography), and pulmonary artery dilation. Color-flow Doppler is used to assess valvular insufficiency, blood flow turbulence associated with stenotic lesions, and left to right shunting congenital defects. Continuous-wave Doppler is used to measure the peak velocity between two chambers, and the modified Bernouilli equation (i.e., pressure gradient = 4× velocity) (Rush 2002) is used to calculate intracardiac and extracardiac (aortic and pulmonary arteries) pressure gradients (see Chapter 7). This technique is necessary to determine the severity of the congenital heart disease and to assess for presence of pulmonary hypertension. Please refer to Chapter 10 for detailed information regarding principles and application of echocardiography for diagnosis of specific congenital heart diseases.

Assessment of diastolic function is not essential to diagnose or treat heart failure, but it may provide information that supports the diagnosis of diastolic heart failure (Zile and Brutsaert 2002). Techniques used to assess diastolic function include pulsed-wave Doppler interrogation of the mitral inflow, pulsed-wave tissue

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Doppler echocardiography, color-tissue Doppler echocardiography, and quantification of left ventricular wall stress and strain. Measurement of mitral inflow velocities is relatively simple and fast and may readily identify delayed relaxation or restrictive filling patterns. Delayed left ventricular relaxation commonly occurs in cats with HCM, most often in the initial stage of diastolic dysfunction. Identification of a restrictive filling pattern (early to late diastolic filling wave ratio [E:A] >2, decreased deceleration time, and decreased isovolumic relaxation period) indicates severe diastolic dysfunction and severely elevated left atrial pressure. Fusion of early diastolic filling wave (E) and late diastolic filling wave (A) during tachycardia (HR > 180 bpm) disables the ability to assess diastolic dysfunction by this technique. Likewise, a pseudonormal pattern may be identified in cats with moderate diastolic dysfunction, which is challenging to differentiate from normal mitral inflow velocity profile (see Chapters 7 and 11). Tissue Doppler imaging (TDI) echocardiography is a sensitive test for diagnosis of diastolic dysfunction in cats with a variety of cardiac diseases. It is not plagued by a "pseudonormal" filling pattern, and there are varying opinions about its validity when E′ and A′ waves are summated during tachycardias whereby an individual E′ wave is not measurable. Pulsed-wave TDI is a fast and relatively simple technique that does not require postprocess analysis and is readily available on many moderate-level echocardiographs. Diastolic dysfunction is identified as a reduced early diastolic wave velocity. Diastolic function of the longitudinal muscle fibers is assessed by measurement of the mitral annular and septal myocardial velocities using the 4-chamber left apical view. Diastolic function of the circumferential myocardial fibers of the interventricular septum and left ventricular free wall is assessed from the right parasternal cross-sectional view at the level of the papillary muscles. The longitudinal fibers are often the first to develop diastolic dysfunction in HCM, so measurement of the lateral mitral annular velocity and septal velocity using the left apical view may be most useful (Koffas et al. 2002). Color TDI echocardiography is another technique to assess diastolic dysfunction and is much less impacted by translational movement of the heart. Color TDI allows for simultaneous assessment of myocardial function in limitless regions of the ventricle and quantifies endocardial to epicardial velocity gradients. Limitations include the need for postprocessing imaging and a higher level of expertise to appropriately analyze the data.

A noninvasive method to assess left atrial pressure would be useful to confirm the diagnosis of left-sided congestive heart failure and track response to therapy. Although there is a lack of data in cats with heart disease, an echocardiographic index of left ventricular filling pressure has been evaluated in people and dogs with heart disease. The index of transmitral early mitral inflow velocity (E) to early diastolic mitral annular velocity (E′) is a useful, noninvasive method to estimate LV filling pressure in normal people (r = 0.87) and people with HCM (r = 0.8) (Nagueh et al. 1997, 1999). E/E′ >10 predicted LV filling pressure (just before atrial systole) of >15 mm Hg, and yielded the best sensitivity (92%) and specificity (85%) compared to TDI measurements (E′) or mitral velocity profiles alone in people (Nagueh 1999). In dogs with acute experimentally induced mitral regurgitation, E/E′ was highly correlated (r = 0.83) with mean left atrial pressure (Oyama et al. 2004). An LA pressure >20 mm Hg was highly probable when mean E/E′ was >9.1 (Oyama et al. 2004). Mitral inflow E/velocity of propagation by TDI was moderately correlated to LV end-diastolic pressure in anesthetized normal cats (r = 0.64) (Chapter 11) (Schober et al. 2003). No studies have evaluated the ability of E/E′ to predict pulmonary capillary pressure in cats with cardiac disease.

Arterial blood pressure

Measurement of arterial blood pressure is an important diagnostic test to evaluate for systemic hypertension or hypotension. Systemic hypertension may contribute to concentric hypertrophy and diastolic dysfunction, but in the absence of other heart disease does not lead to heart failure (see Chapter 21). Systemic hypertension must be distinguished from high sympathetic tone and "white coat" hypertension, which may be present in a stressed cat. Dyspneic cats with high sympathetic tone may have a physiologically elevated blood pressure that improves once they are clinically stabilized with resolution of dyspnea and normalized sympathetic tone. If there is persistently elevated blood pressure (>160 mm Hg) on serial measurements in the stable heart failure patient, antihypertensive treatment of the systemic hypertension is recommended (see Chapter 21). Cats with severe mitral valvular disease and heart failure may benefit from antihypertensive medications as an afterload reducer, and systolic blood pressure should be maintained at or below 140 mm Hg, unless a cat shows intolerance to the medication's effect (i.e., becomes clinically hypotensive). Avoidance of hypotension and reflex tachycardia is important in cats with HCM who have impaired diastolic filling, and hypotension also worsens the severity of left ventricular outflow tract obstruction in these cats. In cardiac patients, systemic hypotension is often an end-stage abnormality in cats with markedly reduced cardiac output and low output heart failure. Identification of systemic hypotension is important, as

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these patients require a reduction or termination of antihypertensive medications if they are receiving them; intravenous therapy with fluid replacement if hypovolemic, or vasopressors if persistently hypotensive when euvolemic; and careful monitoring.

Central venous pressure

Measurement of elevated central venous pressure (>10 mm Hg) may help confirm the diagnosis of right-sided congestive heart failure. A jugular venous catheter may be placed; the tip of the catheter is advanced to the junction of the cranial vena cava and right atrium, and a radiograph is obtained to confirm appropriate placement (Petrollini 2007; de Madron 2011). Multiple invasive pressure measurements are obtained with the manometer placed at the level of the heart. Thoracocentesis should be done prior to measurement of CVP for two reasons: 1) the cat will be more stable and a better candidate for the jugular catheterization procedure, and 2) pleural effusion independently elevates CVP and may obscure one's ability to discriminate right heart failure from other causes of pleural effusion. In an experimental study of cats with congestive heart failure and cats with iatrogenic pleural effusion, there was a positive linear relationship between central venous pressure and pleural fluid volume (Gookin and Atkins 1999). The mean difference in CVP before and after thoracocentesis was 4.5 mm Hg. However, only cats with pleural effusion secondary to right-sided CHF had a CVP >10 before and after thoracocentesis.

Pleural effusion analysis and cytology

Pleural effusion fluid analysis with cytology is a necessary diagnostic test to help refine the differential diagnoses for cats with pleural effusion. Heart failure can be ruled out if the fluid is classified as a septic exudate, nonseptic exudate, or hemorrhagic effusion. Fluid characteristics of cardiogenic pleural effusion are highly variable, and may be classified as a transudate, modified transudate, chylous, or pseudochylous (see Chapter 3).

Measurement of fibronectin concentration of pleural effusion was useful to discriminate heart failure from neoplastic etiologies in cats (Hirschberger and Pusch 1996). Using pooled plasma samples, a discrimination line of 31.5% yielded a sensitivity of 100% for diagnosis of neoplastic pleural effusion (which all had higher fibronectin levels) (Hirschberger and Pusch 1996). Although there is no feline or canine specific test to measure fibronectin concentration, a nephelometric test kit for human fibronectin has been validated for use in cats and dogs. The clinical utility of this test is likely low unless it becomes readily available in commercial veterinary laboratories for clinical samples.

Specific Blood Tests

Specific blood tests include the following:

- Plasma and whole blood taurine levels should be measured in cats with dilated cardiomyopathy to evaluate for taurine deficiency induced myocardial failure.
- Neurohormonal biomarkers for heart disease and heart failure include atrial natriuretic peptide, brain natriuretic peptide, troponin I, and endothelin 1.
- The inactive fragment amino terminal proBNP (NT-proBNP) is a useful screening test to evaluate whether dyspnea is due to heart failure or primary respiratory disease in cats.

Whole blood and plasma taurine

Plasma and whole blood taurine concentrations should be measured in any cat with echocardiographic evidence of significant myocardial failure regardless of diet history (see Chapter 13). It is important to recognize taurine deficiency when it exists since it confers a much better prognosis than the grave prognosis of idiopathic dilated cardiomyopathy. Although taurine deficiency is defined as plasma taurine <60 nmol/ml and whole blood taurine <250 nmol/ml, most cats with taurine deficiency induced myocardial failure have markedly lower plasma taurine concentrations, typically less than 20 nmol/ml and whole blood concentration typically less than 100 nmol/ml.

Circulating biomarker tests

Natriuretic peptides

Natriuretic peptides, including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), are a family of neurohormones that have emerged as useful biomarkers for heart disease, heart failure, and early cardiovascular mortality in people (Bettencourt et al. 2002). BNP is upregulated in various cardiac diseases that result in systolic or diastolic dysfunction and are further elevated in proportion to the severity of heart failure. Veterinary medicine is now exploring the use of these neurohormones as screening tests for heart disease and heart failure in dogs and cats, and early experience is very encouraging.

Natriuretic peptides share common biologic effects of increased renal excretion of sodium and water, vasodilation by inhibiting endothelin I and renin (thereby decreasing angiotensin II), and modulation of the sympathetic nervous system. Atrial natriuretic peptide is synthesized in the atria and stored in granules, which are released when the atria are volume overloaded and walls

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are stretched. Brain natriuretic peptide is normally synthesized as a prohormone (pre-proBNP) in the atria. However, in the presence of increased ventricular wall stress or neurohormonal stimulation (endothelin I and/or angiotensin II), ventricular synthesis of BNP is upregulated. In healthy cats, BNP is concentrated in the right auricle and is present diffusely throughout the left atrium. It has a novel expression in the left ventricle in cats with hypertrophic cardiomyopathy (Biondo et al. 2003). Activation of BNP transcription is one of the earliest and most reliable markers of ventricular cardiomyocyte hypertrophy (Liang et al. 2001). Ventricular BNP secretion also increases with increasing severity of left ventricular dysfunction (Yasue et al. 1994). Upon secretion, pro-BNP is cleaved into an inactive fragment amino-terminal proBNP (NT-proBNP) and BNP. NT-proBNP has a longer circulating half-life than the biologically active BNP molecule.

Measurement of plasma [ANP], [BNP], and [NT-proBNP] is a useful method for diagnosis of heart disease and heart failure in people, dogs, and cats (Maisel et al. 2003; Fine et al. 2008; Boswood et al. 2008; DeFrancesco et al. 2007; Prosek et al. 2007; Fox et al. 2009). Using a rapid point-of care-assay, plasma [BNP] is highly sensitive for diagnosis of systolic heart failure (e.g., DCM) (95%) and diastolic heart failure (e.g., HCM or RCM) (86%) in people, and is an essential tool to help differentiate primary respiratory disease versus heart failure as a cause of dyspnea (Maisel et al. 2003). People with systolic heart failure had significantly higher plasma [BNP] than people with diastolic heart failure (812 pg/ml vs 413 pg/ml, respectively, $P < 0.001$), which may be due to greater ventricular wall stress with dilated cardiomyopathy (Maisel et al. 2003). In a small pilot study of cats, plasma [BNP] and [NT-ANP] were elevated in asymptomatic cats with cardiomyopathy and were further elevated in cats with CHF or arterial thromboembolism (normal cats: mean plasma [BNP] = 11.6 pg/ml and [NT-proANP] = 0.54 pmol/ml; asymptomatic: mean plasma [BNP] = 98 pg/ml and [NT-proANP] = 0.83 nmol/ml; heart failure/ATE: mean plasma [BNP] = 185 pg/ml and plasma [NT-proANP] = 2.3 nmol/ml), although significant overlap existed between the groups (Sisson et al. 2003). BNP appears to have a greater diagnostic potential than ANP given its greater degree of elevation (10-fold increase for BNP versus 4–5-fold increase for ANP) in cardiac disease and CHF in cats (Sisson 2004). A commercially available ELISA test measuring the inactive fragment NT-proBNP has been evaluated in 68 dyspneic cats, and it was useful to discriminate between cats with congestive heart failure (CHF) and cats with primary respiratory disease. Cats with CHF had significantly higher [NT-proBNP] than cats with primary respiratory disease (846 pmol/l vs 53 pmol/l, $P < 0.001$). [NT-proBNP] greater than 265 pmol/l was highly sensitive (90%) and specific (88%) for diagnosis of heart failure in dyspneic cats, although it is important that false positives may exist, and a mildly to moderately elevated [NT-proBNP] may occur in the presence of renal failure and reduced renal clearance of the hormone (Connolly et al. 2008; Schmidt et al. 2009). NT-proANP appears to be less useful than NT-proBNP since it was not different in asymptomatic cats with HCM compared to normal control cats (MacLean et al. 2006) (see Chapter 8 for greater detail).

Plasma [BNP] has also been used to predict a patient's response to treatment and assess prognosis in human medicine (Bettencourt et al. 2002; Cheng et al. 2001; Troughton et al. 2000; Koglin et al. 2001). Serial plasma [BNP] measurements of hospitalized human patients with CHF have been shown to predict treatment outcome and mortality (Bettencourt et al. 2002; Cheng et al. 2001). Patients whose plasma [BNP] declined during hospitalization were much less likely to be rehospitalized or die than patients whose plasma [BNP] increased during hospitalization (Bettencourt et al. 2002; Cheng et al. 2001). Optimal reevaluation period for plasma [BNP] was 7 days following heart failure treatment in a human study (Wu et al. 2004). In one study, when diuretic therapy of CHF was guided by plasma NT-BNP, there were fewer cardiovascular events and the time to the first event was delayed compared to treatment using standard clinical criteria (Troughton et al. 2000). Patients with BNP-guided treatment received higher diuretic doses than patients treated in the standard clinical manner (Troughto et al. 2000). Future veterinary studies are needed to evaluate plasma [BNP] during treatment of CHF, evaluate it as a prognostic indicator of early cardiovascular mortality, and assess whether measurement of plasma [BNP] can be used to help tailor medical treatment of CHF. Currently, NT-proBNP is the most promising feline cardiac biomarker for identifying and monitoring cats with congestive heart failure. Its role appears to be one that complements, but does not replace, the traditional cornerstones of diagnosis: history, physical exam, thoracic radiography, and echocardiography.

Troponin I

Cardiac troponin I is released when there is cardiomyocyte damage. Serum cardiac troponin I (cTnI) has been studied in cats with cardiomyopathy and heart failure, and has been shown to be a sensitive biomarker for heart failure in cats (sensitivity 87%, specificity 84%), but does not distinguish symptomatic cats from asymptomatic cats (Connolly et al. 2003). Another study found contradictory results, where cTnI was increased in asymptomatic cats with cardiomyopathy and was further increased

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in symptomatic cats with heart failure (Herndon et al. 2002). Normal reference ranges are not interchangeable between the different cTnI sandwich assays. A positive cTnI value obligates the clinician to better identify presence of heart disease and possibly heart failure by echocardiography and thoracic radiographs.

Conclusive Diagnosis

Congestive heart failure may be conclusively diagnosed based on radiographic abnormalities of pulmonary edema and/or pleural effusion, cardiomegaly with or without pulmonary venous distension, and echocardiographic evidence of left and/or right atrial dilation. Echocardiography is essential to confirm that there is moderate to severe heart disease, since congestive heart failure is a consequence of severe heart disease. Congestive heart failure occurs when there is significantly elevated left ventricular or right ventricular diastolic filling pressure, which leads to left or right atrial dilation, respectively. Therefore, if atrial size is normal, it can be assumed that the diastolic filling pressure is not significantly increased, and the cat is unlikely to have congestive heart failure. The only exceptions include a recent, acute inciting cause such as subcutaneous or intravenous fluid administration, anesthesia, or repositol glucocorticoid administration, which may lead to heart failure in the face of less substantial left atrial dilation or uncommonly normal left atrial size. Other rare exceptions are significant pericardial effusion causing cardiac tamponade or constrictive pericarditis (a rare disease in cats). The second criterion for conclusive diagnosis of congestive heart failure is the reduction or resolution of fluid accumulation following appropriate diuretic therapy, thus proving that the infiltrates or pleural effusion were actually due to congestive heart failure and not other systemic disease. Pleural effusion characteristics that are consistent with heart failure range from a transudate, modified transudate, pseudochylous, or chylous effusions. If pleural effusion is classified as exudative or hemorrhagic, then the diagnosis is not congestive heart failure. In cats with pleural effusion and/or ascites, measurement of an elevated central venous pressure (≥10 mm, after removal of pleural effusion) supports the diagnosis of right heart failure. A supportive diagnosis (not definitive) may be based on radiographic abnormalities including cardiomegaly and pulmonary edema and/or pleural effusion, with resolution of the fluid accumulation after diuretic therapy. Since radiographic appearance of heart failure in cats is highly variable without a pathognomonic pattern, the clinician is encouraged to obtain an echocardiogram to definitively diagnose the etiology and severity of the heart disease.

TREATMENT

Outpatient Treatment of Mild to Moderate Congestive Heart Failure

Outpatient treatment includes the following:

- Furosemide is the drug of choice for treatment of congestive heart failure.
- Furosemide is a powerful loop diuretic that can be given orally at doses ranging from 1 mg/kg PO q 24 hr for mild congestive heart failure to a maximal dose of 4 mg/kg PO q 8 h for severe refractory heart failure.
- Because furosemide activates the RAAS, it is recommended to combine furosemide and an ACE inhibitor for treatment of heart failure.
- ACE inhibitors (enalapril 0.5 mg/kg PO q 12–24 hr, ramipril 0.5 mg/kg PO q 24 hr, or benazepril 0.5 mg/kg PO q 24 hr) may provide adjunctive benefit for treatment of heart failure.
- ACE inhibitors may cause functional azotemia by reducing angiotensin II and dilating the efferent glomerular arterioles. Azotemia is typically mild, but may be severe and is usually reversible. Monitoring renal function at baseline and 1 week after starting medical therapy is therefore recommended.
- Prophylactic anticoagulant therapy is recommended for cats with spontaneous contrast (i.e., smoke) or a thrombus seen on echocardiography, and also may be indicated for cats with moderate to severe atrial dilation. Choices include clopidogrel (18.75 mg PO q 24 hr with food), baby aspirin (5–81 mg PO q 3 days), enoxaparin (1.5 mg/kg SC q 8–12 h), or warfarin (0.1–0.2 mg/kg PO q 24 hr titrated based on prothrombin time).

The approach to treating congestive heart failure is chosen according to severity of signs (dyspnea) and anticipated timeline of improvement (Table 19.1). In the acute setting, cats may have mild signs for which outpatient treatment is acceptable, and these are presented here first. Patients that are candidates for outpatient home treatment are those that have mild tachypnea or dyspnea, mild pleural effusion or pulmonary edema evident on radiographs, or those having a large volume of pleural effusion removed by thoracocentesis with subsequent normalization or near normalization of respiratory rate and effort. Patients with acute signs that are severe and considered possibly to be life-threatening are discussed second in the section "Treatment of Hospitalized Cats with Acute Congestive Heart Failure." Finally, treatment of chronic or refractory heart failure is discussed in the section "Treatment of Refractory Congestive Heart Failure." These cats continue to display clinical signs of dyspnea due to confirmed congestive

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Table 19.1. Medical therapy and monitoring of cats with congestive heart failure

	Drug	Dosage	Follow-up
Mild heart failure	Furosemide	6.25 mg PO q 12–24 hr	1 week: TXR, BP, chemistry
	ACE inhibitor. Options include:		
	Enalapril	0.5 mg/kg PO q 12–24 hr	3–4 months: TXR, BP, chemistry, PCV/TS (or CBC), ± UA, ± echo
	Benazepril	0.5 mg/kg PO q 24 hr	
	Ramipril	0.5 mg/kg PO q 24 hr	Then every 4–6 months
	Anticoagulant[1]		
	Clopidogrel OR	18.75 mg PO q 24 hr	
	aspirin	5–81 mg PO q 3 days	
	+ specific treatment targeting the functional heart disease present		
Moderate heart failure	Furosemide	12.5 mg PO q 12 hr or 2–3 mg/kg PO q 12 hr	1 week: TXR, chemistry, BP
	ACE inhibitor		1–2 months: TXR, BP, chemistry, PCV/TS (or CBC), UA, ± echo
	Anticoagulant[1]		
	+ specific treatment targeting the functional heart disease present		Then every 3–4 months
Severe heart failure	Furosemide	12.5 mg PO q 8 hr or 3–4–mg/kg PO q 8–12 hr	5–7 days: TXR, BP, chemistry
	ACE inhibitor		Then every 6–8 weeks to increase to every 3–4 months if stable TXR, BP, chemistry, PCV/TS (or CBC), UA, ± echo
	Anticoagulant		
	Low-salt Diet		
	+ specific treatment targeting the functional heart disease present		
Acute heart failure	Furosemide	2–4 mg/kg IV q 1–4 hr until RR decreases to <50/min and effort improves, then 2–3 mg/kg q 6–8 hr	Renal panel q 12–24 hours, TXR q 24–36 hours until clinically stable & discharged
	Oxygen	50–60% FiO2 for <12 hr then <50%	1 week: TXR, chemistry, BP
	± Nitroglycerin	1/8–1/4 inch transdermal q6 hr x 1–2 days; or 12 hr on 12 hr off for 3 days	Then every 6–8 weeks, to increase to every 3–4 months if stable TXR, BP, chemistry, PCV/TS (or CBC), UA, ± echo
	± Dobutamine	5–15 mcg/kg/min	
	+ specific treatment targeting the functional heart disease present		
	ACE inhibitor[2]		
Refractory heart failure	Furosemide	4 mg/kg PO q 8 hr, may substitute or add 1–2 SC doses/week for PO dose	Same as severe heart failure
	ACE inhibitor[2]		
	Hydrochlorothiazide	1–2 mg/kg PO q 12–24 hr	
	± Spironolactone	1–2 mg/kg PO q 12–24 hr	
	Low-salt diet		
	+ specific treatment targeting the functional heart disease present		

[1] If moderate or severe atrial dilation, spontaneous contrast, or intracardiac thrombus.
[2] Once home, eating and drinking. TXR, thoracic radiograph; BP, blood pressure; chemistry, serum biochemistry profile (renal values and electrolytes may be sufficient); CBC, complete blood count; PCV/TS, packed cell volume/total solids; UA, urinalysis; RR, respiratory rate.

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heart failure despite up titration and maximization of furosemide dose (typically 3–4 mg/kg PO q 8–12 h) and standard adjunctive therapy.

General Principles

A combination of furosemide and an ACE inhibitor is the standard treatment of congestive heart failure, irrespective of the specific etiology. Chronic oral dosing of furosemide ranges from 1 mg/kg PO q 24 hr to a generally-accepted maximal dose of 4 mg/kg PO q 8 h. Since the veterinary formulation of furosemide is available as 12.5 mg tablets, cats are typically given 6.25 mg PO q 12–24 h for mild congestive heart failure and 12.5 mg PO q 12 h for moderate heart failure in cases not requiring hospitalization. In order to help clear pulmonary edema rapidly, often an injection of furosemide is given before the patient leaves the hospital, a higher initial dose is used for the first several days to a week, and then the dose is decreased to the lowest effective dose that maintains the cat free from clinical symptoms or radiographic evidence of heart failure. Although there is no clinical evidence that ACE inhibitors increase survival time in cats with heart failure, their use in cats is supported by anecdotal experience and extrapolations from people and dogs with heart failure (Fox 2003).

A majority of cats with heart failure have diastolic dysfunction and preserved systolic function. Diastolic heart failure is also more commonly recognized in human medicine, with the proportion of cases ranging from 40–71% (Kindermann et al. 2008). Even in human medicine, there is "a paucity of evidence for the treatment of heart failure associated with normal left ventricular ejection fraction" (i.e., diastolic heart failure) (Kindermann et al. 2008). There is theoretical rationale to inhibit the RAAS in patients with diastolic heart failure, which would consequently reduce myocardial hypertrophy and fibrosis. However, although there are large numbers of (human) patients enrolled in clinical trials of ACE inhibitors and angiotensin receptor blockers, "the evidence from these trials are inconclusive, and add up to a positive trend for morbidity end points for ACE inhibitors and the angiotensin receptor blocker candesartan, without any conclusive effect on mortality" (Kindermann et al. 2008).

Diuretic Therapy

Furosemide, a potent diuretic, is the drug of choice for treatment of congestive heart failure. As a loop diuretic, furosemide inhibits the sodium-potassium-chloride cotransporter ($Na^+/K^+/2Cl^-$) in the thick ascending loop of Henle of the renal tubule, which causes urinary loss of water and electrolytes including sodium, chloride, potassium, calcium, and magnesium. By reducing plasma blood volume, furosemide decreases diastolic filling pressure and hydrostatic pressure to decrease edema formation. Hemodynamic effects of decreasing preload include reduction in pulmonary capillary pressure, pulmonary artery pressure, and central venous pressure. Because furosemide activates the renin-angiotensin-aldosterone system, concurrent use of an ACE inhibitor is recommended.

Furosemide is efficacious by oral or parenteral administration; the route of administration chosen depends on the severity of the heart failure. Minimal effective dose is typically 1 mg/kg, with a maximal ceiling dose of approximately 4 mg/kg orally and much higher parenterally (see the section "Treatment of Hospitalized Cats with Acute Congestive Heart Failure, later in this chapter). Oral dosing frequency can be as low as daily and as high as every 8 hours, depending on the severity of the heart failure. The lowest effective dose of furosemide that resolves the clinical signs and radiographic evidence of heart failure with minimal side effects should be selected. Often a higher initial dose of furosemide is used for a few days to a week to effectively clear the edema or pleural effusion, and then the lowest effective dose is used to maintain the cat free of symptoms from edema formation. As heart failure severity worsens, increasing frequency of dosing rather than increasing the dose may more effectively increase diuresis, since the duration of diuresis lasts only up to 6 hours after oral administration.

Drug properties of furosemide

Furosemide is highly protein bound (86–91%), trapping it within the vascular space to be delivered to the proximal renal tubule, where 55% is excreted in the urine. The remainder of the drug is eliminated by the liver. Renal excretion of furosemide is dependent on adequate blood flow to deliver the drug and adequate renal function to excrete the drug. Decreased cardiac output and renal blood flow may be a consequence of congestive heart failure. Furosemide has a short half-life of 1.5–2 hours. Once the diuretic effect has dissipated, the nephron avidly reabsorbs sodium in a process called *rebound sodium retention*. This is thought to occur due to distal nephron hypertrophy and is likely an explanation for the lessened diuretic effect seen over weeks to months in the cat and other species. Renal insufficiency prolongs the plasma half-life of furosemide because the excretion is slower, and congestive heart failure prolongs the half-life due to decreased renal perfusion. The average bioavailability of furosemide is 50%, but there is a marked individual variability ranging from 10–100%, creating unpredictability in dose responses (Brater 1998).

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Pharmacodynamic effects of furosemide

In the cat, acute diuresis occurs 5 minutes after intravenous injection of furosemide, with a peak diuretic effect seen at 15 minutes (Friedman and Roch-Ramel 1977). In a study of normal anesthetized cats, urinary flow rate increased by 6, 15, and 18-fold after intravenous injections of 0.2 mg/kg, 1 mg/kg, and 5 mg/kg of furosemide (Friedman and Roch-Ramel 1977). Renal blood flow was increased up to 45% of control in a dose-dependent manner without altering glomerular filtration rate, indicating balanced dilation of afferent and efferent renal arterioles (Friedman and Roch-Ramel 1977). The increase in renal blood flow is abolished by pretreatment with inhibitors of prostaglandin synthesis including indomethacin (Kirschenbaum et al. 1974). Nonsteroidal anti-inflammatory drugs also lessen the diuretic response to furosemide by increasing solute reabsorption at the thick ascending loop of Henle, and this potential contributor to diuretic resistance, particularly in cats taking aspirin or clopidogrel for anticoagulation, has not been investigated in this species (Chennavasin et al. 1980).

Adjunctive physiologic effects of furosemide

Furosemide causes a dose-dependent direct venodilator effect that occurs 5 minutes after intravenous injection, prior to onset of diuresis (Bayne and Williamson 1979). The venodilation appears to be mediated by a local vascular prostaglandin synthesis and local release of nitric oxide (de Berrazueta et al. 2007). Acute pulmonary venodilation decreases preload and lessens pulmonary edema accumulation. Furosemide also causes bronchodilation in horses and people, although no studies have evaluated this in dogs or cats (Niven 2003; Rubie et al. 1993). In horses with recurrent airway obstruction, 1 mg/kg furosemide IV reduced pulmonary resistance and increased lung compliance acutely within 15 minutes after administration, which persisted for 5 hours. This effect was mediated by prostanoids rather than by a diuretic effect. Sometimes cats are incorrectly diagnosed with congestive heart failure yet improve after furosemide administration. An intriguing postulate is that they improve due to furosemide induced bronchodilation, but this has not been studied in cats.

Angiotensin Converting Enzyme Inhibitors (ACEIs)

ACE inhibitors are the standard of care for treatment of congestive heart failure in dogs as well as people, but studies are lacking in cats (Ettinger et al. 1998; IMPROVE Study Group 1995; COVE Study Group 1995; BENCH Study Group 1999). Several clinical trials have identified improved survival, clinical reduction in heart failure class, fewer hospitalizations, reduced morbidity scores, and improved exercise abilities in dogs with CHF due to naturally occurring DCM or mitral valve disease (Ettinger et al. 1998; IMPROVE Study Group 1995; COVE Study Group 1995; BENCH Study Group 1999). Hemodynamic benefits in dogs with CHF include mild reductions in heart rate, mean arterial pressure, pulmonary artery pressure, and marginal reduction of pulmonary capillary pressure (IMPROVE Study Group 1995). There is only one prospective, randomized, blinded multicenter study that has evaluated the effect of enalapril compared to diltiazem or atenolol, on survival in symptomatic cats with congestive heart failure or arterial thromboembolism. 118 cats were enrolled, including 57 cats with HCM and 37 cats with HOCM. Although no treatment improved survival, there was a trend toward improved survival in the enalapril group ($p = 0.06$), and effects may have been underestimated due to the low power of the study (~30 cats/group) (Fox 2003). Early use of ACE inhibitors as monotherapy in asymptomatic cats with HCM does not appear to be warranted, based on a placebo-controlled, blinded, randomized, prospective clinical study in 26 Maine coon cats with familial HCM (MacDonald et al. 2006).

Drug properties of ACE inhibitors

The negatively charged group of the ACE inhibitor binds to the zinc ions of ACE, preventing access by ACE substrates including angiotensin I and the vasodilator bradykinin (Zhu et al. 1997; Brown and Vaughan 1998; Wong et al. 2004). By inhibiting the action of ACE, angiotensin II formation is reduced and bradykinin (a vasodilator) is increased. The potency and duration of an ACE inhibitor depends on its binding characteristics rather than its tissue penetrating properties (Shu et al. 1997; Zeitz et al. 2003). The majority of ACE inhibitors are administered as a pro-drug (i.e., enalapril), which is metabolized by the liver into the active drug (i.e., enalaprilat). Most ACE inhibitors, except benazepril and ramipril, are eliminated entirely by the kidneys, and reduction of dosage is necessary in the face of renal dysfunction (Vuong and Annis 2003). Benazepril is mainly metabolized by the liver (85%), and pharmacokinetics are unaffected by renal dysfunction (King et al. 2002). Likewise, 87% of ramiprilat was eliminated in the feces in healthy cats, although no studies have been done to evaluate whether pharmacokinetics are altered by renal dysfunction (Desmoulins et al. 2008). Gastrointestinal absorption of ACE inhibitors is not affected by presence of food. The clinical relevance of renal versus hepatic elimination of ACE inhibitors applies to cats with acute oliguric or anuric renal failure, who may be unable to effectively eliminate renally excreted ACE inhibitors. Cats with both congestive heart

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failure and acute anuric or oliguric renal failure are uncommon, making the difference between classes of ACE inhibitors clinically trivial. Chronic kidney disease, with gradual loss of renal function, is much more common in cats, and drug dosage adjustments should be made periodically with all drugs based on timely assessment of renal function.

Pharmacokinetic and pharmacodynamic studies have been done with enalapril, benazepril, and ramipril in cats to define appropriate dose and dose intervals. The most important pharmacodynamic effect used to determine appropriate dosing is the magnitude and duration of ACE activity inhibition. Enalapril doses of 0.25 mg/kg, 0.5 mg/kg, and 1 mg/kg PO q 12 or 24 hr were evaluated, and there was equal ACE inhibition when a daily dose of 0.5 mg/kg or 1 mg/kg were given (Uechi et al. 2002). Therefore, an appropriate dose of enalapril is 0.5 mg/kg PO q 24 hr. However, q 12 hr dosing is often clinically used and is also acceptable. Benazepril causes acute and sustained ACE inhibition of >90%, persisting over 24 hours with doses of 0.25–1 mg/kg PO q 24 hr (King et al. 1999). Twenty-four hour trough ACE activity was significantly less in cats treated with 0.5 or 1 mg/kg PO q 24 hr than cats given 0.25 mg/kg PO q 24 hr (King 1999). Therefore, an appropriate dose of benazepril in cats is 0.5 mg/kg PO q 24 hr. Ramipril is a long acting (terminal half-life >20 hr), lipophilic pro-drug that is converted to ramiprilat in the liver. Ramiprilat binds to circulating and tissue bound ACE, and inhibits its action (King et al. 2003). At a dose of 0.5 mg/kg PO q 24 hr, the maximal inhibition of plasma ACE activity was 100%, and 24 hours trough ACE inhibition was 81% in one study (Desmoulins et al. 2008). Therefore, an appropriate dose of ramipril in cats is 0.5 mg/kg PO q24 hr.

ACE and aldosterone escape

Treatment with ACE inhibitors blocks conversion of angiotensin I to angiotensin II (and subsequently, production of aldosterone). Therefore, a properly treated patient should theoretically have very low concentrations of these two hormones (ATII and aldosterone) in circulation. However, a dilemma in ACE inhibitor therapy involves the phenomenon of ACE and aldosterone escape, which may not be synonymous. There are alternative mechanisms aside from ACE for conversion of angiotensin I to angiotensin II, most importantly bradykinin (i.e., ACE escape). Likewise, aldosterone synthesis may be increased by alternative mechanisms aside from angiotensin II, including hyponatremia, hyperkalemia, and adrenocorticotropic hormone (i.e., aldosterone escape) (Struthers 2004; Heintz et al. 1992). In people treated with ACE inhibitors, 15% have an elevated plasma angiotensin II concentration compared to 40% who have an elevation in plasma aldosterone concentration, indicating alternative mechanisms in addition to generation of ATII for stimulation of aldosterone synthesis in the process of aldosterone escape (MacFadyen et al. 1999). Similar to human medicine, persistent aldosterone elevation has been found in 60% of Maine coon cats receiving long-term treatment with ramipril and 50% of dogs given long-term enalapril, despite low ACE activity, although ATII levels were not measured (MacDonald et al. 2006; Haggstrom et al. 1996). These important findings suggest that patients may be receiving inadequate neurohormonal blockade even though they are given the medication as prescribed.

ACE activity ranges from low to high in humans with an elevated plasma ATII concentration while receiving ACE inhibitors. In patients with high ACE activity, noncompliance or inappropriate dose or dosing interval are possible explanations. Because renin and angiotensin I increase during ACEI therapy, even small differences in ACE activity can produce large variations in angiotensin II, making it imperative to have strict compliance with the appropriate dose and dosing interval of the ACE inhibitor (Lee et al. 1999). Chronic ACE inhibitor therapy may up-regulate the production of ACE, which would require higher doses of ACE inhibitors to adequately suppress the activity over time. ACE polymorphisms are another important factor for the amount of ACE activity and ATII generation in people, and the ACE DD genotype is associated with higher serum and tissue ACE concentrations and activity and requires higher ACEi doses for adequate inhibition (Cicoira et al. 2001). It is unknown whether cats or dogs have ACE polymorphisms that could contribute to ACE and aldosterone escape. Therefore, there are multiple factors regarding the amount of ACE inhibitor needed for adequate suppression of ACE activity and reduction in formation of angiotensin II.

Aside from ACE, there are alternate pathways that convert angiotensin I to angiotensin II, including chymase, serine proteases (cathepsin A, D, and G and tonin), and ACE-2 (Wong et al. 2004). Ninety percent of ventricular production of angiotensin II in humans, dogs, and cats is due to ventricular α-chymase conversion of angiotensin I (Balcells et al. 1997; Aramaki et al. 2003). Since renin and angiotensin I are elevated during ACE inhibitor therapy, there is a greater substrate for conversion to angiotensin II by alternative pathways. Extra-RAAS stimuli for aldosterone production include hyperkalemia or hyponatremia, which may be factors for persistent aldosterone elevation despite adequate ACE inhibition (Struthers 2004; Heintz et al. 1992). Aldosterone receptor blockers and angiotensin II receptor blockers have been developed to circumvent the problem of ACE or aldosterone escape and may be used in patients with congestive heart failure who are already

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treated with an ACE inhibitor. Thus, in cats receiving ACE inhibitors, one possible explanation for their lack of any detectable benefit on myocardial hypertrophy even after daily treatment for 1 year is that the body circumvents the pathway being blocked by the ACE inhibitor (MacDonald et al. 2006). This important consideration has led to an interest in angiotensin receptor blockers (ARBs).

Angiotensin receptor blockers (ARBs; e.g., losartan, candesartan, valsartan) block the type I receptor for angiotensin II, which mediates deleterious processes of angiotensin II including vasoconstriction, salt and water retention, hypertrophic responses, and fibrosis. The main reason these drugs were developed were to treat people who were intolerant to ACE inhibitors, typically those with ACE inhibitor induced cough (due to increased bradykinin concentration). There appears to be similar benefit of ARBs compared to ACE inhibitors for treatment of heart failure in people, but addition of ARBs to ACE inhibitors may actually have additive improvement in morbidity and mortality, as evidenced in the CHARM trial (Ravandi and Teo 2009; Pfeffer et al. 2003). The benefit in reduction of all-cause mortality and cardiovascular mortality, and reduction of risk of hospitalizations for heart failure appears to be more pronounced in patients with systolic myocardial failure, and when isolating patients with diastolic heart failure, there is a reduction in risk of heart failure hospitalizations but no difference in all-cause mortality or cardiovascular mortality (Pfeffer et al. 2003 Yusuf et al. 2003). However, only 20% of people in the diastolic heart failure group were also receiving an ACE inhibitor, which may have caused additive benefits. Addition of an ARB to ACE inhibitor therapy may be associated with worsened azotemia in people, making it imperative to closely monitor renal status. No studies have evaluated ARBs in cats, and there are no studies evaluating basic pharmacokinetics in cats. Losartan, although popular in human medicine, is not metabolized into an active metabolite in the dog, limiting the use in this species, and there is no information regarding its metabolism in cats. Other ARBs (valsartan, irbesartan) have been used in experimental models of heart failure in dogs. At this point, since there is a void in basic information regarding pharmacologic properties of ARBs in cats and no safety data available, their use is not recommended for clinical feline patients.

Additional Therapies for Chronic Congestive Heart Failure

Diet

A low-salt diet (<0.6 g/kcal) is not usually implemented at the initial diagnosis of heart failure, but may be helpful over time as heart failure progresses and diuretic resistance develops. Palatability is often a challenge in cats more than dogs, so the primary nutritional goal is for the cat to maintain adequate caloric intake rather than insistence of feeding exclusively a low-salt diet. Moderately salt-restricted commercial renal diets are also often protein restricted, which is contraindicated in patients with heart failure unless there is concurrent severe renal dysfunction. Choices of low-salt cardiac diets include commercially available diets (e.g., Purina CV or Hills H/D) or a home-cooked diet that has been formulated and balanced by a veterinary nutritionist (balanceit.com, petdiets.com [fee involved], Strombeck: *Home-Prepared Dog and Cat Diets: The Healthful Alternative*. Wiley-Blackwell, 1999). Water softeners add salt to the water and should be avoided in animals with heart failure. Omega 3 fatty acids (40 mg/kg PO q 24 hr eicosapentaenoic acid, 25 mg/kg PO q 24 hr docosahexaenoic acid) should be given to animals with progressive weight loss and cardiac cachexia, since their anti-inflammatory properties may lessen the deleterious anabolic effects of pro-inflammatory cytokines (tumor necrosis factor-α and interleukin 1) (Freeman et al. 1998).

Additional medical therapies

Beta blocker therapy should be postponed in cats with HCM and congestive heart failure until the heart failure is compensated, and it is debatable whether to be started at all once heart failure occurs. This is because the body relies on an activated sympathetic nervous system to maintain cardiac function and blood pressure during decompensated heart failure. Once the cat has stabilized with no active heart failure and is normotensive, beta blocker therapy may be considered in particular HCM cases. Beta-blockade is generally not initiated in HCM once heart failure has developed, but may be continued, possibly at a lower dose, in cats already given chronic beta blocker therapy provided that they are not hypotensive or bradycardic (see Chapter 11 for more discussion). Beta blockers or calcium channel blockers may be necessary in cats with active heart failure if there is a significant tachyarrhythmia that worsens the hemodynamic status of the cat—for example, in a cat hospitalized for acute treatment of congestive heart failure that has improved dyspnea and clinical stabilization, but the heart rate remains at 280 bpm (rather than an expected heart rate of 150–220 bpm). Negative chronotropic therapy should be considered, after evaluation by an ECG to characterize the arrhythmia. Diltiazem would be the drug of choice for cats with active heart failure and severe supraventricular tachycardia or rapid atrial fibrillation, whereas injectable lidocaine, procainamide, or esmolol may be used for acute treatment of life threatening ventricular tachyarrhythmias (see Chapter 18).

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Anticoagulant therapy

Congestive heart failure is the end result of severe heart disease and elevated diastolic filling pressures. Most cats with heart failure have moderate or severe atrial dilation, and are at risk for arterial thromboembolism. Anticoagulant therapy is recommended for cats with echocardiographic evidence of spontaneous contrast (e.g., red blood cell aggregation), an intracardiac thrombus, or current or previous arterial thromboembolism. These recommendations are intuitive and are extrapolated from human medicine, but definitive proof to support their benefit in cats is lacking. Therefore, such treatment should be implemented only when there is acceptance and compliance with medication administration and should never replace life-saving therapy with furosemide. It is debatable as to when to start anticoagulant therapy in cats without the previous criteria, but the authors elect to start prophylactic anticoagulant therapy in cats with moderate or severe atrial dilation. Choices of anticoagulants include baby aspirin (5–81 mg PO q 3 days), clopidogrel (18.75 mg PO q 24 hr), low molecular weight heparin (LMWH; enoxaparin 1.5 mg/kg SC q 12 hr) or warfarin 0.1–0.2 mg/kg PO q 24 hr titrated to increase prothrombin time to 1.5–2 times normal (see Chapter 20).

Treatment of Hospitalized Cats with Acute Congestive Heart Failure

Treatment of hospitalized cats with acute congestive heart failure includes the following:

- Thoracocentesis of moderate or severe (i.e., large volume) pleural effusion is a rapidly life-saving technique that should not be delayed.
- Aggressive diuretic therapy with parenteral furosemide (2–4 mg/kg IV q 1–4 hours) is the mainstay of therapy for acute cardiogenic pulmonary edema. The furosemide dose and frequency should be rapidly tapered once there is improvement in the respiratory status.
- Enriched inspired oxygen (FiO_2 50%) can be administered with an oxygen cage, which controls temperature, humidity, and removes excess carbon dioxide.
- Transdermal nitroglycerin (1/8–1/4 inch (2-5 mm) q 6 hr ≤2 days; alternatively application and removal every 12 hours for 3 days) is a venodilator, whose efficacy is unknown in cats. It may lessen pulmonary venous hypertension, thereby decreasing formation of pulmonary edema.
- Dobutamine is a positive inotrope, which may be used in cats with myocardial failure or low output heart failure. Pimobendan is also a positive inotrope as well as arteriolar and venous vasodilator, which may be used in cats with myocardial failure or refractory heart failure.
- ACE inhibitors are not used in the acute setting for heart failure treatment and are added when the cat has returned home and is eating and drinking.

Cats with acute fulminant congestive heart failure are fragile patients requiring intensive 24-hour care and careful handling. These patients have moderate to severe dyspnea with exaggerated abdominal excursions and possibly abducted forelimbs, tachypnea (often respiratory rate > 80 breaths/min), possibly orthopnea, and often have impaired demeanor and marked lethargy. Certainly, there are shades of gray in deciding whether a cat with a less critical level of dyspnea constitutes the need for hospitalization, and consultation with the owner regarding their ability to treat and monitor the cat at home, the cost of hospitalization compared to outpatient treatment, and the emotional aspects of both hospitalizing a pet versus the fear of deterioration at home is necessary to arrive at the best overall decision. Dyspneic cats may succumb to overzealous handling and restraint to obtain diagnostic tests, so minimal restraint is required. These patients are ideally managed in a 24-hour facility equipped with an oxygen cage, intensive cardiovascular monitoring, and critical care capabilities. However, immediate stabilization of the patient is needed prior to referral. The first triage step in a dyspneic cat is to evaluate whether there is significant pleural effusion that can be immediately removed by thoracocentesis for immediate stabilization. The cat can be kept in sternal recumbency and supplemented with oxygen if tolerated while a "triage" thoracic ultrasound is done to evaluate presence of significant pleural effusion and locate the optimal site for thoracocentesis. If an ultrasound is not available, a dorsoventral thoracic radiograph with minimal restraint may be attempted to assess for severe pleural effusion. However, obtaining a radiograph should never be a terminal event. If ultrasound is unavailable and the cat is too unstable for a radiograph, the last option is "blind" thoracocentesis at the right 7th intercostal space using a 19 gauge butterfly catheter. A "blind" approach may cause iatrogenic pneumothorax when the underlying cause of the dyspnea is not from pleural effusion and should be used sparingly if at all (E. Côté, personal observation). Postthoracocentesis thoracic radiographs should be obtained to evaluate for abnormalities such as cardiomegaly and pulmonary venous distension, pulmonary edema, mediastinal mass, or pulmonary mass. A "triage" echocardiogram (see above) is useful to confirm that there is severe heart disease as a cause of the pleural effusion and/or pulmonary edema. Presence of significant left and/or

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right atrial dilation places heart failure high on the differential list, and diuretic therapy can be started.

Medical treatment of acute heart failure includes aggressive diuretic therapy with furosemide, oxygen supplementation, and possibly transdermal nitroglycerin (see Table 19.1). Ideally, an intravenous catheter is placed for repeated intravenous injections of furosemide, and can be done with as minimal restraint and stress as possible, with a prepared oxygen cage ready to immediately place the cat into for rest and recovery after the injection. However, if the cat is too unstable, 3–4 mg/kg furosemide can be given intramuscularly, and the cat placed in oxygen (at 50–60% fractional inspired oxygen) temporarily, until it is able to withstand gentle restraint for placement of an intravenous catheter. Initial furosemide doses range from 2 to 4 mg/kg IV every 1 to 4 hours, depending on the cat's response. Typically, an improvement in respiratory effort is expected within 4 hours after the first injection of furosemide. If improvement occurs within the first hour, as is common when congestive heart failure was iatrogenic and/or mild, then the next dose of furosemide may be given only at 2 or 4 hours after the first. However, if the cat continues to be severely dyspneic 1 hour after the first injection of furosemide, then the second dose of furosemide may be given just 1 hour after the first. Hourly doses are sometimes necessary in the worst cases, but if dyspnea worsens or remains severe after 2–3 hourly doses of furosemide, then the diagnosis of heart failure may be questioned (is it actually primary respiratory disease causing dyspnea?), or the cat has acute, fulminant heart failure requiring additional therapy potentially with a constant rate infusion of furosemide, for more sustained diuretic effect, and possibly nitroprusside if it is not hypotensive and in a critical care setting with an experienced clinician. Acute diuresis occurs 5 minutes after intravenous injection, with a peak effect after 30 minutes, which lasts 2 to 3 hours. Venodilation is an acute ancillary effect of furosemide occurring 5 to 15 minutes after intravenous injection, and is independent from the diuretic effect. Free choice of water and encouragement of drinking is necessary, since dehydration is very common and expected.

Pulmonary edema causes hypoxemia because oxygen cannot diffuse from the alveoli to the pulmonary capillaries. Increasing the inspired oxygen concentration increases the pressure gradient of oxygen to diffuse into the pulmonary capillary bed, which increases the arterial oxygen tension. The percent inspired oxygen concentration is increased from room air (21%) to 40–60%. An oxygen cage is the safest and most effective means to supplement oxygen. The oxygen cage not only controls the percent of inspired oxygen, but it also regulates temperature and humidity, and removes carbon dioxide. If an oxygen cage is not available and the cat is placed in an enclosure with supplemental oxygen, it is important to use a high oxygen flow rate to flush out the carbon dioxide, as well as ice packs to cool the environment. Inhaled oxygen concentration should be decreased to 50% or less within 12 hours to avoid barotrauma induced by high fractional inspired oxygen.

Once the respiratory rate decreases to less than 50 breaths/minute and respiratory effort improves, the dose and frequency of furosemide may be decreased (~2 mg/kg IV q 6–8 hrs). Thoracic radiographs may be obtained 24 to 36 hours after acute diuresis to assess the presence and severity of pulmonary edema, and help tailor continued heart failure treatment and transition to chronic oral dosing of furosemide. Some cardiologists feel that the patient's clinical progression (improvement of clinical signs) is sufficient information for making such treatment decisions and do not obtain repeat radiographs at this time. Renal panels may be monitored every 12 to 24 hours during the acute phase of treatment, to monitor for progressive electrolyte depletion and severity of azotemia. Blood samples for measuring electrolyte levels should be collected in a green top tube (lithium heparin). This is because a red top (plain) tube allows platelet activation/clumping, which releases potassium and can mask clinically important hypokalemia. Potassium infusion (0.05–0.5 mEq/kg/hr IV) can be given for treatment of severe hypokalemia (K < 3 mEq/l), and frequent reevaluations of serum potassium concentration are necessary. Oral potassium gluconate (2–4 mEq PO q 12 hr) may be used in cats with moderate hypokalemia that can tolerate oral medications. Hypokalemia often dramatically improves once the cat is discharged on lower dose oral furosemide for chronic heart failure therapy. Once the cat is stable and has normal to mildly increased respiratory rate or effort, the furosemide can be transitioned to oral administration (6.25–12.5 mg PO q 12 hr). Concurrent use of intravenous fluids and administration of a diuretic to "protect the kidneys" by minimizing the degree of dehydration and azotemia is counterproductive and ineffective, because each treatment negates the other.

Nitrates such as nitroglycerin or sodium nitroprusside are vasodilators that function by increasing nitric oxide production. Nitric oxide binds to guanylate cyclase, which forms cyclic GMP from GTP. Cyclic GMP activates protein kinases that phosphorylate myosin light chains and cause smooth muscle relaxation and vasodilation. Transdermal nitroglycerin causes systemic venodilation, whereas intravenous nitroglycerin is a potent venodilator and arteriolar dilator. Although nitroglycerin has not been studied in cats, it is commonly given to cats with heart failure based on extrapolations from human

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medicine, and is unlikely to cause harm. Gloves must be worn by the administrator of the ointment to avoid absorption. Transdermal nitroglycerin (1/8–1/4 inch [2-5 mm] q 6 hr), applied to hairless region on the inside of the pinna, alternating ears for each treatment; alternative technique is application and then removal 12 hours later, to be repeated with 12 hours on and 12 hours off cycles for 3 days may be administered for 1 to 2 days during hospitalization of acute heart failure. Long-term daily use at home is not recommended due to the tolerance and loss of effect that develops after 18 to 24 hours of treatment, as well as risk of owner absorption of the transdermal medication at home. Sodium nitroprusside can be used in cats with acute severe systemic hypertension or in cats with refractory severe heart failure that are not responding to aggressive diuretic therapy. Nitroprusside is a balanced arterial and venous vasodilator with a very short half-life, facilitating rapid titration. Nitroprusside is sensitive to light, heat, and moisture, and deterioration is evidenced by a color change to brown or blue. It should be protected from light by wrapping the container and IV line with aluminum foil and can be used for up to 24 hours. Careful blood pressure monitoring is necessary to avoid significant hypotension. Hypotension can be quickly reversed by discontinuing the drug, and blood pressure usually recovers within several minutes. Nitroprusside can cause cyanide toxicity in people and likely in animals. In a study of pediatric cardiac patients, elevated cyanide levels were independently predicted by mean dose, cumulative dose, and acid-base excess values (Moffett and Price 2008). Doses of ≥1.8 mcg/kg/min predicted an elevated cyanide concentration with 89% sensitivity and 88% specificity (Moffett and Price 2008). There are no pharmacologic studies evaluating nitroprusside in cats, and doses reported are anecdotal (0.5–10 mcg/kg/min) and extrapolated. Given the potential of cyanide toxicity, the recommended dose is <2 mcg/kg/min for less than 24 hours for acute, short-term treatment of fulminant heart failure.

Dobutamine is a potent beta-adrenergic agent that stimulates the beta-1 adrenergic receptors and increases myocardial contractility. It may be used in animals with acute heart failure secondary to systolic dysfunction (e.g., DCM, end-stage ventricular volume overload from mitral regurgitation or ventricular septal defect) and is often combined with the balanced vasodilator nitroprusside for synergistic effects of increased cardiac output, decreased afterload, and decreased diastolic ventricular filling pressures. Doses of 5–15 mcg/kg/min increase cardiac index in healthy, anesthetized cats by 2 to 2.5 times baseline and increase contractility greater than dopamine or epinephrine (Pascoe et al. 2006). Mild sinus tachycardia may occur at subinotropic doses of 2.5 mcg/kg/min, and heart rate increases in a dose-dependent manner in healthy anesthetized cats (Pascoe et al. 2006). Dobutamine can be used in cats with hypotension and low output heart failure, significant hypoperfusion evidenced by marked elevation in lactate and decreased venous oxygen partial pressure (PvO_2), or in cats that are not responding adequately to aggressive diuretic therapy with end-stage diseases causing myocardial failure or ventricular volume overload (i.e., ventricular septal defect, mitral regurgitation). In human cardiology, dobutamine is used routinely as a bridge to final resolution of the heart problem (e.g., heart transplantation). Since short-term cures are uncommon in feline cardiology, the use of dobutamine should consider the patient's context. For example, in one cat with end-stage DCM, dobutamine may be appropriate to provide the owner with an assurance that every option was used (and indeed the cat may respond and have an acceptable quality of life for some time thereafter), but in another similar cat the same application of dobutamine may be perceived as delaying an inevitable death. It is clearly indicated for initial stabilization of cats with a reversible form of heart disease, such as taurine deficiency induced myocardial failure or tachycardiomyopathy. Because HCM is more common than myocardial failure in cats, low output heart disease may be first addressed in these patients by restoring intravascular blood volume with fluid resuscitation if the cat is hypovolemic, and if there is a lack of improvement in hypotension, vasopressors such as dopamine may be started rather than dobutamine.

Pimobendan is a potent positive inotrope with additional moderate balanced vasodilating properties. It is used (off-label) in cats with congestive heart failure and myocardial failure (i.e., DCM, end-stage ventricular volume overload caused by a ventricular septal defect or mitral regurgitation), but its use in cats with heart failure from other cardiac diseases is controversial. No feline pharmacokinetic studies have been done, but a dose of 0.1–0.25 mg/kg PO q 12 hr has been reported anecdotally in cats with heart failure (MacGregor et al. 2010; Sturgess and Ferasin 2007). Adverse side effects appear to be uncommon (5/161 cats, 3%) and may include vocalization, agitation, anorexia, vomiting, and constipation, and may not require discontinuation of the drug (MacGregor et al. 2010); however, retrospective studies such as these cannot document the absence of adverse effects with certainty. One cat with congestive heart failure due to mitral valve dysplasia and systolic anterior motion of the mitral valve developed severe hypotension (systolic blood pressure decreased from 97 mm Hg to 60 mm Hg) several hours after administration of pimobendan, necessitating discontinuation of the drug (Gordon 2010). Pimobendan is a phosphodiesterase III inhibitor and a calcium sensitizing agent, which increases contractility by increasing the binding of calcium to

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troponin C. Inhibition of phosphodiesterase III reduces degradation of cAMP, an important second messenger involved in contraction and relaxation. Pimobendan increases myocardial contractility to a degree that is comparable to dobutamine, but without increasing myocardial oxygen consumption (Fitton and Brogden 1994). It also improves diastolic function and reduces diastolic filling pressure, which is an important therapeutic target in cats with heart failure. Pimobendan moderately reduces systemic vascular resistance, reduces pulmonary vascular resistance (~30%), dilates coronary arteries, and increases renal blood flow (van Meel and Diederen 1989; Kanno et al. 2007). Unlike dobutamine, pimobendan improves myocardial efficiency by reducing afterload, increasing myocardial contractility, and increasing myocardial perfusion, without increasing myocardial oxygen consumption. Pimobendan also reduces several inflammatory negative inotropic cytokines including tumor necrosis factor-α, interleukin-1, and inducible nitric oxide synthase.

Pimobendan is used in both acute and chronic heart failure in dogs. There is early positive anecdotal experience in cats with heart failure, but further studies are needed to determine for which diseases it should be used. At this time, it is recommended to be used in cats with heart failure secondary to myocardial failure (i.e., DCM) and possibly in cardiac diseases causing severe volume overload such as degenerative valve disease (uncommon in cats) or in heart diseases that have a component of systolic dysfunction. Use in cats with unclassified or restrictive cardiomyopathy is not routine or well described; these cats may benefit from the vasodilating properties of the drug in the presence of elevated diastolic filling pressures seen in heart failure (Sturgess and Ferasin 2007). At this time, it is not recommended to use a positive inotropic agent in cats with hypertrophic cardiomyopathy, but further studies are needed. In an uncontrolled retrospective study of 161 cats treated with pimobendan, cats with larger end-diastolic diameter treated with pimobendan and standard therapy lived longer ($P = 0.03$) and cats with greater concentric hypertrophy of the left ventricular free wall lived a shorter time when treated with pimobendan and standard therapy ($P = 0.02$); whether these results reflect natural disease progression or drug effect is unknown (MacGregor et al. 2010).

ACE inhibitors are used for chronic heart failure therapy, but acute hemodynamic effects appear to be mild and intermittent (IMPROVE Study Group 1995). ACE inhibitors may cause functional azotemia in some cats secondary to decreased efferent arteriolar glomerular tone, which may be potentiated by decreased renal blood flow during aggressive diuretic therapy. Symptomatic benefits of ACE inhibitors tend to occur after a couple of weeks to months of therapy, not within the first couple of days. Therefore, when feasible, it is the authors' recommendation to postpone ACE inhibitor therapy until the patient is at home and is eating and drinking. If the cat is currently receiving an ACE inhibitor, it can be continued, provided that the cat is able to tolerate oral medications, is eating and drinking, and does not have moderate azotemia, because stopping it could cause a rebound RAAS activation due to high levels of angiotensin I from the ACE inhibition. Sometimes in cats with moderate dehydration and azotemia due to acute aggressive diuretic therapy, the ACE inhibitor may be temporarily postponed during the first few days of the initial acute heart failure treatment.

Sedation may be necessary for severely anxious, distressed hospitalized patients, or in fractious animals that require emergency care. An attractive sedation protocol is the combination of an opioid (butorphanol 0.02 mg/kg or hydromorphone 0.05 mg/kg) and midazolam (0.2 mg/kg), which can be given as a single subcutaneous injection. If midazolam is not available, low-dose acepromazine (0.01–0.05 mg/kg) may be substituted. Sublingual buprenorphine (0.01 mg/kg orally) is another sedation option for cats resisting injections. This is an attractive option for owners to administer at home to the cat prior to the car trip to the doctor's office in cats that become severely distressed in the car or cats that are intractable once in the hospital. The last resort is box anesthesia with inhaled isoflurane, because it will decrease blood pressure and contractility and depress spontaneous respirations (see Chapter 27).

Treatment of Refractory Congestive Heart Failure

Treatment of refractory CHF includes the following:

- Furosemide dose should be maximized (4 mg/kg PO q 8 h) in cats with refractory heart failure that continue to develop pulmonary edema or pleural effusion despite medical therapy.
- Addition of a second diuretic such as hydrochlorothiazide (1–2 mg/kg PO q 12–24 h) or torsemide (0.1–0.3 mg/kg PO q 12 h) may be needed in cats with refractory heart failure despite maximal furosemide doses. These cats are very fragile and are prone to develop significant dehydration and azotemia, which may negatively impact overall quality of life. Substitution or supplementation of one or more oral doses per week of furosemide with subcutaneous injections is another option in cats receiving maximal oral furosemide doses.
- A low-salt cardiovascular diet (0.15–0.2 g sodium/1000 kcal) should be fed to cats with refractory heart failure, if palatable. A professionally formulated home-cooked low-salt diet is an option in finicky cats.

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- Treatment of moderate (nonregenerative) anemia with erythropoietin may lessen degree of volume overload to the heart and improve oxygen handling capacity.
- Pimobendan is a positive inotrope and balanced arteriolar and venous vasodilator and is used to treat refractory heart failure in all etiologies except hypertrophic cardiomyopathy. Treatment of refractory heart failure secondary to HCM with pimobendan is controversial, with some positive anecdotal experience.

Refractory heart failure patients are defined as suffering from recurrent pulmonary edema or pleural effusion despite multidrug therapy including high dose furosemide (3–4 mg/kg PO q 8 h) and an ACE inhibitor (see Table 19.1). These patients most commonly have been undergoing chronic treatment for months to years and have suffered relapses in heart failure that have responded to increases in diuretic doses. Typically these cats continue to have a good quality of life in the owner's opinion. Treatment of refractory heart failure is differentiated from terminal heart failure by subjective assessment: the owner and the attending veterinarian agree that treatment and monitoring for improvement are humane and justified based on the cat's demeanor and medical status. Eventually, refractory heart failure deteriorates into a terminal state, when there is failure to respond to rescue/refractory treatments, and end-of-life decisions must be discussed.

In cats with refractory heart failure, the first task is to increase the furosemide dose to the maximal tolerable dose, and the maximal oral effective dose above which no further diuretic effect is achieved is generally considered to be 4 mg/kg orally every 8 hours. If heart failure continues to recur, addition of a second diuretic (hydrochlorothiazide 0.5–1 mg/kg PO q 12 hr or torsemide 0.1–0.3 mg/kg PO q 12 hr)provides additional diuresis by inhibiting sodium absorption distal to furosemide's site of action. Cats receiving high dose furosemide and hydrochlorothiazide (1–2 mg/kg PO q 12 h) are prone to developing significant dehydration and azotemia. The goal in these patients with advanced cardiac disease is to balance some degree of dehydration and azotemia with reduced dyspnea and improved quality of life. Thiazide diuretics are 1/3 as potent as furosemide for urinary sodium excretion. They inhibit the sodium chloride cotransporter in the distal convoluted tubule, downstream from the site of action of loop diuretics, thus exerting "sequential nephron blockade" (Brater 1998). In an experimental feline isolated kidney model, chlorothiazide doubled the urinary excretion of sodium and increased urinary loss of water and potassium (De Lima and Lockett 1961). Spironolactone (1–2 mg/kg PO q 12–24 h), an aldosterone antagonist, is uncommonly used in cats with refractory heart failure, but it may lessen hypokalemia and reduce potential deleterious effects of aldosterone on the cardiovascular system. Spironolactone is an extremely weak diuretic, so it should not be expected to significantly reduce the severity of edema or pleural effusion accumulation (Jeunesse et al. 2007). In a study of Maine coon cats and Maine coon crossbred cats with familial HCM, one-third of cats treated with spironolactone developed severe ulcerative dermatitis attributed to a cutaneous drug reaction, and other cardiologists have similar anecdotal reports in some Maine coon cats (MacDonald et al. 2008). Another option for refractory heart failure is substituting 1 to 2 subcutaneous doses of furosemide a week for the oral doses, since oral bioavailability of furosemide is only ~50% and may be lower if GI edema, inappetence, or other factors interfere with absorption. If palatable, a low-salt diet (0.15–0.2 g sodium/1000 kcal) will help limit sodium and water retention and should be tried. However, any commercial diet is preferable to anorexia, and the furosemide dose is then raised accordingly to offset increased sodium intake. Pimobendan (0.25 mg/kg PO q 12 h) may be added in cats with refractory heart failure from all etiologies except pressure overload or hypertrophic cardiomyopathy. Treatment of cats with HCM and heart failure with pimobendan is controversial and may be contraindicated if there is significant left ventricular outflow tract obstruction.

Other Loop Diuretics: Torsemide

Torsemide is a loop diuretic that has 10 times the potency of furosemide. Although it is not typically used in clinical medicine, there are several potential advantages over furosemide. Torsemide has a longer acting diuretic effect, with a peak effect in cats seen 4 hours after oral administration (0.3 mg/kg) that persists for 12 hours, compared to only 6 hours of diuretic effect after oral administration of furosemide (Uechi et al. 2003). Torsemide is nearly completely absorbed from the gastrointestinal tract, and has a high bioavailability of 80–100% in dogs, compared to approximately 50% bioavailability of furosemide in dogs (Ghys et al. 1985). Another advantage of torsemide over furosemide is that it inhibits the secretion and receptor-ligand binding of aldosterone (Uchida et al. 1992; Goodfriend et al. 1998). Torsemide, but not furosemide, decreases myocardial fibrosis and collagen synthesis in people with heart failure, which may be due to its inhibition of aldosterone (Lopez et al. 2004). Similarly, torsemide improves left ventricular diastolic function in heart failure patients to a greater extent than furosemide and is associated with a lower mortality than furosemide in people with heart failure (Yamato et al. 2003; Cosin et al. 2002). Currently, the authors consider adding torse-

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mide (0.1–0.3 mg/kg PO q 12 h) to an existing drug regimen of high dose furosemide (3–4 mg/kg PO q 8–12 h) and an ACE inhibitor when pulmonary edema or cardiogenic pleural effusion continue to rapidly recur and cause dyspnea (i.e., refractory heart failure patients). Typically, a dosage of 0.1–0.3 mg/kg PO q 12 h is used, with the lower dosage selected first when the patient is already receiving furosemide, and some cardiologists recommend reducing the furosemide dose by 30–50%. Long-term efficacy and safety are unknown in the cat. Ototoxicity occurs in 50% of cats treated with 20 mg/kg torsemide, similar to the ototoxic furosemide dose (18 mg/kg) (Klinke and Mertens 1988). Adverse effects such as ulcerative facial dermatitis seen in cats receiving spironolactone have not been reported to date with torsemide, making it a superior choice to this drug pending further data. Torsemide is available as 5, 10, 20, or 100 mg tablets (brand name: Demadex), such that compounding may be necessary for accurate dosing in cats. The superior diuretic effect may likewise cause greater electrolyte disturbances and/or volume depletion, and routine monitoring, as for furosemide, is necessary.

Treatment of Anemia

Anemia is an independent risk factor for mortality in people with systolic or diastolic heart failure (Groenveld et al. 2008; Silverberg et al. 2008; Klapholz et al. 2009; Besarab et al. 1998). Anemia decreases the oxygen-carrying capacity of blood, and induces a high output cardiac state that worsens volume overload to the heart. Correction of anemia using erythropoietin has been studied in people with heart failure, and is associated with 90% reduction in heart failure hospitalizations, decreased furosemide dose, increased exercise capacity, decreased functional heart failure class, and slower decline in glomerular filtration rate (Silverberg 2001, 2008). The incidence of anemia in cats with heart failure has not been studied, but it may be common. Correction of underlying or precipitating causes of anemia is necessary. In cats with a nonregenerative anemia, use of erythropoietin may be helpful to normalize the hematocrit, and intermittent doses may be needed to maintain a normal hematocrit. Correction of anemia may be particularly important in cats with progressive or refractory heart failure (see Chapter 24).

COMPLICATIONS AND MONITORING

Possible complications, and monitoring instituted to identify them early should they occur, include the following:

- Dehydration and azotemia are the most common complications in cats treated for heart failure. Other complications that may occur in chronic heart failure include cardiac cachexia, arterial thromboembolism, or tachyarrhythmias.
- The mainstays of therapeutic monitoring of cats with heart failure include serum chemistry profile, thoracic radiographs, and systemic blood pressure.
- Echocardiograms may be helpful to identify myocardial failure, spontaneous contrast or intracardiac thrombus, and assess the severity of atrial dilation during chronic therapy.

The most common complications that occur with heart failure treatment are dehydration and azotemia. Progressive weight loss and loss of muscle mass (i.e., cardiac cachexia) often occurs with end-stage chronic heart failure and may be due to decreased caloric intake as well as a catabolic state caused by increased proinflammatory cytokines (tumor necrosis factor-α, interleukin 1, interleukin 2, interleukin 6) or neurohormonal imbalance including resistance to insulin, growth hormone, and ghrelin (von Haehling et al. 2009; Pajak et al. 2008). Arterial thromboembolism may occur in cats with heart failure. A left atrial thrombus may form secondary to one or more alterations in Virchow's triad, including blood stasis within a severely dilated left atrium, left atrial endothelial disruption, and a procoagulable state. Development of tachyarrhythmias such as atrial fibrillation, supraventricular tachycardia, or ventricular tachycardia may lead to further decompensation of heart failure, because tachycardia increases diastolic filling pressure.

The most common diagnostic tests used for monitoring cats with heart failure are radiographs, blood chemistry, and systemic blood pressure. Cats treated for acute heart failure require frequent in-hospital monitoring including, at minimum, renal panels every 12–24 hours and radiographs every 24–36 hours. Once discharged from the hospital, a recheck should be planned in 5–7 days for assessment of hydration status, degree of azotemia, radiographs for assessment of heart failure status, and systemic blood pressure measurement. Nonhospitalized cats treated for mild heart failure should be seen 1–2 weeks after initiation of therapy, for radiographs, serum chemistry, and systemic blood pressure measurement. A recheck echocardiogram may be performed after several weeks to months to assess myocardial function, degree of atrial dilation, and presence of spontaneous contrast or an intracardiac thrombus.

Azotemia

Progressive azotemia is not uncommon in patients treated with loop diuretics and vasodilators (ACE inhibitors) for heart failure (see Chapter 24). Azotemia in

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heart failure patients may be caused by concurrent intrinsic renal disease as well as "vasomotor nephropathy," a reversible and secondary cause of azotemia. Factors involved with vasomotor neuropathy include poor cardiac output and reduced renal perfusion, increased renal venous pressure (if right heart pressures are increased), neurohormonal activation, high dose loop diuretic therapy, or excessive vasodilator therapy. Vasomotor nephropathy is often termed *cardio-renal syndrome* and is found in approximately 20–30% of human patients treated for acute heart failure (Nohria et al. 2008. Progressive azotemia is one of the most important factors in early cardiovascular mortality in people and is also associated with severity of heart failure and diuretic use in dogs treated for heart failure (Gheorghiade and Pang 2009; Boswood and Murphy 2006; Nicolle et al. 2007). Chronic kidney disease is also common in aged cats, with a prevalence of 30% in cats 15 years of age or older (Lulich 1992). Acute renal failure may be caused by renal thrombosis in cats suffering from arterial thromboembolism. Persistent severe hypotension and a volume underloaded state causes renal ischemia and potentially irreversible renal failure. Often, a combination of intrinsic renal disease and secondary factors involved with the cardiorenal syndrome contribute to a decline in glomerular filtration rate and renal function in cats treated for heart failure. A comprehensive assessment of baseline renal status (i.e., urinalysis, serum chemistry at minimum) is needed to identify patients with a higher risk for decline in renal function during heart failure treatment. Patients with known renal dysfunction may be treated with more cautious diuretics and careful monitoring of renal values (q 12–24 hr) during acute treatment, as well as 5–7 days postdischarge. Improvement in cardiac output may help increase renal perfusion and can be done with dobutamine or pimobendan in cats with hypotension or myocardial failure. Pimobendan increases cardiac output and improves renal blood flow, may help reduce the need for high dose loop diuretic therapy, and can be used in cats with myocardial failure or progressive/refractory heart failure (controversial in HCM, to be avoided at this time in cats with moderate or severe SAM). ACE inhibitors are usually postponed during the acute diuresis phase and started once the patient is home and eating/drinking. In patients with azotemia, lower doses of ACE inhibitors should be started first and may be up-titrated based on renal values (see Chapter 24).

Mild to moderate azotemia (BUN <60 mg/dl [21 mmol/l], creatinine <2.5 mg/dl [220 mmol/l]) is relatively common during aggressive diuresis for acute heart failure. Usually the azotemia improves during chronic lower dose furosemide therapy, as long as the cat is eating and drinking. Fluid therapy is reserved for cats with moderate to severe azotemia (BUN > 60 mg/dl [21 mmol/l], and creatinine >2.5 mg/dl [220 mmol/l]) if baseline values were normal) that are simultaneously symptomatic for dehydration including anorexia and lethargy. Half-maintenance rate of intravenous fluids with half-strength saline (0.45% NaCl, 2.5% dextrose) can be used in cats requiring careful rescue from their dehydration and moderate to severe azotemia. Administration of subcutaneous fluids (50–75 ml) is another option for cats that are not severely symptomatic for their dehydration and moderate to severe azotemia. However, concurrent administration of fluids and diuretics is counterproductive for routine treatment of heart failure. In such patients, the clinician must decide whether the patient's intravascular volume needs to be expanded (e.g., from overt dehydration) or reduced (e.g., from excessive fluid retention, such as pulmonary edema); it is not possible to do both. Most cats with concurrent azotemia and heart disease have one of the two problems that is clinically predominant, and treatment is aimed at it. For example, a veterinarian who wants to treat a patient with injectable fluids, but the patient is receiving diuretics, may achieve the same goal simply by reducing the diuretic and giving no fluids. A majority of azotemic patients do not require rescue with fluids postdiuretic therapy. See Chapter 24.

Electrolyte Abnormalities

Hyponatremia, hypochloremia, and hypokalemia are common electrolyte derangements seen during aggressive diuretic therapy but are less common in cats receiving low to moderate doses of oral furosemide. Loop diuretics exert marked natriuresis and nonosmotic release of antidiuretic hormone triggered by renal hypoperfusion. Hyponatremia rarely requires specific therapy with hypertonic saline, but it may indicate the need for reduction of diuretic dose if it is moderate or severe. Mild to moderate hypokalemia is a common abnormality during aggressive parenteral furosemide administration to cats with acute heart failure. Supplementation is usually instituted if there is severe hypokalemia ($K^+ < 3$ mEq/l) or severe ventricular arrhythmia (and $K^+ < 4$ mEq/l). Potassium may be supplemented acutely in hospitalized patients with potassium chloride CRI (0.05–0.5 mEq/kg/hr). The low end of the dose (0.05–0.1 mEq/kg/min) is an hourly maintenance dose, whereas 0.5 mEq/kg/min is the highest dose that is reserved for patients with severe symptomatic hypokalemia (DeFrancesco 2008). Frequent monitoring of electrolytes every 6–12 hours is needed, especially in cats receiving middle to high doses. Oral potassium gluconate (2 mEq PO q 12 h, titrating upward as necessary) may be

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used for chronic oral therapy of significant hypokalemia (K < 3 mEq/l). Acid-base abnormalities are also common in cats with acute heart failure. Metabolic acidosis, diagnosed by low bicarbonate concentration, may reflect low output heart failure causing poor tissue perfusion and lactic acidosis. Concurrent low venous oxygen partial pressure (PvO_2 < 30 mm Hg) is consistent with poor tissue perfusion and increased tissue extraction of oxygen. Therapeutic targets are to improve contractility and increase cardiac output. Respiratory acidosis (elevated PCO_2) is an ominous sign of impending respiratory failure and the potential need for mechanical ventilatory support for the fatiguing respiratory muscles. Respiratory alkalosis is not uncommon in dyspneic or tachypneic patients. Hyperventilation is triggered by hypoxia, stimulation of atrial stretch receptors, or pulmonary edema stimulating pulmonary nociceptive J receptors, and it usually improves as the edema is cleared.

Monitoring for Recurrent Heart Failure

Blood pressure, radiographs, and blood chemistry are the most essential diagnostic tests to monitor during acute and chronic heart failure therapy. Vasodilators (ACE inhibitors) in combination with other cardiac medications such as furosemide and antiarrhythmic therapy (atenolol or diltiazem) may lead to hypotension and may necessitate reduction in dose or discontinuation. Atenolol and diltiazem are reserved for patients with significant tachyarrhythmias because they may worsen acute heart failure. Respiratory status may be simply assessed by monitoring resting respiratory rate and effort, while the cat is resting in the cage without manipulation. Radiographs are useful to assess for persistent pulmonary edema or pleural effusion after diuretic therapy, and helps the clinician plan appropriate diuretic doses during transition to chronic oral therapy. Assessment of hydration status by physical examination, PCV/TS, and severity of azotemia or electrolyte derangements on blood chemistry are essential to form a treatment plan for chronic heart failure therapy.

A respiratory log recorded by the owner is a simple and practical tool to monitor for recurrence of heart failure. On a daily basis, the owner records the resting respiratory rate and effort, appetite, and clinical demeanor, and the clinician can review the log intermittently during a phone consultation with the owner. A resting respiratory rate that is persistently ≥40 breaths/min increases the clinician's suspicion of ongoing heart failure and may preempt a recheck or a trial increase of furosemide dose with reassessment of the respiratory log a week later.

Recheck echocardiograms are useful in cats with spontaneous contrast or intracardiac thrombi that are placed on anticoagulant therapy, and they can be done ~2 weeks after initiation of therapy. Recheck echocardiograms can be done every 3–6 months for assessment of atrial size, myocardial function, spontaneous contrast or intracardiac thrombus, or pulmonary hypertension. Progressive, severe atrial dilation despite medical therapy indicates that the patient may be at risk of developing refractory heart failure. Myocardial failure may develop in some patients that initially had preserved systolic function. Patients with myocardial failure are good candidates for positive inodilator therapy with pimobendan. Echocardiography is the test of choice to evaluate for development of pulmonary hypertension that may develop in animals with severe heart failure. Right ventricular concentric and eccentric hypertrophy, right atrial dilation, pulmonary artery dilation, and increased velocity of tricuspid regurgitation (>3 m/s) are all consistent with the diagnosis of pulmonary hypertension. Sildenafil (1 mg/kg PO q 8 h) may reduce symptoms, severity, and frequency of syncope, and reduce pulmonary artery pressure in animals with significant pulmonary hypertension (consider if right ventricle: right atrial pressure gradient >55 mm Hg) (see Chapter 25).

OUTCOME AND PROGNOSIS

Outcome and prognosis include the following:

- Heart failure is an advanced stage of severe heart disease.
- Diseases associated with the shortest survival once heart failure occurs include idiopathic dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and restrictive cardiomyopathy. Survival ranges from days to a few months.
- Survival is widely variable in cats with concurrent hypertrophic cardiomyopathy and congestive heart failure and ranges from months to 1.5 years or longer.
- Negative prognostic indicators for cats with heart failure secondary to HCM include tachycardia at presentation, (increased) age, and left atrial size.

Survival in cats with heart failure is highly variable and dependent on the etiology of the heart disease. Cats with heart failure secondary to idiopathic dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, or restrictive cardiomyopathy tend to have very short survival times and usually succumb within several weeks to months (median survival time: DCM 11 days (Ferasin et al. 2003), ARVC 30 days (Fox et al. 2000), RCM 132 days (Ferasin et al. 2003)). However, survival of cats with heart failure secondary to HCM is highly variable. Median survival times in two retrospective,

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large-scale studies of cats with CHF secondary to HCM were highly disparate and ranged from 92–563 days (Rush et al. 2002; Atkins et al. 1992). Similarly, there are contradicting results regarding negative predictors for survival in cats with HCM and heart failure. One study found that survival was not influenced by the age at onset, sex, body weight, or breed, but tachycardia (>200 bpm) at presentation was a negative prognostic indicator (Atkins et al. 1992). In contrast, another study found that left atrial size and increased age were independent negative prognostic indicators (Rush et al. 2002). Cats that have an identifiable precipitating factor—such as long-acting corticosteroid administration, surgery, fluid administration, or a stressful tachycardic event (e.g., being chased by a dog)—tend to live longer than cats with severe HCM and severe left atrial dilation that develop heart failure without a precipitating event. Increased left atrial volume is also an important marker for severity of disease in people with HCM and was associated with more serious cardiovascular events, greater diastolic dysfunction, and higher diastolic filling pressures (Yang et al. 2005). Negative prognostic indicators for early cardiovascular mortality in people with acute heart failure include hypotension, renal impairment, hyponatremia, clinical congestion at the time of discharge, increases in brain natriuretic peptide levels during therapy, and poor functional capacity at the time of discharge (Gheorghiade and Pang 2009).

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SECTION H

Arterial Thromboembolism

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20

Arterial Thromboembolism

Key Points

- Although many authors have suggested a grave outcome associated with feline thromboembolic disease, recent reports suggest that with aggressive treatment and diligent supportive care, a significant subset of cats can recover and lead good quality lives.
- Initial therapy is directed at pain management, anticoagulant therapy, and control of congestive heart failure (if present). This therapy can be instituted immediately and prior to echocardiographic evaluation.
- Chronic therapy typically includes medical management of the underlying heart disease with or without heart failure, and anticoagulant therapy (typically antiplatelet agents).
- Cats often succumb to heart failure, although recurrence rates for ATE range from 24–75% (Lunsford and Mackin 2007).
- Prevention of ATE in asymptomatic cats should be considered when risk factors suggest ATE is likely (significant left atrial enlargement [LA : Ao > 1.9 with echocardiography or severe LA enlargement radiographically if an echocardiogram is not possible] or when spontaneous echogenic contrast is visible in the left atrium (echocardiographically). However, anticoagulation is not generally recommended if these findings are not present (e.g., feline patient with a murmur and normal heart size).

INTRODUCTION

Arterial thromboembolism (ATE) has long been associated with cardiomyopathy. The syndrome is most often associated with hypertrophic cardiomyopathy (HCM), likely because this is the most common type of heart disease in cats. One study found the prevalence of HCM to be 14.5% in a population of asymptomatic cats (n = 103). Although a majority (89–92%) of cats with ATE have cardiogenic emboli, neoplasia (in particular bronchogenic carcinoma), was the cause of ATE in 5% of cats, and 3% of cats had no identifiable cause of the ATE (Smith et al. 2003; Laste and Harpster 1995) Thrombosis is the formation of a clot within a cardiac chamber or blood vessel. Thrombi may be located within the left atrium, left ventricle, or both. Embolization occurs when a clot is carried by blood flow to lodge in a vessel (Figure 20.1). In cats, most thromboembolisms involve the left heart and systemic arteries, which causes obstruction of the affected artery. In addition to this obstructive effect, vasoactive mediators released by the clot result in constriction of collateral vessels. It is believed that these vasoactive mediators, rather than the obstruction to blood flow, are primarily responsible for the clinical signs associated with feline ATE. This theory is supported by the fact that ligation of the distal aorta in cats fails to reproduce the clinical syndrome (Butler 1971; Imhoff and Tashjian 1961), and clinical signs are ameliorated if cyproheptadine, a serotonin antagonist, is administered prior to thrombus formation (Olmstead and Butler 1977). Similarly, aspirin therapy (resulting in thromboxane inhibition) prior to a surgically produced aortic thrombosis preserves collateral circulation (Schaub et al. 1982).

PATHOPHYSIOLOGY AND GROSS PATHOLOGY

Pathophysiology

Virchow's triad describes the three prerequisites required for thrombogenesis:

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Figure 20.1. The terminal aorta from a cat affected with ATE. Note the saddle embolus in the distal bifurcation of the vessel. Photograph courtesy of Dr. John Bonagura.

1. Abnormalities in the vessel wall
2. Abnormal blood flow
3. Altered blood coagulability

These prothrombotic factors are usually present to some degree in cats with cardiomyopathy, which predisposes them to embolic events. Endothelial fibrosis and patches of endomyocardial necrosis have been described in the left atrium and/or left ventricle of cats with heart disease (Liu 1977). These lesions present reactive substrates, (i.e., von Willebrand's factor, tissue factor, and exposed collagen) to circulating blood and may trigger a thrombotic process by inducing platelet adhesion and aggregation. The intrinsic clotting cascade can be secondarily activated.

Blood stasis, the second arm of Virchow's triad, is also often present when significant chamber dilation has developed, especially when severe systolic or diastolic dysfunction is present and when cardiac emptying is abnormal. Since left atrial dilation occurs when there is significant systolic or diastolic dysfunction and elevated left ventricular filling pressure, it is no surprise that cats with severe left atrial dilation are more likely to develop ATE, likely because of blood stasis. Blood flow stasis occurs at very low blood flow velocities and may lead to red blood cell aggregation. One study showed that peak blood flow velocity in the left atrial appendage was lower in cats with cardiomyopathy than in normal cats, and even lower in cats with evidence of ATE (Schober et al. 2003). More recently, the same group linked reduced left atrial appendage peak blood flow velocity to the presence of intracardiac spontaneous echocardiographic contrast (SEC) in cats with cardiomyopathy. In fact, left auricular velocity <0.20 m/s was the only independent variable that predicted SEC. SEC is a possible indicator that a cat is at increased risk for ATE (Schober et al. 2006).

Results regarding hypercoagulability in cats with heart disease have been variable; however, a hypercoagulable environment is present in some cats. For example, feline platelets are particularly reactive and responsive to adenosine diphosphate (ADP) and other agonists of platelet aggregation. One study showed that platelets from cardiomyopathic cats required less ADP to induce aggregation than did platelets from normal cats (Helinski and Ross 1987), while another demonstrated decreased platelet responsiveness to ADP, but increased responsiveness to collagen (Welles et al. 1994). Another study, which defined systemic hypercoagulability as two or more laboratory abnormalities reflecting coagulation excess, inhibitor deficiency, or thrombin generation, noted approximately half of the ATE cats and cats with SEC were hypercoagulable (Stokol et al. 2008). These results were supported by another group as well (Bedard et al. 2007). Neither left atrial size nor congestive heart failure (CHF) was associated with hypercoagulability in Stokol's study, which suggests that a subset of cats with cardiomyopathy which develop ATE may be hypercoagulable compared to those cardiomyopathic cats that do not develop thromboembolic disease irrespective of atrial enlargement. Moreover, their results further support the hypothesis that SEC is a risk factor for ATE. Another study that assessed platelet closure time (the time it takes for a platelet plug to form and occlude flow) was unable to identify a difference in normal cats versus a group of cats with HCM. However, no cats with ATE were included in the study (Jandrey et al. 2008). In a study that measured feline antithrombin activity and D-dimer concentration (using a chromogenic AT assay and an immunoturbidimetric D-dimer assay), mean AT activity was increased in cardiomyopathic cats while the D-dimer assay did not appear to effectively measure feline D-dimer (Brazzell 2007). In contrast, D-dimer concentration was elevated in 50% of ATE affected cats and 17% of healthy cats in another study (Stokol et al. 2008). These studies used different reagents and assay methods (Stokol et al. 2008). Taken together, these studies show that hypercoagulability is unlikely to be the primary factor in thrombus development since it was not present in a large subset of the ATE cats.

Cats with cardiomyopathy and ATE were shown in another study to have low plasma B_{12} and arginine concentrations, which suggests peripheral vascular disease and endothelial dysfunction may play a role (McMichael et al. 2000). Finally, a genetic tendency for thromboge-

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nicity in some cats cannot be ruled out (Smith and Tobias 2004). Therefore, feline cardiogenic ATE is a multifactorial process, with the most important factor being blood flow stasis associated with dilated left atrium; other contributing factors such as endothelial damage or hypercoagulability may be involved to a lesser extent.

Gross Pathology

In general, arterial thrombi are composed primary of platelets and fibrin because the rapid intravascular blood flow tends to exclude erythrocytes. Consequently, they are most often pale beige or gray in appearance. However, red blood cells are often enmeshed in saddle thrombi and they can therefore have a reddish appearance. This is in contrast to postmortem clots, which tend to be red, soft, and gelatinous (or the appearance of a "chicken fat clot" secondary to settling of erythrocytes leaving a yellow, gelatinous layer on the surface of the clot) (Mosier 2007).

The lack of an adequate blood supply to the hindlimbs results in coagulative necrosis, in which tissue architecture is maintained because lysosomal enzymes are denatured and do not cause proteolysis of tissues. Grossly affected muscle appears paler than surrounding well vascularized tissue and it will be dry on the cut surface. Because muscle cells are labile and undergo mitosis, they will replicate following the insult and will help reform the tissue.

It is important to consider other possible sites of embolism and underlying inciting factors. A 17-year, retrospective study at the University of Pennsylvania veterinary school, which analyzed records from cats evaluated through the necropsy service from 1986 to 2003, found that out of 3400 feline necropsies, 131 cats had thromboembolic disease as a major factor contributing to their illness or death (3.9%). Seventy of these cats had saddle emboli associated with heart disease. Thirty-eight cats had thromboemboli in other arteries and/or veins associated with the following: cardiac disease (n = 2), neoplasia (n = 9), multisystemic inflammation/sepsis (n = 12), chronic tubulointerstitial nephritis (n = 4), undetermined (n = 6), hyperthyroidism (n = 3), pericardial/diaphragmatic hernia or trauma (n = 2) (Van Winkle 2010).

Prevalence

When cardiogenic emboli develop in cats they result in significant morbidity and mortality. Most clinical studies have reported incidences of arterial thromboembolism ranging from 12 to 28% of cats with heart disease. Specifically, reported percentages of cats that develop ATE with the various cardiomyopathy ranges from 56% with restrictive cardiomyopathy (Stalis et al. 1995), 12–17% with HCM (Rush et al. 2002; Atkins et al. 1992), 18% with dilated cardiomyopathy (Ferasin 2003; Sisson et al. 1991). The prevalence tends to be higher in necropsy based reports (up to 48% of HCM cats).

In the general feline population, the reported prevalence has ranged from 1 in 142 (Buchanan et al. 1966) to 1 in 175 cats evaluated (Smith et al. 2003).

SIGNALMENT

Male cats have been reported to be overrepresented, but one study suggests they are at increased risk for HCM or hypertrophic obstructive cardiomyopathy (HOCM) rather than specifically for ATE (Smith et al. 2003). The age of affected cats ranged from 1 to 20 years with a mean of 7.7 years and a median of 10.5 years (Laste and Harpster 1995).

HISTORY AND CHIEF COMPLAINT

Most cats presenting for ATE have underlying heart disease; however, clinical manifestations often are absent prior to the ATE event (Smith et al. 2003). Thus, the thromboembolic event is often the first overt sign of heart disease in a subset of cats. The site of cardiogenic embolization varies, but the distal aorta ("saddle embolus") is the most common site, representing 71% of the cases in one large study (Smith et al. 2003). Historically, it was believed that the right brachial artery was more likely to be obstructed than the left brachial artery (Bond 2005). However, a larger objective study showed the frequency of involvement was similar between the right and left forelegs (Smith et al. 2003). Less commonly, various abdominal organs can be embolized. The location of the occlusion is dependent on the size of the embolus as well as the vascular anatomy.

Affected cats can present a variety of initial signs depending on the site of embolization, the duration of occlusion, and the degree of functional collateral circulation. Distal arterial embolization affecting the limb(s) usually results in peracute signs of paresis (Figures 20.2, 20.3), vocalization, and pain. Many animals present with concurrent congestive heart failure (CHF) with typical clinical signs (dyspnea, tachypnea, etc.). Radiographic evidence of CHF has been reported to range from 40–66% in cats affected with ATE (Smith and Tobias 2004). A murmur, gallop heart sound, or arrhythmia may lend additional support to a diagnosis of cardiogenic thromboembolism, although many cats (39%) have normal auscultation findings (Laste and Harpster 1995). Therefore, one cannot rule out underlying heart disease based on a normal auscultation. Additionally, auscultation of abnormal sounds may be obscured by respiratory noise or vocalization secondary to pain.

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Figure 20.2. A cat presenting with the typical caudal paresis following ATE of the terminal aorta. Photograph courtesy of Dr. John Bonagura.



Figure 20.3. A cat with nonweightbearing, knuckling of the distal limb due to ATE affecting the left forelimb. Photograph courtesy of Dr. John Bonagura.



Figure 20.4. Footpads from a cat presenting with ATE. Note the foot that is not affected has normal, pink color (above) and the affected foot pads are cyanotic (below).

Unfortunately, most cats presenting with ATE display tachypnea because of pain, making a definitive diagnosis of CHF very difficult without thoracic radiographs. In addition to clinical signs associated with CHF, clinical signs secondary to the specific tissue or organ embolized are to be expected.

Clinical signs that relate to the extremities have been characterized by the "five P's": Paralysis, Pain, Pulselessness, Pallor, and Poikilothermia (Smith and Tobias 2004, Flanders 1986). The neuromuscular ischemia secondary to vascular occlusion causes severe pain and paresis. When the terminal aorta is involved, femoral arterial pulses are typically poorly palpable (distal/partial embolus) or not palpable (absence of femoral arterial circulation) and the distal limbs are cold.

The cranial tibial and gastrocnemius muscles become firm within 10 to 12 hours postembolization due to ischemic myopathy, and remain painful on palpation. Usually they become softer 24 to 72 hours later; however, in some cats the degree of firmness will increase over the first few days, suggesting poorer perfusion. The nail beds and pads may appear pale to cyanotic depending on the severity and duration of ischemia (Figure 20.4); often there is progression from pallor to cyanosis over the first 12 hours of embolization. Neurologic examination typically reveals a sciatic neuropathy with absent deep pain and withdrawal, but usually normal patellar reflexes. Rectal tone is typically maintained, and urinary bladder function is usually maintained. Less common embolization sites include the renal, mesenteric, pulmonary, coronary, and cerebral arteries. Occlusion of these vessels may lead to azotemia, bloody diarrhea, or sudden death and other abnormalities, such as renal infarctions on ultrasound or neurologic abnormalities such as seizures may be present. Most affected cats are clinically dehydrated and/or hypothermic. Rectal hypothermia was noted in 66% of the cats in which a rectal temperature was measured in one large study. This was likely to be due to poor systemic perfusion rather than obstruction of rectal perfusion since cats with forelimb emboli were also hypothermic (Smith et al. 2003).

DIFFERENTIAL DIAGNOSIS

Differential causes of acute posterior paresis include trauma, intervertebral disc extrusion, spinal lymphoma,

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and other neoplasias, as well as fibrocartilaginous embolism-induced infarction. Acute forelimb paresis can be caused by trauma, foreign body, or brachial plexus avulsion. Usually the diagnosis of arterial thromboembolism is fairly easy to confirm on physical examination. If the cause is cardiogenic, thoracic radiographs will often demonstrate cardiomegaly. However, in some cats, particularly those that are obese, this diagnosis can be difficult. Moreover, pulse identification can be challenging in the forelimbs and partial occlusion of appendicular arteries can cause limb paresis in the presence of palpable femoral pulses. Doppler evaluation of blood flow can be helpful to lend additional support to a diagnosis of ATE. Severe serum elevations in muscle enzymes (creatine phosphokinase and aspartate aminotransferase) are frequently present with ATE, as a result of muscle ischemia. One study showed that local venous glucose was significantly lower than central venous glucose and local venous lactate was significantly higher than central venous lactate in cats affected with appendicular ATE (McMichael et al. 1998). However, the value of these diagnostic tests beyond the physical examination abnormalities remains to be proven. When there are partial thrombi or equivocal findings, they may be supportive of a diagnosis of ATE.

DIAGNOSTIC TESTING

If thromboembolism is suspected, a minimum database should include thoracic radiographs, electrocardiography (ECG), echocardiography, biochemical profile, and urinalysis. Thoracic radiographs usually reveal cardiomegaly; however, a small percentage (11%) of cats with thromboembolism had normal cardiac silhouettes in one study (Laste and Harpster 1995). Many affected cats have evidence of CHF (40–60%) (Smith and Tobias 2004; Schoeman 1999). Radiographs are particularly important to definitively diagnose the presence of CHF, since some cats will manifest pain with tachypnea and medical treatment for CHF could worsen perfusion in cats that are not truly in CHF. Electrocardiography was shown to be informative in a large retrospective study of cats presenting with ATE, with 85% of affected cats having ECG changes in heart rate or rhythm (Laste and Harpster 1995). The most common ECG abnormalities included a left ventricular enlargement pattern (39%), sinus tachycardia (28%), ventricular premature beats (19%), supraventricular premature beats (19%), prolongation of the QRS interval (16%), and a left atrial enlargement pattern (16%) (Laste and Harpster 1995). The presence of bradycardia or atrial standstill with a sinoventricular rhythm is suggestive of marked hyperkalemia, a dire consequence of reperfusion muscle injury and/or renal thromboembolism, which requires emergency treatment. Other factors that may contribute to these arrhythmias may include hypocalcemia and/or acidosis (see Chapter 18, Figure 18.1). Approximately half of affected cats had elevated BUN and serum creatinine levels. Mild prerenal azotemia is common since many cats are dehydrated. However, significant or progressive azotemia suggests renal infarction may be playing a role. Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are common and indicate hepatic and hepatic or skeletal muscle inflammation and necrosis, respectively. These values usually peak by 36 hours. As already stated, skeletal muscle enzymes are significantly elevated, consistent with cellular injury. Hyperglycemia, a mature leukocytosis, lymphopenia, and hypocalcemia may also be present. Hyperthryoidism has historically been thought to be linked to ATE through secondary cardiac remodeling. However, Smith's retrospective study results (2003) suggest hyperthyroidism may pose a risk factor for ATE independent of the cardiac effects. Therefore, cats of the appropriate age should be screened for hyperthyroidism. Coagulation abnormalities may also be detected, especially in cats without significant cardiac disease, or findings may be normal. Urinalysis may show pigmenturia, (myoglobinuria), which resolves over the first couple of days.

When echocardiography is available, it allows one to rapidly and noninvasively evaluate the cardiac structure and function to choose the optimum chronic therapy for the underlying heart disease of the individual patient, once the acute crisis has resolved. An echocardiogram is not essential to diagnose ATE, and in the acute crisis, management of thromboembolism and/or heart failure takes priority over chronic cardiac therapies. The sonographer should search for possible intracardiac clots, which can be small and attached to the ventricular wall or in the left atrial appendage, large echogenic masses visible in the left atrium (Figure 20.5). In some patients, spontaneous echocardiographic contrast (SEC, "smoke") can be visualized in the left atrium or ventricle. Often an obliqued view results in optimal assessment of spontaneous contrast in the dilated appendage (Figure 20.6). This finding has been associated with blood stasis and is considered a marker for increased thromboembolic risk. The mechanism of SEC formation has been attributed to erythrocyte or platelet aggregation at low blood flow velocities. Left atrial enlargement is usually present in ATE cats; however, a small subset of them do not have cardiac abnormalities detected on echocardiography. For example, one study of cats diagnosed with distal aortic thromboembolism found the left atrium was severely enlarged in 57%, moderately enlarged in 14%, and mildly enlarged in 22%, with only 5% of cats having a normal left atrial size (Laste and Harpster 1995). Other etiologies of thromboembolism should be considered in

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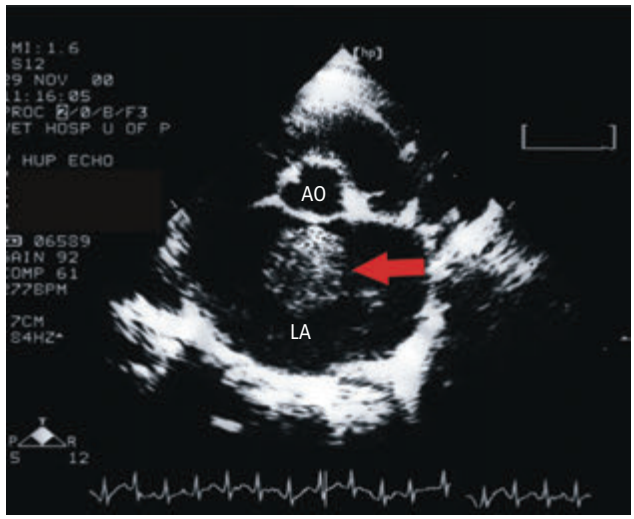


Figure 20.5. A short-axis echocardiogram from the right parasternum obtained at the heart base showing the aorta and left atrium. Note the hypoechoic thrombus (arrow) within the body of the left atrium (LA); aorta = Ao.

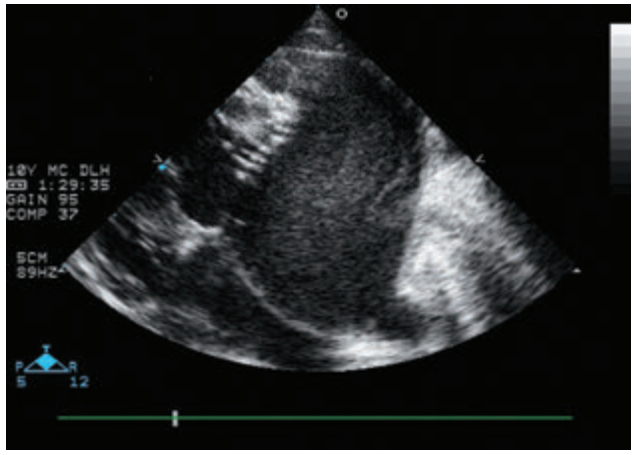


Figure 20.6. A short-axis echocardiogram from the right parasternum obtained at the heart base and showing the aorta and left atrium. Note the hypoechoic or grey debris in the left atrium (arrows). In real time, this spontaneous contrast is visible swirling around the left atrial chamber and represents red blood cell aggregation. Left atrial smoke in the modified left parasternal long-axis view.

these patients (neoplasia, systemic inflammation or other systemic diseases). Neoplasia was identified as the underlying disease in 5% of the cats with ATE in one study (Smith et al. 2003).

Occasionally, more invasive diagnostic testing may be warranted to confirm the diagnosis of ATE. Abdominal ultrasound, angiocardiography (Figure 20.7), and nuclear scintigraphy have all been used to evaluate the obstructed site further. Procedures requiring sedation should only be attempted in clinically stable patients.

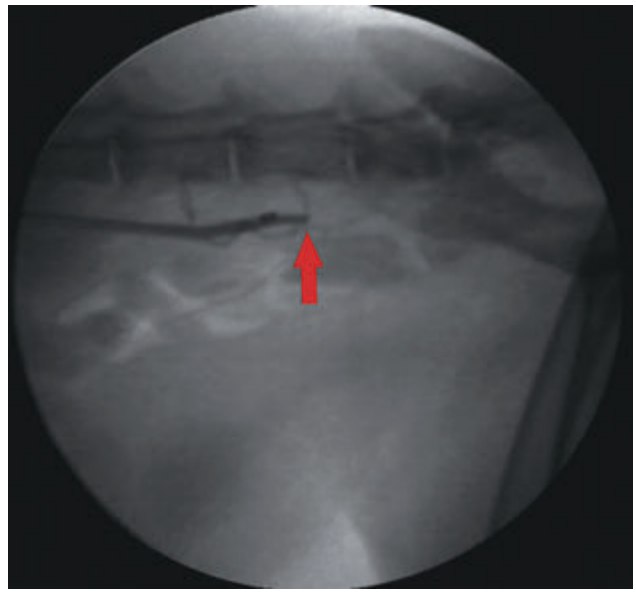


Figure 20.7. An aortogram obtained from a cat with a "saddle" embolus. Note the contrast in the aortic blood is blocked cranial to the pelvis because of a clot in the terminal aorta (arrow), and no collateral circulation is present to the pelvic limbs. Image courtesy of Dr. Mark Kittleson.

TREATMENT

Acute Case Management

Acute therapy of ATE patients is directed toward managing pain, CHF, or significant arrhythmias when present; general patient support, notably involving pain management; and adjunctive therapies to limit thrombus growth or future thrombus formation. In the acute phase, a 24-hour care facility is best suited for these cases, because there may be acute life-threatening deterioration at any time during the first several days after ATE has occurred. If CHF is present, therapy should be initiated similarly as in other cats with CHF (see Chapter 19 for discussion of CHF management). Analgesia is crucial in these patients, particularly for the first 24 to 48 hours, because after that time period, there is often lack of pain noted in cats with a saddle embolus. In humans with peripheral vascular disease, axonal degeneration begins after 24 hours of ischemia and severity of the pathologic change is dependent on the duration of ischemia (Nakuda et al. 1996). Analgesia can be addressed with various medications such as fentanyl (2–5 µg/kg/hr as a CRI for 12–18 hours until a fentanyl patch takes effect), butorphanol (0.1 to 0.2 mg/kg IV every 4 to 6 hours), or buprenorphine (0.005 to 0.015 mg/kg IV every 6 to 8 hours). See Figure 20.8 for an algorithm breaking down the acute and long-term care of a cat with ATE.

Vasodilators, such as acepromazine, have been suggested to encourage arterial vasodilation; however, arte-

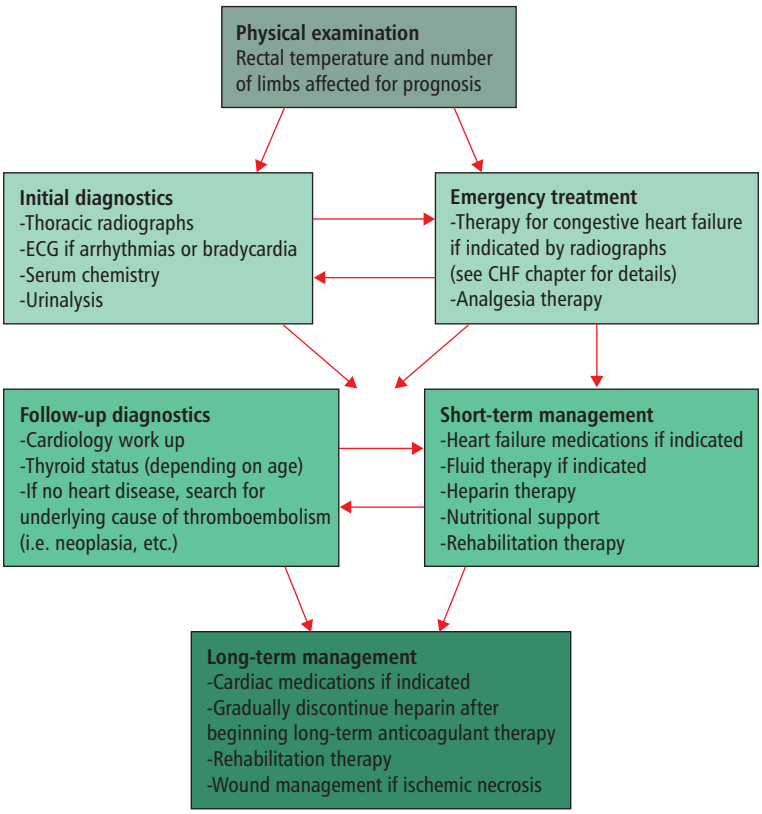


Figure 20.8. An algorithm for a clinical approach for cats presenting with ATE.

rial vasodilation is often not uniform and flow to muscle beds may ultimately be unchanged. Also, these agents can cause hypotension. Their efficacy is therefore uncertain and their use has fallen out of favor. Hypothermia is a manifestation of poor systemic perfusion and shock rather than just local blood flow changes due to a saddle thrombus; improving it is one of the most important goals in managing the acute crisis in ATE patients. However, addressing perfusion can be very difficult in these patients. Fluid therapy is warranted for dehydrated patients, as long as CHF is not present, but it must be used with caution in cats with significant heart disease. Vigilant monitoring of respiratory rate, effort and auscultation for the development of a gallop is particularly important in these patients. External warming can lead to peripheral vasodilation and worsening of core perfusion. Therefore it must be used cautiously for these patients. Excellent supportive care in the form of good nutritional support, manual voiding of the urinary bladder if necessary, and maintaining clean and comfortable bedding is critical in this patient population. In some cats, a nasoesophageal feeding tube may be necessary for alimentation during the early stages of treatment. Self-mutilation of devitalized limbs occurs in a subset of patients and is characterized by excessive licking or chewing of the toes or hock. Application of a loose fitting bandage barrier is usually effective.

Appropriate clinical laboratory patient monitoring is dependent on the individual's status. Biochemical profiles are useful to assess renal function and electrolyte status. Coagulation profiles (activated partial thromboplastin time [aPTT], prothrombin time [PT], activated clotting time [ACT], fibrin split products, platelet count) are necessary to evaluate anticoagulation therapy and detect disseminated intravascular coagulation.

Sudden hyperkalemia can result from reperfusion syndrome (ischemic rhabdomyolysis and reperfusion), which occurs when arterial blood flow is reestablished to a previously ischemic region, resulting in acute catastrophic release of potassium into the systemic circulation (9.4% of cases in one study; Laste and Harpster 1995). Continuous recording of the ECG is one way to screen for circulating potassium increases. Hyperkalemia is usually associated with PR interval prolongation and concurrent flattening and disappearance of the P waves, widening of the QRS complexes, increasing T wave amplitudes, and a slowing heart rate on the ECG. In addition to the detection of hyperkalemia, the development of reperfusion syndrome can be identified on clinical laboratory results by elevated blood lactate

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Box 20.1. Treatment of life-threatening hyperkalemia (reperfusion injury)

Drug	Dose	Onset of action
10% calcium gluconate	0.5–1.5 ml/kg IV slowly over 5–10 minutes	3–5 minutes
Sodium bicarbonate	1–2 mEq/kg IV slowly over 15 minutes	15 minutes
25% dextrose	0.7–1 g/kg IV over 3–5 minutes	<1 hour
25% dextrose with insulin	Regular insulin at 0.5 U/kg IV with dextrose at 2 g/U of insulin administered	30 minutes

Modified from: Riordan LL, Schaer M. Potassium disorders. In: Small Animal Critical Care Medicine, Silverstein DS, Hopper K, eds. St. Louis, Saunders Elsevier, 2009.

and acidosis. It is a life-threatening condition that usually occurs hours to several days after the embolic event due to systemic release of the metabolic byproducts associated with ischemia. Treatment should be aggressive and immediate. Hyperkalemia can be addressed with calcium gluconate and/or insulin and glucose to drive K+ intracellularly. If a secondary bradycardia is present, atropine may be indicated. Fluid therapy with sodium bicarbonate is warranted to address metabolic acidosis. Unfortunately, the prognosis in cats that develop reperfusion syndrome is poor, and many cannot be rescued. See Box 20.1 for emergency therapy for cats in a hyperkalemic crisis.

Thrombolytic therapy seems intuitive because rapid resolution of the arterial occlusion theoretically would be beneficial for the patient. However, streptokinase and urokinase act by generating the nonspecific proteolytic enzyme plasmin, which can lead to a generalized lytic state with the hazard of bleeding complications. Tissue plasminogen activator (t-PA) has a lower affinity for circulating plasminogen and does not induce a systemic fibrinolytic state. Rather, t-PA initiates local fibrinolysis with limited systemic proteolysis. No controlled clinical trials have evaluated the use of thrombolytic agents in cats with ATE. However, in the case series that have been published so far, the approach (with any of these agents) does not appear to significantly alter case outcome. In a series of 46 ATE cats that were treated with streptokinase, 33% survived to discharge (Moore et al. 2000). Although these results were better than the 0% survival noted in an older report of 8 cats treated with high dose streptokinase (Ramsey et al. 1996), it was still no better than conservative therapy. Indicators of poor outcome were similar to other feline ATE studies (azotemia and hypothermia) while having one limb affected was associated with better outcome (Moore et al. 2000). Similar results were reported in an abstract describing the use of t-PA in 6 ATE cats, with 3 cats surviving to discharge from the hospital (Pion et al. 1987). Another study initiated to evaluate efficacy of t-PA in cats with ATE was terminated due to a high frequency of adverse outcomes (Welch et al. 2010). Adverse effects were seen in 100% of treated cats (11/11) including azotemia (n = 5), neurological signs (n = 5), cardiac arrhythmias (n = 5), hyperkalemica (n = 4) acidosis (n = 2) and sudden death (n = 1). Twenty-seven percent (n = 3) of t-PA treated ATE cats in this study were ultimately discharged from the hospital (Welch et al. 2010). Considering the expense involved with these therapies, their use at this time is difficult to justify. Moreover, if thrombolytic therapy is elected, cats require intensive 24-hour monitoring for acute life-threatening reperfusion syndrome and their use should be avoided in cats with intracardiac thrombi due to risk of new embolic events as the clot undergoes lysis.

A case series described efficacy of a commercially available rheolytic thrombectomy system in 6 ATE cats (Reimer et al. 2006). This intravascular system mechanically breaks down the embolus, and resulted in successful embolus dissolution in 5 of the 6 cats. However, despite successful thromboembolectomy, only 3 cats survived to discharge and the remaining succumbed to systemic hypotension during or after the procedure. It is possible that with more experience the procedure will result in improved success; however, at this time the expense of the procedure (similar to medical thrombolytic therapy) is difficult to justify since a hospital discharge rate of 50% is similar to what is reported for cats treated conservatively (Smith and Tobias 2004).

Anticoagulant Therapy

Anticoagulant therapy has no effect on established thrombi; however, by retarding clotting factor synthesis, or accelerating its inactivation, thrombosis from activated blood-clotting pathways can be prevented. The theoretical aim of anticoagulant therapy in the acute phase is to prevent or reduce thrombus extension. Heparin binds to lysine sites on plasma antithrombin,

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enhancing its ability to neutralize thrombin and activated factors XII, XI, I, and IX, which prevents activation of the coagulation process. Although heparin has proven effective in human trials and experimental animal models, it has never been evaluated in spontaneously occurring feline arterial thromboembolism and reported dosages vary widely.

Unfractionated (UF) Heparin

In spite of this limitation, heparin is part of the standard of care for hospitalized patients during the early, acute stage of ATE because of these theoretic benefits. Heparin should not be administered intramuscularly because of the risk of injection site hemorrhage. In normal cats, a UF heparin dosage of 250–300 U/kg administered subcutaneously every 8 hours resulted in acceptable plasma concentrations (Smith et al. 2004). If the patient is in shock, the first dose can be administered intravenously. Because of significant variations in the sensitivity of aPTT reagents and the poor correlation between heparin levels and aPTT, some authors do not recommend routine monitoring of these values when heparinizing cats with UF heparin (Smith and Tobias 2004). The ACT is even less predictive of plasma heparin concentrations and level of anticoagulation (Smith and Tobias 2004). However, the traditional monitoring recommendation was to maintain the aPTT or ACT at 1.5–2.5 times the pretreatment value or normal control value (Lunsford and Mackin 2007; Smith et al. 2008). Plasma heparin concentration measured by chromogenic factor Xa assay is more accurate; however, it is not readily available to many practices (see the section "Long-Term Management," below).

Low Molecular Weight Heparin (LMWH)

Because small heparin polysaccharides are unable to bind thrombin and antithrombin (AT) simultaneously, they are unable to catalyze the inactivation of thrombin by AT, but retain the ability to enhance the inhibition of activated factor X and other coagulation factors by AT. Since there is less anti-II activity, LMWHs do not alter PT and APTT times, and LMWH level assessment requires measurement of anti-Xa activity (see the section "Heparins," below). In humans they have more predictable bioavailablility, requiring less monitoring of the patient's coagulation status and less frequent dosing than UF heparin. Additionally, they are less likely to cause thrombocytopenia than unfractionated heparin (1–2% risk vs 2–5%) (Nutescu et al. 2005). Meta-analyses of the various human trials have concluded that the risk of major bleeding events is also improved using LMWH compared to UFH (0.8–2.2% compared to 2.6–4.7%, Gouin-Thibault et al. 2005).

However, previous research suggests important species differences in the pharmcokinetics of LMWH. In particular, compared to humans, the half-life and peak activity of LMWHs appear to be very different in the cat (see the section "Heparins," below). In any case, for the acute phase of therapy in the hospital (when thrice daily dosing is not cumbersome) they do not offer a significant advantage over UF heparin, and are much more costly.

Aspirin

Cyclooxygenase (COX) converts arachidonic acid to prostaglandin, which is the immediate precursor of several different products including prostacyclin and thromboxane A2. Prostacyclin is produced in endothelial cells and effects include inhibition of platelet plug formation and vasodilation; whereas thromboxane A2 is a vasoconstrictor, which stimulates activation of new platelets and increases platelet aggregation. Aspirin induces a functional defect in platelets by irreversibly inhibiting COX and therefore the production of thromboxane A_2. It is irreversible because platelets have no DNA, so they are unable to synthesize new COX once aspirin has irreversibly inhibited the enzyme. In contrast, the nucleated endothelial cell will eventually produce increased COX levels because of gene activation. Therefore, aspirin therapy initially has little or no effect, but eventually the effect of prostaglandin predominates. This aspirin-induced platelet inactivation is irreversible and persists for the life of the platelet, which is 7–10 days. Although the initial anticoagulant effect is thought to be negligible with aspirin therapy, cats treated with oral aspirin 1 hour before thrombus occlusion of the aorta had better collateral circulation than did those cats that did not receive aspirin in an experimental feline ATE model (Schaub et al. 1982). Therefore, some clinicians initiate aspirin therapy as soon as the patient is stable enough to begin oral medications (Smith 2004).

Although not widely recommended, some clinicians have advocated administration of aspirin by the owner immediately at the onset of clinical signs suggesting ATE. If there is a high index of suspicion of ATE (previously diagnosed significant heart disease, prior ATE events, etc.) and oral administration of medications is possible in a quickly and atraumatic fashion, then administration of ¼ to 1 baby aspirin is unlikely to cause harm.

Long-Term Management

In retrospective studies, the proportion of affected cats with recurrence of ATE has ranged from 24 to 75 percent and was the ultimate cause of death or euthanasia in 20 to 50 percent of the cats (Smith and Tobias 2004; Smith et al. 2004; Lunsford and Mackin 2007). Subjectively, it

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appears that a large majority of cats suffering from ATE have recurrent ATE, and a majority likely succumb to this disorder. Published percentages of 20–75% may reflect regional differences or underreported cases. However, although the diagnosis of cardiogenic ATE carries a poor prognosis, it is important to keep in mind that treating these patients can still be fulfilling and may result in good quality of life for an extended period of time. In one report, when evaluating ATE cats that were discharged from the hospital (19/49), the mean survival time was 13.4 months (range of 3 days to 73 months). Four cats were still alive at the time the report was published, with the longest having survived 39.5 months at that time (Schoeman 1999). In general, most studies have reported that 1/3 of affected cats survive to discharge (Smith and Tobias 2004). However, as suggested by Dr. Smith in her review, these results may reflect clinician and owner bias in the face of a disease with a poor prognosis. In general, in cases where the patient's pain can be adequately controlled and there is not evidence of catastrophic disease (for example, azotemia associated with renal artery embolization), the authors often suggest initiating therapy to assess response over the first few days. It is important to consider possible factors suggestive of a worse prognosis in the individual patient (hypothermia, etc.) when making these decisions.

Therapy directed at the underlying cause of thromboembolism (most often cardiomyopathy) and CHF (when present) is crucial for these patients. CHF also significantly impacted long-term survival, suggesting that the ability to control underlying heart disease is a significant factor in survival of these cats. The mainstay of CHF treatment in veterinary medicine is medical management (see Chapter 19 for additional information regarding case management of cats with congestive heart failure).

In most cats, motor and neurologic function of the affected limb(s) returns over several days to weeks; however, in some cats post-ATE, limb function does not completely return, due to neurologic dysfunction, tendon contracture, or tissue necrosis. Wound management is successful in many (Figure 20.9); however amputation may be necessary in some patients. A bandage may be useful in those patients with tendon contracture (Figure 20.10). Rehabilitation therapy may be instituted after the first 2 days of ATE and includes gentle passive range of motion, supporting the cat in a standing position to retrain normal placement of the pelvic limbs and feet, and very gentle antegrade massage from the feet to the hip. Owners can be trained how to administer rehabilitation therapy, which can be performed every 6 hours for the first 1–2 weeks of recovery, then tapered depending on neuromotor status.



Figure 20.9. A wound secondary to tissue necrosis in a hindlimb following an episode of ATE in a cat. Photograph courtesy of Dr. Kristin MacDonald.



Figure 20.10. A soft brace placed on a cat post-ATE to address hock weakness and improve mobility. Photograph courtesy of Dr. Kristin MacDonald.

There are currently no survival data available to clearly define the superiority of one anticoagulant over another; however, one prospective trial evaluating clopidogrel is underway and it is possible this statement will become outdated in the near future. Until that time comes, most veterinary recommendations for anticoagulant therapy come from anecdotal experience and limited experimental and clinical trials (Lunsford and Mackin 2007). Of the available options, low-dose aspirin therapy is a low-risk and inexpensive option with theoretic benefit. Clopidogrel is more costly but also appears to be low risk. At this time, there are no nutraceuticals that have been proven to reduce the risk of ATE in cats. Dietary modification with omega-3 fatty acids have been recommended by some. However, one study which evaluated supplemented normal cats, found no alteration in bleeding time or platelet function using up to 1.689 g EPA and 0.936 g DHA with 60 IU vitamin E per cat (Bright et al. 1994).

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The decision to begin long-term anticoagulant therapy is case and clinician dependent. Although there are currently no studies that show these therapies are beneficial, the general consensus is that therapy should be initiated in cats that have experienced ATE, with most clinicians currently choosing aspirin or clopidogrel therapy. Beginning therapy in asymptomatic cats is less clear cut. In general, therapy is not recommended without evidence of heart enlargement (i.e., a cardiac murmur alone is not an adequate reason to begin anticoagulant therapy). See Box 20.2 for factors to consider before initiating anticoagulant therapy in the asymptomatic feline patient.

In cardiomyopathic cats with atrial enlargement and spontaneous echocardiographic contrast (a change that suggests that the patient is at risk for thromboembolic events), most clinicians recommend prophylactic therapy. The decision is less clear in cats with heart disease without evidence of spontaneous echocardiographic contrast. Regardless of the underlying heart disease, the main factor in deciding whether to start anticoagulant therapy is the severity of atrial dilation. The authors usually recommend anticoagulation if left atrial enlargement is severe, depending on discussion with the owner. With mild to moderate left atrial enlargement, anticoagulant therapy is rarely recommended unless there are other factors suggesting the individual patient may be at risk.

In those asymptomatic cats that cannot be examined by echocardiography, if the radiographic heart size is normal, anticoagulant therapy is not empirically recommended. However, in those cats with significant left atrial dilation on thoracic radiographs (even when an echocardiogram cannot be performed), empirical anticoagulant therapy is a reasonable option. Echocardiography is the ideal way to assess left atrial size and risk of ATE. See Figure 20.11 for an algorithm describing the decision tree for beginning anticoagulant therapy in asymptomatic and symptomatic cats with heart disease. It is also important to reserve therapy for those patients likely to benefit from it. Otherwise, particularly in patients that are difficult to pill, the risk of patient/owner burnout and noncompliance is great.

Box 20.2. Timing of initiation of anticoagulant therapy in asymptomatic patients

Very High risk (begin anticoagulant therapy) Echocardiographic spontaneous contrast or thrombus, prior ATE event

High risk (consider anticoagulant therapy) Severe left atrial enlargement (echocardiographic left atrium : aorta >1.9 or subjective severe LAE on radiographs if echocardiography not available)

Low risk (anticoagulant therapy not recommended) Normal left atrial size or mild-moderate left atrial enlargement (echocardiographic, or radiographic if echocardiography is not available)

Antiplatelet Therapies: Clopidogrel, Aspirin, and Abciximab

Antiplatelet therapies focus on the principle that exposure of blood to subendothelial connective tissue leads to rapid platelet activation, platelet plug formation and subsequent thrombus. A clinical trial comparing efficacy of aspirin and clopidogrel in cats that have experienced ATE is currently underway. The results should identify the optimal therapeutic choice in these patients. Until these results are available, the general consensus is that clopidogrel is likely more effective than aspirin for prevention of ATE. However, it is important to weigh the specific advantages and disadvantages of aspirin and clopidogrel to choose the best option for the individual patient and owner.

Clopidogrel is more expensive than aspirin and it should be given with food. In a human study, clopidogrel was associated with significantly fewer gastrointestinal tract events than aspirin (27.14% vs 29.82%); however, more adverse dermatologic events were associated with clopidogrel (15.81% vs 13.08%) (Hogan et al. 2004). Clopidogrel administration is objectionable to some cats because of its bitter flavor, but most cats tolerate the medication in pill pockets or gel caps. It must be given daily, so in cats which are particularly difficult to pill, aspirin administration every third day may be more reasonable for the owner. Transdermal administration of neither clopidogrel nor aspirin has been studied and is not recommended. Some clinicians prefer to avoid aspirin in patients with renal disease because of possible gastric acidity; clopidogrel may be superior in these patients as long as it does not alter their appetites.

Aspirin

As stated above, cats given aspirin orally 1 hour before thrombus occlusion of the aorta had better collateral circulation than did those cats that did not receive aspirin (Schaub et al. 1982), suggesting aspirin therapy may be beneficial even during the acute thromboembolic event. In cats, aspirin effectively inhibits platelet function (Greene 1985; Behrend et al. 1996) and is relatively safe; therefore it is a reasonable option for chronic therapy. The optimum dose that will inhibit thromboxane A production, yet spare prostacyclin synthesis has not yet been established for cats. However, no difference was detected between low (5 mg/cat q 72 hours, n = 24)

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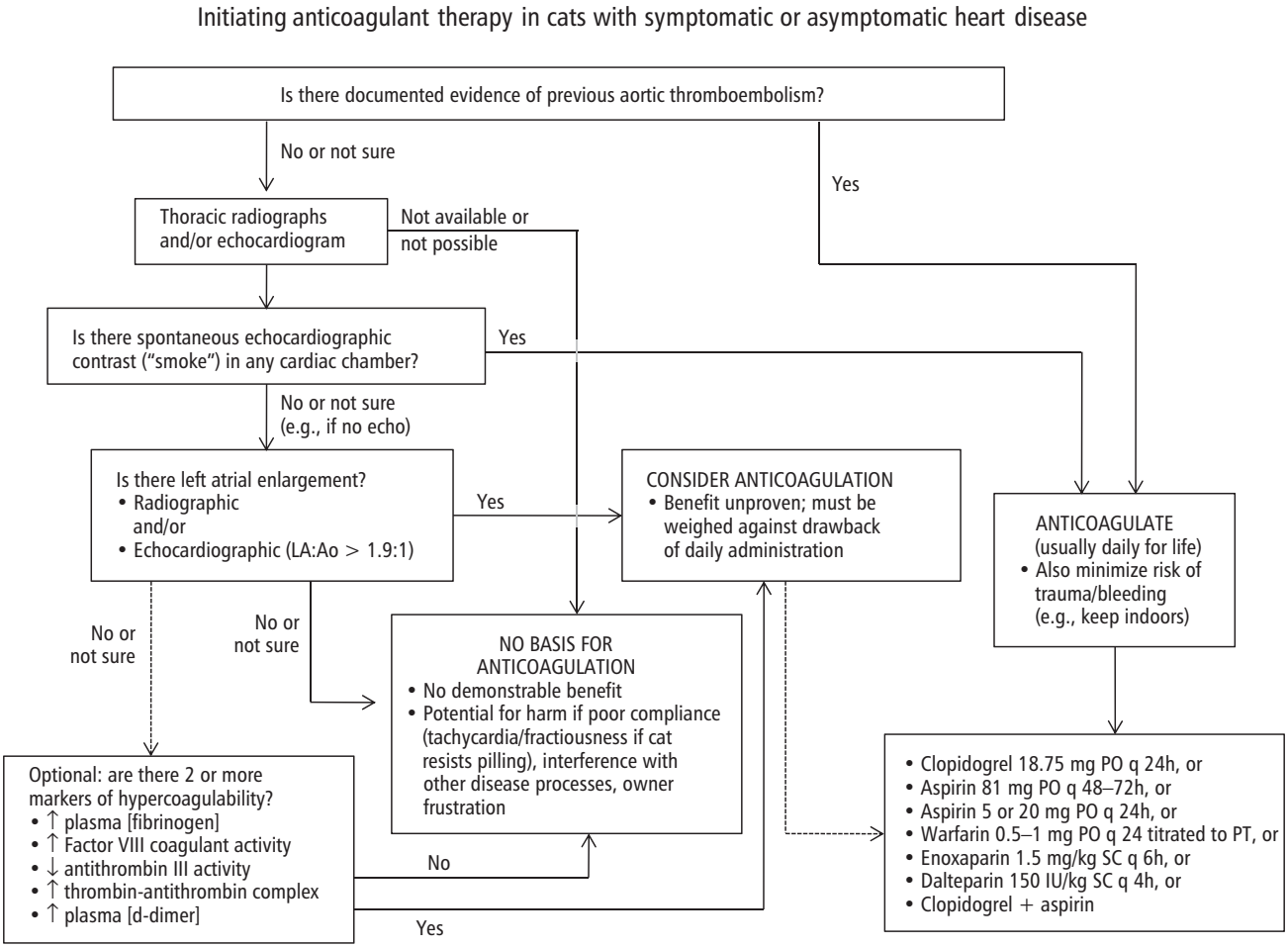


Figure 20.11. An algorithm for describing the decision-making process for initiating anticoagulant therapy in symptomatic and asymptomatic cats.

and high dose (≥40 mg/cat q 24 hours, n = 18) aspirin therapy in recurrence of ATE (a total of 11 (25%) cats had ATE recurrence) in a large retrospective study and fewer adverse effects were noted with the lower dose (Smith et al. 2003). No studies evaluating platelet function were performed in either group. Twenty-two percent of the cats receiving high-dose aspirin exhibited gastrointestinal signs compared to 4% of the cats in the low dose aspirin group (Smith et al. 2003). Using a dose of 5 mg/cat requires compounding which adds an additional owner expense. Using one-quarter of a baby aspirin every 3rd day does not require compounding and is a reasonable option (1/4 baby aspirin corresponds to 20.25 mg aspirin). Aspirin use requires no specific anticoagulation monitoring and adverse effects (particularly with the low dose) are uncommon. Aspirin does not have the prothrombotic effects of warfarin and therefore overlapping of therapy with heparin is not necessary.

Clopidogral and Abciximab

Clopidogrel is a thienopyridine derivative which irreversibly antagonizes ADP receptors on platelet membranes, thereby interfering with primary and secondary platelet aggregation. It has no direct effects on arachidonic acid metabolism. Clopidogrel also inhibits the ADP-induced conformational change of the glycoprotein IIb/IIIa receptor and reduces myointimal proliferation in vascular smooth muscle (Hogan et al. 2004). In vitro, there is a reduced response to vasoactive substances, including serotonin. The drug is used extensively in human medicine and results from several small feline studies are encouraging that it will find a place for veterinary use as well. One small feline study demonstrated that clopidogrel administration compared to placebo resulted in improved motor and neurologic function during recovery in a feline embolic model (Hogan et al. 2006) but not change in collateral perfu-

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sion in 6 cats. When administered at dosages ranging from 18.75–75 mg/cat once daily, clopidogrel resulted in significant antiplatelet effects and none of the treated cats developed adverse effects associated with drug administration in this dose range (Hogan et al. 2004). However, in a study designed to determine the utility of Plateletworks® ADP tubes for use in monitoring clopidogrel therapy in cats, 33% (3/9) of cats treated with clopidogrel developed mild diarrhea (Hamel-Jolette et al. 2009). In this study, platelet aggregation was significantly lower in the clopidogrel treated cats, suggesting the drug is effective in cats. Moreover, Plateletworks® ADP tubes appear to be a viable way to monitor efficacy of antiplatelet medications in cats (Hamel-Jolette et al. 2009). A prospective clinical trial is currently underway evaluating clopidogrel in cats with ATE.

Occasionally clopidogrel treated cats may require a surgical procedure. Anecdotal evidence suggests the risk of bleeding complications is low with this medication. However, in a group of normal cats, platelet function values returned to baseline 7 days after discontinuing therapy whether a high (75 mg q 24 h), moderate (37.5 mg q 24 h), or low (18.75 mg q 24 h) dose of clopidogrel was administered (Hogan 2004). Moreover, no adverse effect of the drug (or its discontinuation, such as rebound hypercoagulability) was noted in this study. Therefore, it seems most appropriate to suggest discontinuing the drug for a week prior to proceeding with a surgical procedure which is elective.

Abciximab, a glycoprotein IIb/IIIa antagonist, is a potent inhibitor of platelet aggregation. This drug was evaluated in a feline model of arterial injury. Cats in the abciximab plus aspirin group had significantly greater reduction in platelet function than the group of cats which received aspirin alone (Bright et al. 2003). However, this drug is not being used routinely in ATE cats at this time.

Vitamin K Antagonists: Warfarin

Warfarin (Coumadin) impairs hepatic vitamin K metabolism, a vitamin necessary for synthesis of procoagulants (factors II [prothrombin], VII, IX, X) as well as regulatory proteins C and S through its inhibition of vitamin K epoxide reductase. Warfarin therapy does not appear to reduce the risk of ATE recurrence over aspirin therapy (Smith and Tobias 2004). One study, which compared warfarin and a LMWH (dalteparin) in 31 ATE cats, reported a median survival time of 69 days and 24% recurrence of ATE in the 17 cats treated with warfarin (DeFrancesco et al. 2003). Three cats treated with warfarin had bleeding complications compared to no reported complications in dalteparin-treated cats. The survival curves for the 2 groups were not significantly different (DeFrancesco et al. 2003). Moreover, warfarin is highly protein-bound in cats and minor shifts in albumin status or concurrent use of other, highly protein-bound drugs, may result in massive alterations in active drug levels and the degree of anticoagulation (Smith and Tobias 2004). Catastrophic hemorrhage is a potential complication and the agent is therefore not recommended in cats that are allowed outside. The reported frequency of fatal hemorrhage in cats treated with long-term warfarin is 11% (Smith et al. 2004). Diet and disease state can potentially affect the pharmacokinetics of warfarin, which already has an unpredictable pharmacokinetic pattern in the cat (Lunsford and Mackin 2007). Therefore, regular therapeutic drug monitoring and good owner compliance is crucial with this agent.

Historically, the prothrombin time (PT) is the laboratory test recommended for monitoring warfarin activity. The PT is the result in seconds that it takes the plasma to clot after addition of tissue factor (which measures the extrinsic and common coagulation pathways). The amount of time for an individual varies depending on the type of analytical systemic used to perform the test; in human medicine the international normalized ratio (INR) was introduced in the early 1980s to standardize results so that comparisons can occur across time and among various laboratories. Warfarin causes an initial prothrombotic effect (due to decreased protein C and S levels) and ATE patients receiving warfarin should continue to receive heparin the first 4–5 days of treatment to counteract the initial procoagulant effect of warfarin (Smith and Tobias 2004). Monitoring with INR or PT testing is recommended to be weekly during the first 4 weeks of therapy, followed by evaluation every 2 to 3 months during chronic therapy. The target PT is 1.5 to 2.5X normal, whereas an INR of 2.0–3.0 is generally recommended in cats (Smith and Tobias 2004, Lunsford and Mackin 2007). Despite small changes in dose, there are often large changes in PT making a dose-dependent prediction of anticoagulant effect challenging. Additionally, there is significant risk of hemorrhage, and if pulmonary hemorrhage occurs it can be difficult to differentiate from CHF and pulmonary edema. Considering the risk of complications to warfarin therapy and the cost of therapeutic drug monitoring, warfarin is not typically recommended for therapy of ATE cats.

Heparins: Unfractionated (UF) and Low Molecular Weight Heparin (LMWH)

For chronic therapy, UF heparin has traditionally not been used commonly in veterinary medicine because it requires frequent parenteral administration every 6–8 hours. In humans, LMWHs require less frequent

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administration and there has been interest in using these products in cats with ATE. However, current evidence suggests that the LMWHs currently on the market, dalteparin and enoxaparin, require more frequent parenteral administration than once daily. In a study of healthy cats, administration of 100 IU/kg dalteparin SC twice daily and enoxaparin at 1 mg/kg SC twice daily failed to induce sustained anti-Xa activity that was significantly different from baseline, placebo, or UF heparin. However, cats treated with UF heparin consistently attained anti-Xa activity within or above the therapeutic range (Alwood et al. 2007). This result was further substantiated by a pharmacokinetic model for enoxaparin in the cat, presented by the same group, which suggests that both dosage and dosing interval of LMWH would need to be increased in the cat to maintain the anti-Xa within the target zone and suggested a dose of 1.5 mg/kg and q 12 h or more frequent dosing interval. Another group reported similar results in 8 healthy cats. In this study, 100 IU/kg of dalteparin was administered subcutaneously to 8 healthy cats twice daily for 13 doses. Four of the treated cats developed anti-Xa activity within the proposed therapeutic range (0.3–0.6 U/ml) at one time point. However at other time points in these cats, and at all time points in the other 4 cats, anti-Xa activity was only trace or not measurable, suggesting that although LMWH may be useful therapeutically, the optimum dose has yet to be determined (Vargo et al. 2009). It is likely that drug effects in cats with cardiomyopathy or other predisposing factors to thrombosis will be different than those effects seen in normal cats, and studies in this population are warranted. However, a previously published retrospective study, which used once or twice daily dosing with dalteparin, was unable to show that therapy reduced the recurrence rate of ATE (Smith et al. 2004). A third-generation heparin medication has also been evaluated in healthy cats (Fiakpui et al. 2010). Fondaparinux is a homogenous synthetic pentasaccharide preparation, which has antithrombotic effects confined to Xa inhibition. Based on a pharmacokinetic model, two doses were evaluated in healthy cats over a 7-day period: 0.06 mg/kg SC q 12 hours (thrombophrophylactic dose) and 0.2 mg/kg SC q 12 hours and 0.2 mg/kg SC q 12 hours (thrombosis treatment). The thromboprophylactic protocol approximated median peak and trough antiXa activities seen in humans considered effectively treated with fonaparinux. The higher dose approximated only peak activities consistent with effective treatment in humans. The higher fondaparinux regimen altered some thromboelastography variables (increased R and K, decreased α-angle and MA), but not platelet aggregation studies. No significant thromboelastography (TEG) or platelet aggregation effect was noted with the lower dose (Fiakpui et al. 2010). The optimal protocol in cats for thromboprophylaxis or thrombosis treatment remains unclear and additional studies are warranted. Moreover, the effects of LMWH and/or fondaparinux in cats with disease will need to be better evaluated with clinical trials that use outcome measures before efficacy is definitively ascertained. Currently, the cost may be as high as several hundred dollars a month, but it can often be acquired internationally for a lower cost. This comparatively higher cost, and the likely frequent administration that will be required, may make this therapeutic option nonviable for many pet owners. Moreover, whether using UF heparin or LMWH, bleeding is a possible complication. Therefore, jugular venipuncture and/or cystocentesis should probably be avoided in these patients.

An additional benefit of LMWHs in human medicine is that, because of its more predictable bioavailability in this species, routine monitoring is recommended only in certain populations who are at risk of hemorrhage (the elderly, pregnant, etc.). Because LMWH does not bind to thrombin, it has little impact on the aPTT. Measurement of factor Xa inhibitory activity (anti-Xa assay) is considered the standard laboratory test for monitoring LMWH activity, usually at peak activity in humans. Considering the rapid absorption and elimination kinetics of LMWH in normal cats, it is advisable to monitor drug effect in patients in which this treatment regime is chosen to ensure an appropriate drug level is achieved. The Cornell University Department of Population Medicine and Diagnostic Sciences Comparative Coagulation Service (http://www.diaglab.vet.cornell.edu/coag/) offers comprehensive coagulation tests including the anti-Xa activity level, which is the gold standard assay.

An alternative for monitoring LMWH activity appears to be thromboelastography (TEG). TEG is a bedside blood test that can be used to define viscoelastic properties of blood. The cost of equipment has limited its widespread availability in veterinary medicine to date; however, new and used units are becoming increasingly accessible. At this time, equipment is rarely available outside the academic and large (referral) private practice setting.

Conventional coagulation tests typically evaluate one portion of the coagulation system; however, TEG is a technique that provides information about the entire coagulation system (Donahue and Otto 2005). Specifically, TEG provides information regarding platelet activation, fibrin formation, and clot retraction (Klein et al. 2000), deriving data from the quality of the clot as well the dynamics of its formation (Donahue and Otto 2005). The TEG-generated tracing is called the *thromboelastogram* and consists of 3 zones (Figure

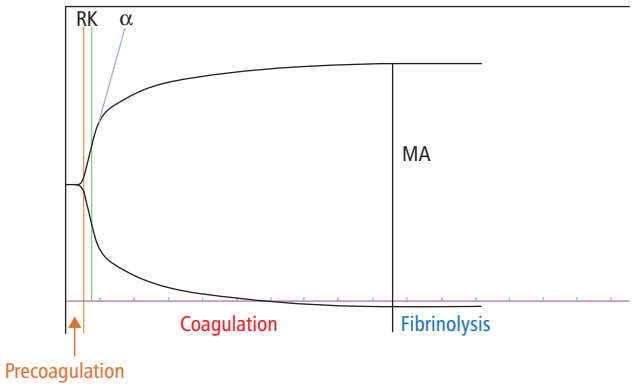


Figure 20.12. A normal TEG tracing from a feline patient identifying the 3 zones of coagulation: precoagulation, coagulation, and fibrinolysis. R = reaction time (precoagulation time); K = clot formation time, the angle between the midline and the tangent to the curve(α); MA = maximal amplitude.

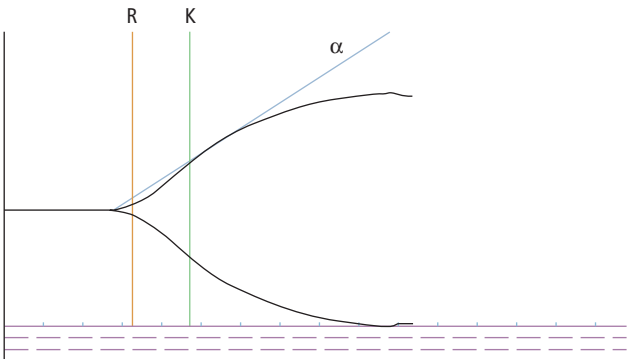


Figure 20.13. A TEG tracing from a heparinized cat. Note the prolongation of R (reaction time) and K (clot time) compared to the normal trace in Figure 20.12.

20.12). The reaction time (R) evaluates the intrinsic pathway (factors VIII, IX, XI, and XII). The clot formation time (K) is influenced by factors II, VII, platelet count and function, thrombin formation, fibrin precipitation, fibrinogen concentration and hematocrit whereas the maximal amplitude (MA) reflects final clot strength. The MA is affected by fibrin and fibrinogen concentration, platelet count and function, thrombin concentration, factor XIII, and hematocrit (Donahue and Otto 2005). TEG has been used as a surrogate monitor of LMWH in humans with one study demonstrating that TEG R values correlated significantly with peak and trough levels of anti-Xa activity after administration of enoxaparin (Klein et al. 2000). Results from the Alwood study suggest TEG results can be used as a surrogate for anti-Xa monitoring of LMWH and UF heparin effect on coagulation in cats (Alwood et al. 2007). See Figure 20.13 for a TEG tracing obtained from a heparinized cat. Because LMWHs (depending on the formulation) affect the coagulation cascade at multiple sites beyond their primary effect on factor Xa (platelet function, tissue factor-endothelial cell interactions and antithrombin activity), TEG, which provides a global assessment of the clotting process, may be superior to monitoring with anti-Xa activity levels (Klein et al. 2000).

Combined Anticoagulation Therapy

Human clinical trials evaluating combined anticoagulant therapy (usually warfarin) with antiplatelet therapy (usually aspirin) have generally concluded that antiplatelet treatment alone affords better outcome than combined therapy for long-term management of peripheral arterial disease (Mohler 2007; Younossi et al. 1997). Antiplatelet therapy has remained the primary approach to prevent vascular events in human medicine; however, some studies have demonstrated superiority of aspirin while others suggest superiority of clopidogrel. The discrepancy likely represents the variable forms of thromboembolic disease in humans (Diener et al. 2004). Studies have evaluated combining clopidogrel with aspirin therapy and also show mixed results. However, a metanalysis of these trials demonstrated that clopidogrel plus aspirin has no clear benefit over aspirin alone except in one disease subgroup. In humans with acute coronary syndrome, there is evidence that the benefit outweighs possible harm (bleeding) (Squizzato 2009).

Some veterinary cardiologists will also recommend combined antiplatelet therapy in cats. This approach is typically limited to those patients that appear to be at particularly increased risk of ATE (i.e., those cats which continue to have SEC or develop a left atrial thrombus in spite of already receiving therapy).

COMPLICATIONS AND MONITORING

Acute phase complications and monitoring recommendations were discussed under the "acute case management" section.

Chronic phase monitoring is largely dependent on the individual patient. In those patients with underlying heart disease, appropriate cardiac medications should be initiated and cats should be followed the appropriate diagnostic modalities to ensure therapy is optimal (i.e., thoracic radiographs, electrocardiography, echocardiography). Echocardiography allows follow up assessment of possible left atrial thrombus formation and SEC, which would be suggestive of suboptimal therapy. Suboptimal anticoagulation therapy could be due to owner compliance issues or may suggest inadequate anticoagulation and support the decision to switch to a different treatment option or begin combined therapy. It is useful to have the owner keep a log of the patients

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resting respiratory rate. An increase in rate or effort should prompt a reexamination and thoracic radiographs to screen for CHF. The recommended coagulation profile testing is dependent on the treatment being used and is discussed with the specific medications above.

LONG-TERM OUTCOME AND PROGNOSIS

Although the diagnosis of cardiogenic ATE carries a poor prognosis, it is important to keep in mind that treating these patients can still be fulfilling and may result in good quality of life for an extended period of time. Otherwise, the outcome for a disease such as ATE can be a self fulfilling prophecy with owners encouraged to elect euthanasia (due to poor survival statistics) resulting in a further reduction in survival statistics. The short-term prognosis depends largely on the nature and responsiveness of the underlying heart disease and heart failure. Most older studies have suggested extremely poor survival times for cats with ATE (Rush et al. 2002; Laste and Harpster 1995; Moore et al. 2000). However, most of these reports did not distinguish between euthanasia with no attempt to treat versus euthanasia due to lack of response to treatment, which is clearly an important comparison in a disease such as ATE with significant bias (Smith and Tobias 2004). In one study that attempted to evaluate these differences, survival to discharge was 45% when cats that did not receive therapy were excluded. Moreover, survival over the course of the 9-year study improved over time, with a discharge rate of 73% in the last year reviewed (Smith and Tobias 2004).

Findings that conferred a better survival rate were having a single limb rather than bilateral limb involvement and continued motor function at presentation. However, a number of findings suggest a more grave prognosis including refractory CHF or development of malignant arrhythmias, acute hyperkalemia (secondary to reperfusion injury), clinical evidence of multiorgan or multisystemic embolization, presence of an LA or LV thrombus, rising BUN/creatinine values, disseminated intravascular coagulation, and/or unresponsive hypothermia. The owners' commitment to therapy and nursing care is an important factor, particularly in those patients with declining limb viability. Notably, having a lower rectal temperature was a significant risk factor, and a rectal temperature of ≤98.9°F on admission predicted a 50% survival rate (Smith and 2004). Thus, it is valid to begin therapy, as long as the patient's pain can be controlled, taking these variables into account and frequently reassessing the patient's clinical status.

Affected limbs have the potential for complete return of function (Smith et al. 2004). However, rarely irreversible loss of limb viability and necrosis requires amputation as an alternative to euthanasia. Although the risk of future thromboembolic events is not altered, some cats will have good quality of life following amputation. Other cats sustain permanent flexure of their metatarsus secondary to severe atrophy of their cranial tibial muscle group. In the University of Minnesota's large retrospective study, although the presence of CHF did not effect survival to discharge, cats with CHF at presentation had a median survival of 77 days compared to cats without CHF at presentation, in which the median survival was 254 days. Thus, it appears the underlying heart disease is the most common cause of death. This hypothesis is corroborated by the fact that only 20% of the cats died or were euthanized due to recurrent ATE (Smith et al. 2003). Similarly, in another study, which included 57 cats at risk for ATE, of the 30 deaths or euthanasias, the majority were due to CHF (12) while only 4 were secondary to recurrence of ATE (Smith et al. 2004).

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SECTION I

Systemic Hypertension

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21

Systemic Hypertension

Key Points

- Systemic hypertension is said to be present when a cat has a systolic arterial blood pressure that is repeatedly 180 mm Hg or greater, under conditions such as quiet surroundings and presence of the owner that aim to minimize environmental influences (reduction of "white coat effect"), when target organ damage is identified, or both.
- The white coat effect, and technical considerations when measuring blood pressure, are very common causes of misdiagnosis of systemic hypertension in cats. An optimal environment and exact techniques must be used for obtaining accurate blood pressure measurements. Otherwise, the white coat effect alone can cause alterations of −27 to +75 mm Hg in the systolic blood pressure of cats.
- Virtually all cases of systemic hypertension in cats are secondary to an underlying cause; the two most common are chronic kidney disease and hyperthyroidism. Essential hypertension is rare and constitutes a diagnosis of exclusion.
- Physical manifestations of systemic hypertension include such ocular changes as hyphema or retinal detachment, neurologic signs such as seizures, cardiac changes including left ventricular concentric hypertrophy, and perpetuation of chronic renal injury.
- Treatment of systemic hypertension fundamentally involves treating the inciting disorder. Adequate treatment of the cause may partially or entirely eliminate systemic hypertension.
- Patients with systemic hypertension that require antihypertensive treatment in addition to treatment of the inciting disorder should be treated with the aim of lowering the blood pressure to a level that is less likely to cause target organ damage, rather than the aim of fully normalizing the blood pressure.
- With correct treatment both of the underlying disorder and, as needed, of systemic hypertension proper, the desired outcome is maintenance of status quo in patients without apparent target organ damage and partial or complete clinical resolution of clinical signs in cats with overt hypertensive lesions.

INTRODUCTION

Systemic hypertension is a sustained increase in systemic arterial blood pressure (BP) (Brown et al. 2007). In the clinical setting, systemic hypertension is considered to be present when a cat's systolic BP is repeatably 180 mm Hg or greater, under conditions such as quiet surroundings and presence of the owner that aim to minimize environmental influences (reduction of "white coat effect"), when target organ damage is identified, or both (Brown et al. 2007). A level of uncertainty exists when a cat's systolic BP is between 150 and 180 mm Hg under such ambient conditions, because this range encompasses many normal cats as well as those with mild or moderate systemic hypertension. In such cases, the presence or absence of lesions caused by systemic hypertension ("target organ damage") and repeated measurements, are used for distinguishing between normal and hypertensive patients (Figure 21.1).

The concern with systemic hypertension is target organ damage. Such damage can manifest acutely, as in cases of intracranial or intraocular lesions (Figures 21.2–21.8), or chronically and without immediate signs, as in cases of hypertensive nephropathy or left ventricular hypertrophy. The approach to a patient with suspected systemic hypertension therefore involves

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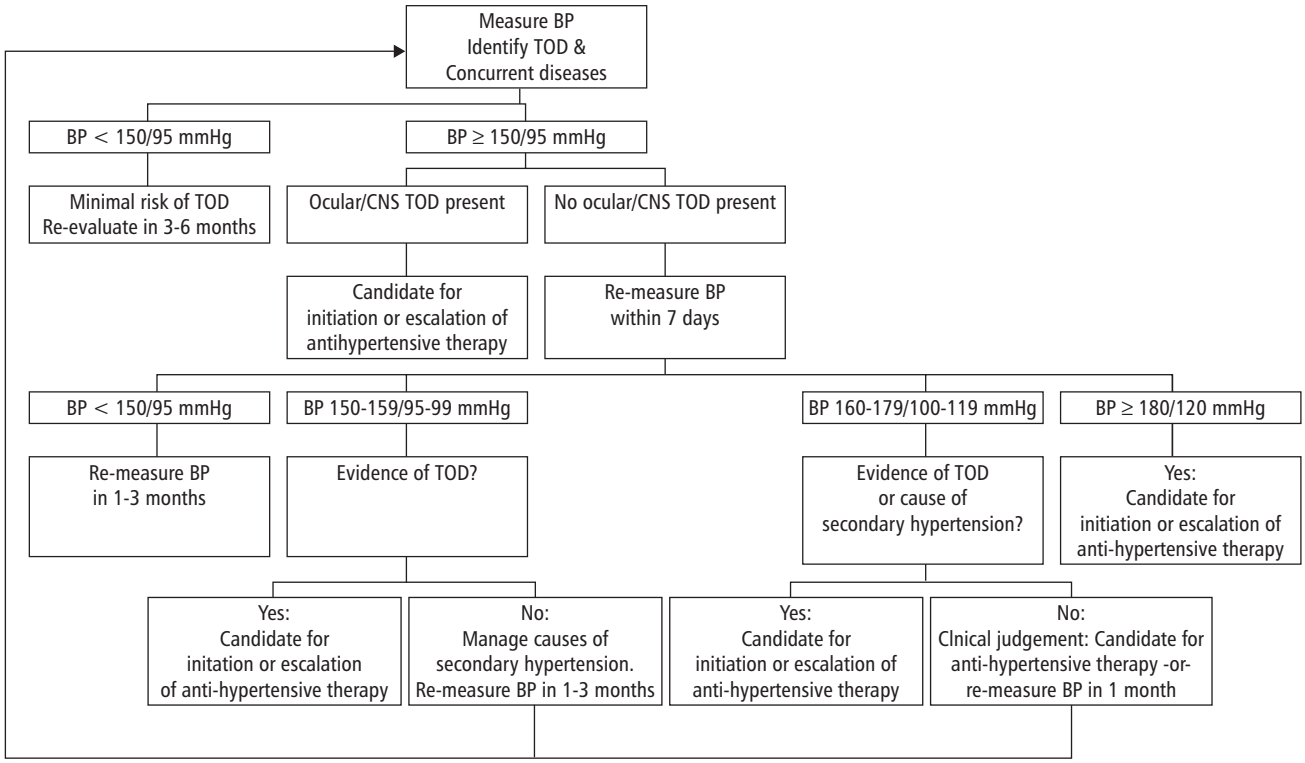


Figure 21.1. The recommended approach to patient evaluation is based on reliable measurements of blood pressure (BP). However, the identification and characterization of pre-existing target organ damage (TOD), the recognition of concurrent conditions (especially those causing secondary hypertension), and the categorization of risk for further TOD form the basis for treatment decisions. Algorithm from ACVIM Consensus Statement.

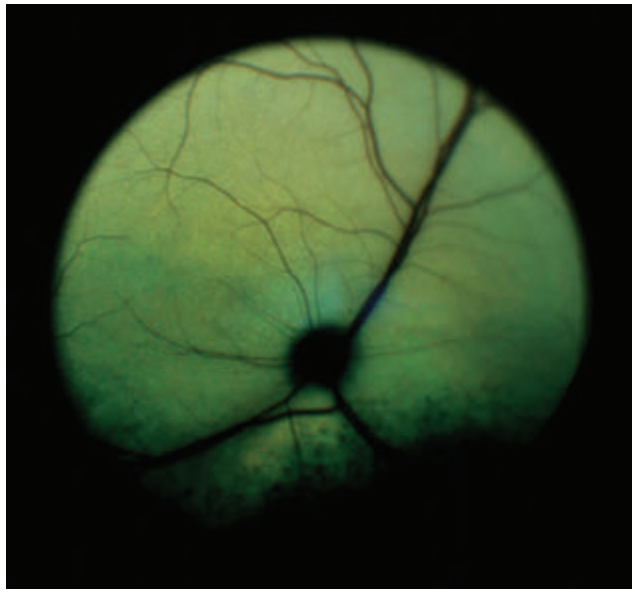


Figure 21.2. Normal feline fundus, for comparative purposes. The tapetal fundus is seen throughout the image, with normal retinal vessels radiating from the optic nerve head in the lower region of the image. Courtesy of Christa Robinson, DVM, MS.

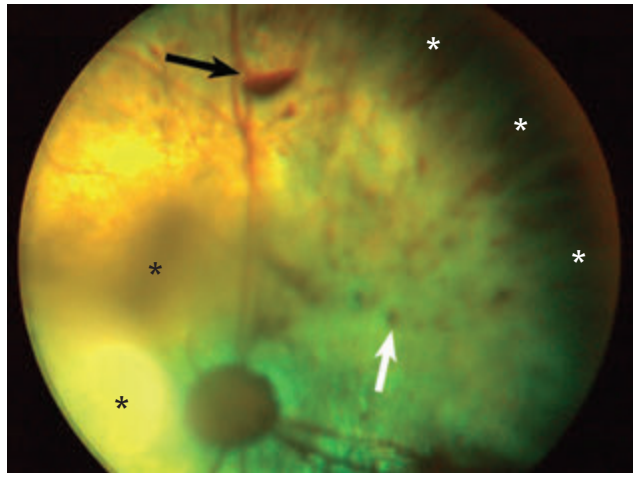


Figure 21.3. Fundus photograph of a geriatric cat with systemic hypertension. Notice the multifocal intraretinal and subretinal hemorrhages (black and white arrows, respectively) and the peripapillary and dorsal tapetal retinal detachments (black and white asterisks, respectively). Photo courtesy of Cheryl Cullen, DVM, MVSc, DACVO.

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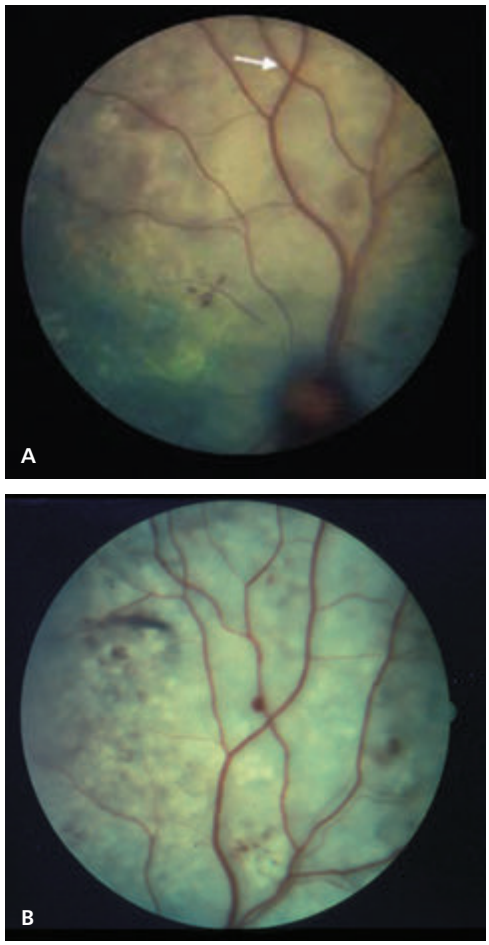


Figure 21.4. Ocular manifestations of untreated systemic hypertension. Domestic shorthair, approximately 8-year-old, male, castrated; right eye shown, both eyes affected. Average systolic BP, 210 mm Hg. **(A)** Widespread attenuation of the retinal arterioles. Obliteration because of presumed occlusion in arteriole at 10 o'clock. There is also diffuse retinal edema and detachment as well as pigmentary disturbance. Focal intraretinal hemorrhage is present to each side of the retinal arteriole in the 10 o'clock position. The optic nerve head is not clearly defined because of edema. The arrow denotes the region shown in (B). **(B)** The same cat 2 weeks later with an average systolic BP of 250 mm Hg. There is now an aneurysmal dilatation in the arteriole at the site indicated in the previous illustration. "Beading" of the arterioles because of variations of caliber is also more obvious than in the previous illustration. Focal intraretinal hemorrhages, retinal edema, and pigmentary disturbance are apparent as before. Reproduced with permission from Crispin and Mould, 2001.

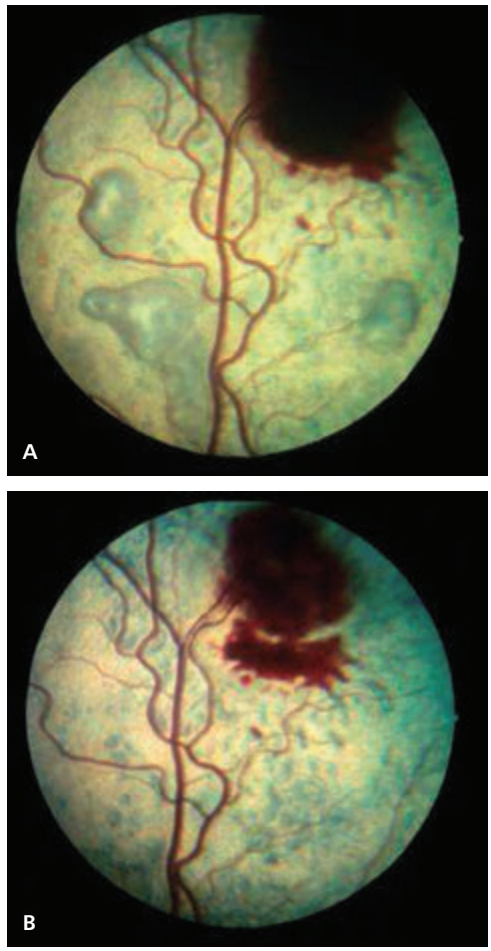


Figure 21.5. Ocular manifestations of controlled systemic hypertension. Domestic shorthair, exact age unknown, 7–11 years, male, castrated, right eye shown, both eyes affected. Average systolic BP, 280 mm Hg. **(A)** Initially, there is variation of caliber and tortuosity of the dorsal primary retinal arteriole (the vein is to the left of the arteriole and straighter). A large preretinal hemorrhage is present dorsally at 1 o'clock. Multiple bullous detachments are present that show no association with the dorsal primary vessels and are therefore likely to be a manifestation of hypertensive choroidopathy. **(B)** The same cat within a week of commencement of antihypertensive therapy (average systolic BP, 210 mm Hg). The large hemorrhage is resorbing and appears to have two foci of origin, a darker patch dorsally and a lighter patch below it, which might indicate venous and arteriolar origin, respectively, rather than fresh and older hemorrhage. The tortuosity of the dorsal primary arteriole has not apparently altered, despite the blood pressure being lower than previously. The multiple bullous detachments have reattached. Reproduced with permission from Crispin and Mould, 2001.

a series of steps that begin with confirmation of hypertension and ultimately are aimed at reducing or abolishing the risk of such complications if they are likely to occur.

The prevalence of systemic hypertension in the cat population at large is not known; estimates are inherently difficult to make, given the white coat effect. In specific groups, the prevalence of systemic hypertension has been identified. In cats with chronic kidney disease, a prevalence of 19.4% (n = 20/103) was found when systemic hypertension was defined as systolic arterial

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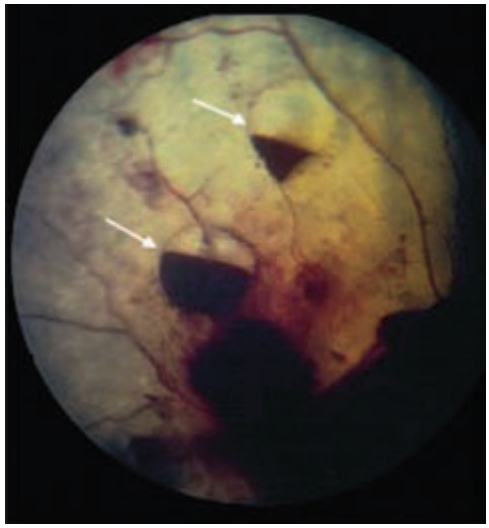


Figure 21.6A. Ocular manifestations of controlled systemic hypertension. Domestic shorthair, 13 years, male, castrated, right eye shown, both eyes affected. Mean systolic BP, 360 mm Hg. Multiple hemorrhages and retinal detachment. There is a large and superficial hemorrhage ventrally, and ventral to the optic nerve head there was also a ventral retinal detachment, which cannot be seen in this photograph. All the visible vessels are abnormal and two of the hemorrhages in blood-filled bullae (arrows) appear to have originated from rupture of aneurysms. Reproduced with permission from Crispin and Mould, 2001.

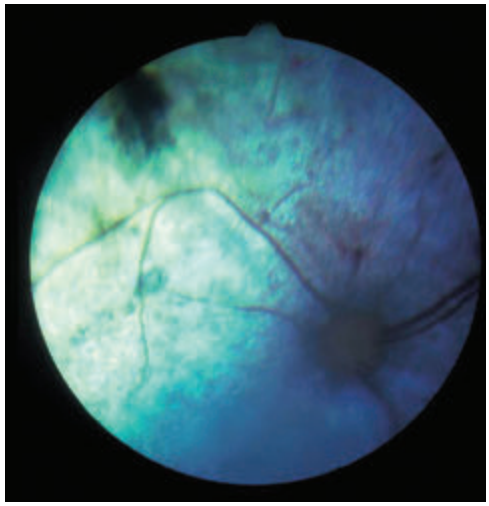


Figure 21.6B. The same cat as shown in Figure 21.6A after treatment with amlodipine besylate and benazepril hydrochloride for 4 months. The fundus shows end-stage damage after severe hypertensive disease. The hemorrhage has almost completely resolved and the retina has reattached, but the dorsal retinal vasculature is abnormal. There is a patch of pigmentary disturbance dorsally and generalized tapetal hyperreflectivity because of retinal degeneration; early optic atrophy is also present. Reproduced with permission from Crispin and Mould, 2001.

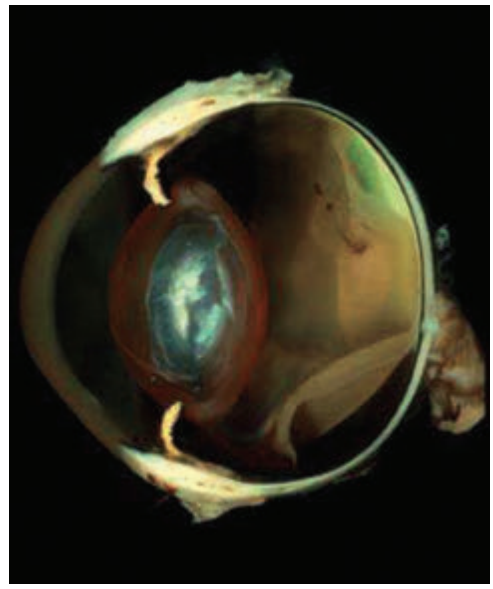


Figure 21.7. Gross pathologic specimen from cat with systemic hypertension. Retinal detachment as a consequence of subretinal fluid accumulation associated with hypertensive choroidopathy. There is a small amount of preretinal hemorrhage, especially dorsally, and more extensive hemorrhage in the region of the ventral ora ciliaris retinae and ciliary body. Extensive pigmentary disturbance was present beneath the retinal detachment ventral to the optic nerve head, but cannot be clearly seen in this photograph. Reproduced with permission from Crispin and Mould, 2001.

BP > 175 mm Hg on 2 or more occasions, or on 1 occasion with compatible ocular lesions (Syme et al. 2002). An earlier study identified a higher prevalence (17/28, 61%) in cats with chronic renal disease when hypertension was defined as a systolic BP > 2 standard deviations above that of 33 normal control cats in the same setting (none had systolic arterial BP > 140 mm Hg) (Kobayashi et al. 1990). A third study resembled the latter study and found 15/23 (65%) of cats with chronic renal disease were hypertensive, defined as having systolic BP > 160 mm Hg (Stiles 1994). Finally, cats with polycystic kidney disease (PKD) have a low prevalence of systemic hypertension (0/6 in one study [Miller et al. 1999]; the blood pressure was 145/96 [mean 120 ± 11] mm Hg in 14 PKD cats versus 132/86 [mean: 107 ± 11] mm Hg in 7 controls) (Pedersen et al. 2003).

The prevalence of systemic hypertension in hyperthyroid cats ranges from 23% (3/13 cats) to 87% (34/39 untreated cats, compared to in-house healthy controls) (Kobayashi et al. 1990). The prevalence may or may not change with antithyroid treatment: a small but significant decrease (from 144.9 ± 16.8 mm Hg to 139.8 ± 21.3 mm Hg) occurred in 100 hyperthyroid cats treated with carbimazole or thyroidectomy, but euthyroidism was then associated with the appearance of sys-

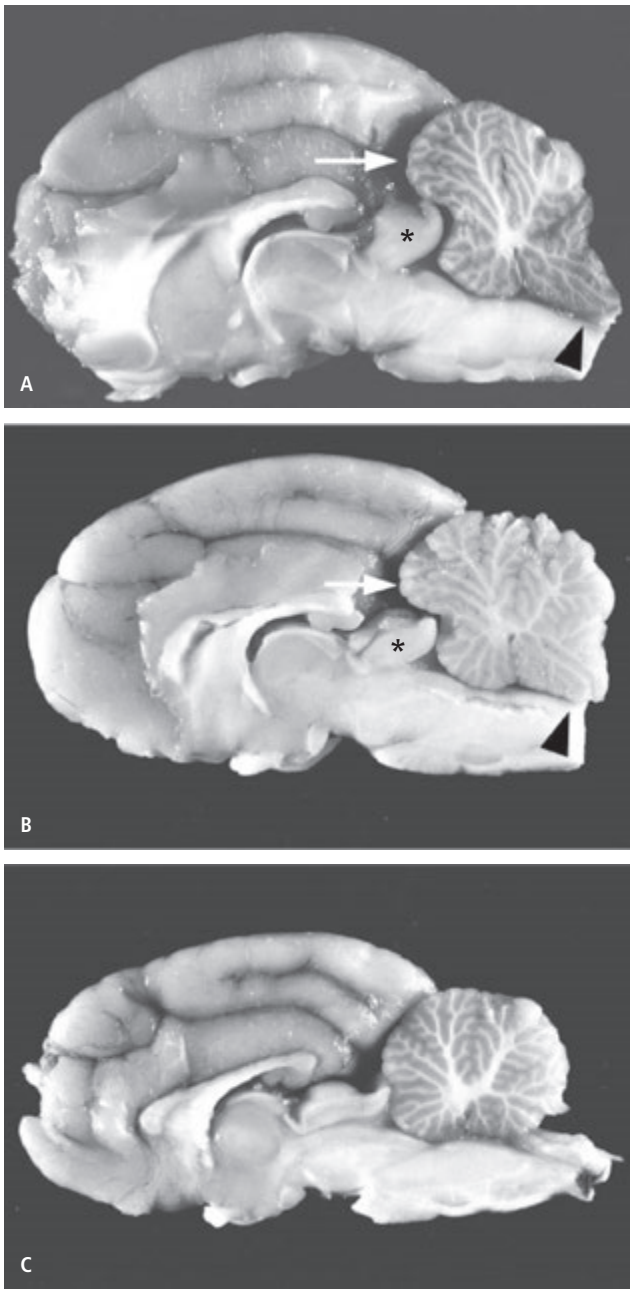


Figure 21.8. Gross pathologic specimens from cats with subacute encephalopathy due to systemic hypertension. Brain in sagittal plane; 2 cats. **(A)** and **(B)** Brain edema with expansion of the cerebellum cranially over the corpora quadrigemina (asterisk) and caudally toward the foramen magnum (arrowhead). The cerebral gyri are widened and flattened. **(C)** Normal brain for comparison. Reproduced with permission from Brown et al., 2005.

temic hypertension in 9/40 (22.5%) previously normotensive cats (Syme and Elliott 2003), suggesting an unmasking of concurrent chronic kidney disease or other hypertensive factors.

The prevalence of systemic hypertension in obese cats and in feline diabetes mellitus is low or near-zero, respectively, in contrast to human or canine counterparts (Brown et al. 2007). Such other disorders as pheochromocytoma and primary hyperaldosteronism have a high prevalence of systemic hypertension, but these disorders are very uncommon in cats (Brown et al. 2007).

ETIOLOGY, PATHOPHYSIOLOGY, AND GROSS PATHOLOGY

The concept of normal regulation of blood pressure is central to systemic hypertension, since it is regulation failure that underlies the clinical disorder of systemic hypertension. Blood pressure regulation refers to the array of autonomic, endocrine, and other mechanisms that maintain a cat's arterial blood pressure within an optimal range. Excess function of pathways that raise blood pressure, failure of adequate function in pathways that reduce blood pressure, or both, can lead to systemic hypertension.

Long-term control maintenance of normotension requires the interaction of several systems (Figure 21.9) (Brown 2005). Principal among these is the renin-angiotensin-aldosterone system (RAAS). The powerful vasoconstricting effects of angiotensin II, classically the product of angiotensin converting enzyme (ACE)-mediated transformation of circulating, inactive angiotensin I (in turn created from the action of renally derived renin in hepatically synthesized angiotensinogen), are central in the normal prevention of *hypo*tension. Angiotensin II elicits the release of aldosterone from the adrenal cortex, augmenting sodium resorption in the distal renal tubule and thus increasing circulating blood volume. Aldosterone's binding to mineralocorticoid receptors in the peripheral vasculature causes vasoconstriction (Franco et al. 2007). Dysregulation of these and other elements of the RAAS is an important contributor to systemic hypertension (Franco et al. 2007). In some cats with chronic kidney disease-associated systemic hypertension, the plasma aldosterone level, or the ratio of aldosterone to plasma renin activity, is elevated compared to healthy controls, suggesting that excessive plasma aldosterone concentrations could contribute to hypertension in chronic kidney disease (Jensen et al. 1997; Pedersen et al. 2003). The autonomic nervous system plays an important role in maintaining or raising BP. Adrenergic stimulation of the heart raises myocardial contractility and heart rate, both of which increase BP, and adrenergic stimulation of vascular smooth muscle causes vasoconstriction, which also increases BP. These effects are at least partly responsible for systemic hypertension associated with hyperthyroidism because thyroid hormone sensitizes the myocardium to the

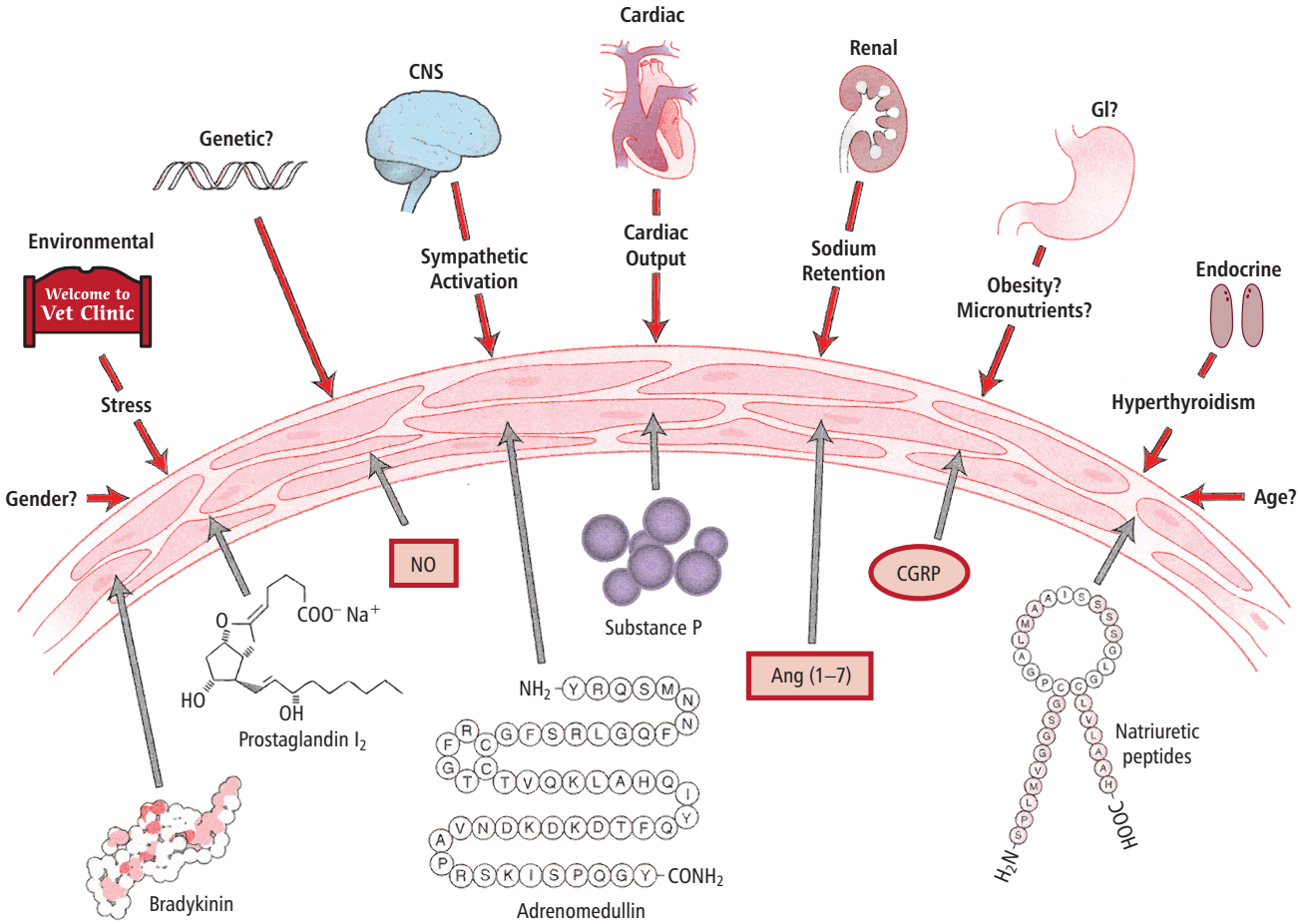


Figure 21.9. Schematic diagram showing the pathways involved in long-term regulation of blood pressure and the abnormalities through which systemic hypertension may develop. Modified with permission from Franco et al., 2007. Ang (1-7) = angiotensin-(1-7); CGRP = calcitonin gene-related peptide; CNS= central nervous system; GI = gastrointestinal; NO = nitric oxide.

effects of catecholamines (Brown 2005). Other mechanisms responsible for maintaining an adequate blood pressure include vasopressin/antidiuretic hormone (released in response to high serum osmolality, and increasing circulating blood volume by binding to V2 receptors in the distal renal tubule and collecting ducts, thus reducing free water elimination), endothelin, and very poorly understood factors in hypertensive cats including the roles of heredity, gender, and age (Figure 21.9).

These hypertension-promoting mechanisms are counterbalanced by systems that promote lowering of the blood pressure. Atrial natriuretic peptide and B-type natriuretic peptide are produced in the atria and ventricles, respectively, in response to mural stretch. They cause vascular smooth muscle relaxation and natriuresis, both of which reduce BP. Nitric oxide, bradykinin (the degradation of which is reduced by ACE inhibitors), and certain prostaglandins (PGs) such as PGI_2 are other vasodilators that counter the pathways that otherwise lead to systemic hypertension.

An imbalance in hypotension-promoting versus hypertension-promoting mechanisms in favor of the latter underlies systemic hypertension. Once systemic hypertension exists, the process may become to some extent self-sustaining. For example, hypertensive cats with reduced kidney function may sustain ongoing renal injury due to direct transmission of elevated arterial pressure to the glomerulus (Brown 2005), and with an ensuing reduction in renal function, further systemic hypertension is possible, creating a vicious circle. Similarly, proteinuria augmented by systemic hypertension can contribute to ongoing renal tubular injury.

Primary or "essential" hypertension refers to systemic hypertension for which an inciting disorder is not found. It is very common in humans but appears to be very rare in cats. Sporadic reports have identified rare cases (Turner et al. 1990) but in general, essential hypertension is a diagnosis of exclusion that is reached reluctantly because artifacts such as the white coat effect and poor technique are so much more commonly to blame for unexplained elevations in BP.

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SIGNALMENT

In the cat, systemic hypertension is secondary to an underlying process such as chronic kidney disease or hyperthyroidism in the majority of cases. Therefore, the signalment of patients with systemic hypertension is the signalment of patients that have the primary diseases that cause it. In 58 hypertensive cats, mean age (13 ± 3.5 years) was significantly higher than in 130 normotensive peers (9.6 ± 5.0 years) (Chetboul et al. 2003). No differences between males and females are apparent.

HISTORY AND CHIEF COMPLAINT

Because signs associated with hypertension-causing diseases may be subtle or initially not apparent to owners, obtaining a complete history is important and questions must be asked in a manner that does not deliberately lead to a desired answer and ultimately an erroneous diagnosis of systemic hypertension. Common examples of such a mistake include investigating the presence or absence of polyuria and polydipsia, where questions such as "Have the litterbox habits changed?" or "Are you aware of any decrease or increase in thirst?" are preferable to "Is he/she drinking and urinating more than usual?"; another example is questions about lethargy, where "Have you noticed a change in his/her activity level lately?" is more likely to elicit a useful answer than "Is he/she slowing down?" This nuanced history-taking is a further step away from misdiagnosis of white-coat hypertension as "clinically significant" hypertension.

Specific aspects of the history that should be investigated in cats thought or known to be hypertensive include general demeanor, appetite, water consumption, urine production, and absence of vomiting (to identify signs of chronic kidney disease, hyperthyroidism, and other causative disorders). For example, in a survey of 58 hypertensive cats, a history of polyuria and polydipsia was present significantly more often in these cats (31/58, 53%) than in 113 normotensive peers (33/113, 29%) (Chetboul et al. 2003). An owner's observations of a cat's bumping into objects, or of subtle or intermittent change in eye color (iris, anterior chamber), may indicate manifestations of intraocular hemorrhage or other hypertensive ocular disorder. Similarly, disorientation, ataxia, behavior change, or seizures may be caused by hypertensive encephalopathy or intracranial hemorrhage; a rare differential diagnosis to consider in cats with these signs is pheochromocytoma, which can cause systemic hypertension.

The clinician obtaining the history should take into account that systemic hypertension in cats presents in two different contexts: overt manifestations due to end-organ damage, and incidental finding. Overt manifestations of end-organ damage (ocular or neurologic) typically are identified as part of the chief complaint given by the owner. "Incidental finding" can refer to 1) the discovery of a high systemic BP in a patient with a disorder that is known to be associated with systemic hypertension, 2) the discovery of a high systemic BP in a patient without an identifiable underlying cause, or 3) the discovery of a lesion—rather than of hypertension itself—where the lesion, such as an ocular abnormality or left ventricular hypertrophy, is the first identified abnormality, and both systemic hypertension and ultimately the underlying cause are found subsequently. The historical findings associated with these categories are addressed in turn in the following sections.

Overt Manifestations of Systemic Hypertensive Decompensation

Acute clinical signs attributable to systemic hypertension can involve the eyes, the central nervous system, the heart, or the kidneys. Large retinal detachment, hyphema, and extensive retinal hemorrhages occur less often than pinpoint or multifocal retinal hemorrhages (Stiles et al. 1994) but are more likely to cause the chief complaint of vision loss (Sansom et al. 1994;Stiles et al. 1994). Blindness or impaired vision was a chief complaint in 2/15 (13%) of cats with chronic renal failure and secondary systemic hypertension, for example (Stiles et al. 1994). Likewise, 8/58 (14%) of hypertensive cats in another case series were blind, and 28/58 (48%) had ocular lesions (Chetboul et al. 2003). Systemic hypertension may be a very common cause of acute onset of blindness or intraocular hemorrhage in general; of 16 cats referred for these problems, 11 (69%) were hypertensive (13/15 with evidence of impaired renal function and 1 hyperthyroid) (Sansom et al. 1994).

Neurologic signs caused by systemic hypertension may consist of lethargy, ataxia, blindness, focal (and generally asymmetrical) deficits indicating an intracranial lesion, stupor, and seizures (Brown et al. 2005). These signs have been described in association with herniation of the brain during acute sustained systemic hypertension (48–72 hours after onset of systolic BP reaching 198–234 mm Hg) in 2 cats (Brown et al. 2005); intracranial arterial rupture (true hemorrhagic stroke), infarcts, and arteriolar spasm are other mechanisms by which signs of intracranial disease can occur with systemic hypertension. The onset of neurologic signs in hypertensive cats generally carries a poor prognosis.

Overt decompensation of the cardiovascular system (e.g., congestive heart failure [Wey and Atkins 2000], severe arrhythmia causing syncope, or thromboembolism) or the urinary system (e.g., acute renal failure) are

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uncommonly recognized as the principal manifestation of systemic hypertension in cats.

Incidental Finding of Hypertension or Hypertension-Associated Abnormality

A cat's BP may appropriately be measured for the first time when the diagnosis of chronic kidney disease or hyperthyroidism is made. If systemic hypertension is identified, questions in the history should seek to better define the extent of clinical signs associated with the primary disease (e.g., polyuria, polydipsia, appetite alterations, perceived weight gain or loss, vomiting, stamina) as well as investigate signs of ocular compromise or encephalopathy.

The unexpected finding of an elevated arterial BP in an otherwise healthy-appearing cat should invariably prompt investigation rather than intervention. Specifically, the history should be reviewed to identify medications such as alpha-2 agonists (e.g., dexmedetomidine) that elevate BP. The presence in the history of clinical signs consistent with diseases that cause systemic hypertension should be viewed with reasonable skepticism to avoid over- or underestimating their impact on the patient. The lack of such signs, furthermore, increases the suspicion of a spuriously elevated BP reading. Next, the BP measurement must have been performed under ideal conditions eliminating all possible stressors or other elements likely to artificially increase it. If that was not the case, it should be repeated in an optimal environment (see Figure 21.1). A truly hypertensive patient that appears otherwise healthy should have a complete physical exam, including fundic exam, and should undergo basic diagnostic testing (see below).

In many cats, an abnormality is identified that is thought to exist because of systemic hypertension, but systemic hypertension had not been considered until then. This finding leads to BP measurement and can confirm systemic hypertension. Such "tip of the iceberg" lesions include ocular—especially fundic—changes, asymmetrical or diffuse intracranial signs, left ventricular hypertrophy, epistaxis, and proteinuria. The history in these patients can be very different from the history typical of hypertensive patients. An echocardiogram reveals left ventricular hypertrophy after having been prompted by the auscultation of a murmur or gallop, or the observation of cardiomegaly on thoracic radiographs taken for some other reason; proteinuria is noted on a routine urinalysis performed because of an unrelated issue; or ocular or neurologic abnormalities are noted during a routine exam. These scenarios are typical of the history for this category of patient.

PHYSICAL EXAMINATION

The initial, hands-off portion of the examination is extremely informative in the cat known or suspected to have systemic hypertension. Prior to handling the patient, the clinician can assess demeanor, mentation, gait, and posture. Deficits in these simple but vital parameters could suggest the presence of hypertensive encephalopathy. A cat's ability to walk around the exam room normally identifies its ability to see, whereas its bumping into walls and cabinets suggests vision loss. A poor haircoat may indicate chronic illness such as chronic kidney disease or hyperthyroidism, and the latter condition is further suspected if the body condition is poor despite a good appetite. The presence or absence of blood around the nostrils should be noted, since systemic hypertension is a recognized cause of epistaxis. Respiratory effort is evaluated at this stage also; abnormalities beyond those expected with exam-room anxiety suggest respiratory compromise or, in a very lethargic cat, possibly metabolic acidosis as seen with severe chronic kidney disease. Specifically, dyspnea or tachypnea should lead to the suspicion of primary respiratory disease, pleural effusion, or pulmonary edema. Although systemic hypertension is not known to routinely cause these disorders, it may contribute to other diseases and cause decompensation.

The ophthalmic examination is essential in all patients suspected of having, or known to have, systemic hypertension. Ocular signs, consisting of retinal hemorrhages, detachments, or both, were found in 28/58 (48%) hypertensive cats, compared to a prevalence of 3/113 (3%) in normotensive peers (Chetboul et al. 2003). As mentioned previously, blindness occurs in a fraction of hypertensive cats with ocular lesions; 8 of the 58 cats in this case series (14%) were blind. Systolic BP was significantly higher in hypertensive cats with retinal lesions (average = 262 mm Hg) than in hypertensive cats without retinal lesions (average = 221 mm Hg), supporting the logical deduction that retinal lesions occur when systemic hypertension is more severe (Chetboul et al. 2003). Fundic abnormalities in systemic hypertension can include increased tortuosity of retinal vessels, retinal edema, foci of intrarenal serous exudates, and pinpoint retinal hemorrhages (see Figures 21.3–21.5). These abnormalities reinforce the diagnosis of systemic hypertension or first lead to its suspicion if they are noted before the BP is ever measured. These lesions rarely cause impairment of vision. Hypertensive ocular lesions that are more severe include large intraretinal or preretinal (i.e., within the vitreous or anterior chamber) hemorrhages, large retinal detachments, and possibly resultant hyphema with or without secondary glau-

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coma. Old retinal hemorrhages or scars may be seen as retinal hyperreflectivity (see Figure 21.6).

In hypertensive cats, palpation of the heartbeat can reveal an abnormally strong apex beat if there is considerable ventricular hypertrophy. Cardiac auscultation may reveal a heart murmur, gallop sound, or both. Heart murmurs in otherwise normal-appearing cats are a common reason for referral of feline patients for BP measurement and complete cardiovascular examination. This may explain the high prevalence of heart murmurs in both hypertensive cats (36/58, 62%) and normotensive controls (81/113, 72%). A gallop sound, however, is significantly more likely to be associated with systemic hypertension (9/58 cats, 16%) than normotension (0/113, 0%). The presence of the gallop sound is independent of the degree of hypertension: 9/58 hypertensive cats with a gallop sound had a mean systolic BP of 245 mm Hg, whereas 49/58 hypertensive cats without a gallop sound had a mean systolic BP of 244 mm Hg.

Palpation of the neck of cats with systemic hypertension may reveal thyroid gland enlargement or a thyroid nodule. The presence of such changes does not equate to hyperthyroidism, since the thyroid lesion may not be functional, and serologic assessment of thyroid levels is warranted (Feldman and Nelson 2004). Similarly, the absence of a palpable thyroid is not a basis for ruling out hyperthyroidism if other elements of the history and physical exam are suggestive, and here again thyroid serology is appropriate if other clinical findings support hyperthyroidism because an adenomatous thyroid gland may simply have descended through the thoracic inlet or originated from ectopic thyroid tissue in the thorax, where it is not palpable (Feldman and Nelson 2004). Abdominal palpation may reveal diffusely small kidneys in the cat with typical chronic renal disease or enlarged (typically bilaterally) kidneys in chronic renal disease caused by polycystic kidney disease or renal lymphoma. An extremely unusual finding would be the palpation of an adrenal mass, consistent with two very rare causes of systemic hypertension in the cat: hyperaldosteronism and pheochromocytoma.

DIFFERENTIAL DIAGNOSIS

In many instances, determining the presence or absence of a truly and clinically significantly elevated blood pressure is the most difficult question concerning systemic hypertension. Is a given feline patient hypertensive or not?

Figure 21.1 presents the consensus recommendation issued by the American College of Veterinary Internal Medicine for answering this question. Some common errors lead to misdiagnosis of systemic hypertension, and troubleshooting to abolish these errors is essential for optimal patient care.

White Coat Effect

In an experiment, healthy cats with radiotelemetric implants measuring direct arterial pressure continuously were allowed to acclimate for at least 2 weeks to their housing. One at a time, each of 6 such cats then underwent simulated veterinary visits consisting of a short drive in a car to the veterinary hospital, transportation to a noisy waiting room for a 10-minute wait, a complete physical examination, and a standard blood pressure measurement using the Doppler technique. The radiotelemetry equipment identified that during these mock visits, the systolic BP of cats varied from –29 (decrease of 29 mm Hg compared to resting) to +75 (increase of 75 mm Hg) compared to radiotelemetry-recorded 24-hour baseline (Belew et al. 1999), with a mean of +18 mm Hg. There was variation between the cats, but also within each cat during repeated visits, and the artificial increase in BP tended to decrease with subsequent visits. This experiment clarifies the white coat effect in cats, and it reinforces the importance of careful selection of the proper environment for measuring blood pressure (Belew et al. 1999). Because of this substantial confounding effect, some veterinarians, technicians, and other cat owners with access to Doppler equipment measure cats' BP at home. The same parameters for determining normotension versus hypertension apply; home measurement merely reduces the travel and veterinary facility components of the white coat effect. Therefore, and as for in-clinic measurements, serial home measurements may provide important, additional information beyond 1 or 2 one-time BP determinations.

Wrong Cuff Size

A falsely high BP may be recorded if an excessively large sphygmomanometer cuff is used (see below for discussion of cuff size).

Wrong Cuff Location—Too Proximal

A falsely high BP may be recorded if the cuff is placed proximal to the tarsus or elbow, as was originally suggested when the Doppler technique was introduced in cats.

Sphygmomanometer Calibration

The clinical standard in feline medicine is a spring-operated sphygmomanometer and cuff apparatus. However, these instruments are not routinely calibrated against direct arterial measurements, but such calibration

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should be part of the upkeep of BP monitoring equipment.

Differential Diagnosis for Causes of Systemic Hypertension

The disorders that most commonly are associated with systemic hypertension in the cat are chronic kidney disease (commonly causes hypertension), hyperthyroidism (commonly causes hypertension), pheochromocytoma (commonly causes hypertension, but rare disease in cats), hyperaldosteronism (commonly causes hypertension, but rare disease in cats), and essential hypertension (rare condition in cats; diagnosis of exclusion). Diabetes mellitus (reported as causing systemic hypertension in only 2 cats) (Maggio et al. 2000) and obesity are conspicuous in their lack of association with systemic hypertension in cats.

DIAGNOSTIC TESTING

When should BP be measured in a cat? The measurement of a cat's BP is indicated when 1) overt signs suggesting target organ damage (ocular, intracranial problems) are identified, 2) a cat is found to have a disease that is recognized commonly to be associated with systemic hypertension (chronic kidney disease, hyperthyroidism), or 3) as part of the evaluation of a patient with abnormalities suspected of arising from systemic hypertension (left ventricular hypertrophy, retinal lesions, proteinuria, epistaxis). Continuous BP monitoring is also useful in cats under general anesthesia and in critically ill/unconscious cats.

In cats, the clinical gold standard for measurement of arterial blood pressure uses Doppler ultrasonography for identification of the arterial pulse and a manually inflated cuff connected to a spring-loaded sphygmomanometer (Figure 21.10). Systolic blood pressure readings obtained by this technique more closely correlate with measurements from a direct arterial catheter than do measurements obtained using an oscillometric instrument, particularly at higher BP where oscillometry reports artifactually high BP in cats (Binns et al. 1995).

Technique for Measuring BP

A room or area that is quiet and free of traffic is chosen. Many clinicians prefer to measure a cat's BP in the presence of his/her owner, which can be useful for limiting the white coat effect. A table with a padded surface is recommended for the cat's comfort.

Two individuals are usually needed: one to perform the procedure, the other to hold the patient. The person providing the restraint should be willing to talk softly and reassuringly to the cat, again in order to reduce the artifact of environmental stimulation (white coat effect).

Arterial BP may be measured on a cat's forelimb, hindlimb, or tail. A 2×2 cm area of skin that lies over the palmar metacarpal, metatarsal, or coccygeal artery, respectively, is clipped of hair; typically a band of 1 cm or so of unclipped hair separates the clipped area from the metatarsal pad, whereas the clipped area of hair reaches completely to the metacarpal pad (see Figure 21.10). For the tail, the area that is clipped is on the ventral surface of the tail as close to the base of the tail as possible, factoring in the width of the sphygmomanometer cuff, which will need to be interposed between the Doppler probe and the tail base. The hairless area is lightly moistened with isopropyl alcohol and then smeared with a small amount of ultrasound coupling gel. A sphygmomanometer cuff is then chosen. The width (not circumference) of the cuff should be approximately 40% of the circumference of the limb or tail around which it will be wrapped. Most cats use a 2 or 2.5 cm cuff, and a tape measure is useful for optimal measurement (see Figure 21.10). The cuff is wrapped around the limb or tail and additional white clinic tape can be applied to the cuff to prevent the cuff from opening midmeasurement. The limb should be positioned so the point of measurement (Doppler probe) is approximately at the same vertical level/height as the right atrium. The cuff is maintained in full deflation, and the Doppler probe is placed, concave surface to the patient, lightly but entirely on the clipped area. It is important not to press firmly on the Doppler probe, because doing so can reduce or obliterate the pulse, producing false BP readings. Small movements of the probe on the patient's skin are often necessary to find the location for optimal transmission of the Doppler signal. Once this location is found, the cuff may be inflated carefully, 10–30 mm Hg at a time, rather than all at once which can startle a cat and in turn increase the white coat effect. The pressure is increased until the Doppler signal is no longer audible, approximately 20 mm Hg greater than the point at which the pulse was still audible. The release valve on the sphygmomanometer is gently activated to gradually deflate the cuff (1–5 mm Hg/second). The first reappearance of the sound of the pulse (first Korotkoff sound) corresponds to the systolic pressure, and this is noted in the cat's medical record. Occasionally, with ongoing release of cuff pressure, a transition from brief, choppy pulse sounds to fuller, longer-lasting sounds is noted. This corresponds to the emergence of the diastolic pressure, and its presence is unpredictable using this technique in cats. The procedure is repeated a total of 5 times, with a 30 sec to 1 min rest period between each, because momentary variation

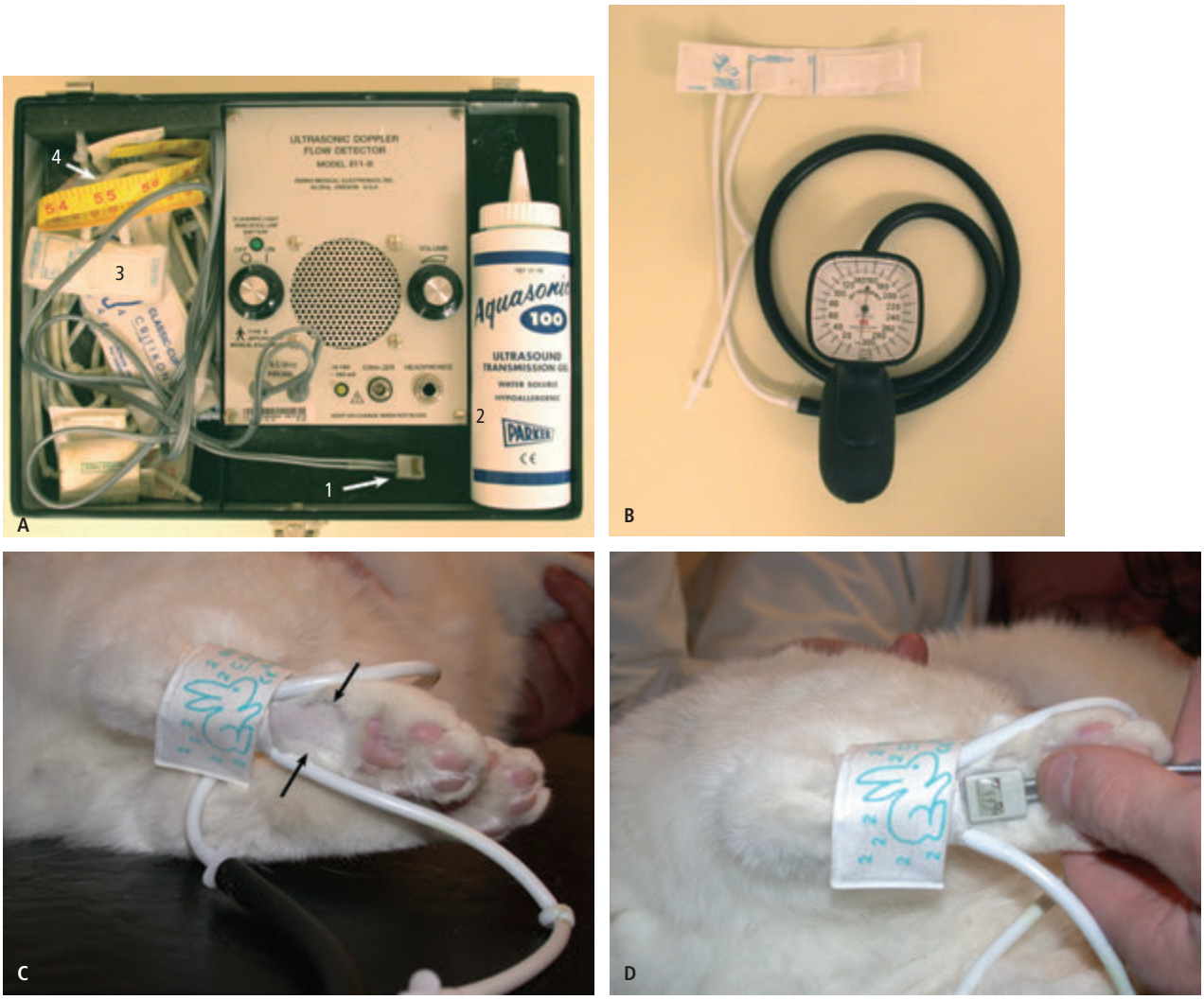


Figure 21.10. Instrumentation for routine measurement of BP in cats. **(A)** The Doppler ultrasonic unit, with probe (1), a bottle of ultrasonic coupling gel (2), assorted cuffs of various sizes (3), and a measuring tape for accurate cuff sizing (4). **(B)** A standard, spring-operated sphygmomanometer with cuff. **(C)** Plantar surface of a cat's right metatarsus; the cat is in left lateral recumbency facing away from the camera, and the tail is off the left side of the image (not seen). Minimal restraint (gentle holding of the forelimbs only, hindlimbs unrestrained), soft speaking to the cat, and gentle petting of the head are part of a calm environment that is least likely to produce anxiety-related hypertension in this cat. A square of hair has been shaved away from the area over the metatarsal arteries, on the plantar surface ≤1 cm proximal to the metatarsal pad (arrows). **(D)** Proper placement of the Doppler probe, concave side to the cat, on the area shown in (C). Note that the finger holds the probe wire for good contact between the probe and the patient, but minimal to no pressure is placed on the probe itself. This precaution helps avoids inadvertent occlusion of the artery, which could hamper the measurement or give erroneous results. Photos courtesy of E. Côté.

in BP of up to 15 mm Hg is normal, and a mean of 3 readings (discarding the highest and lowest) is determined to be the cat's systolic arterial BP.

If a cat is fractious, seems very anxious, or otherwise does not allow BP measurement that appears to the clinician to reflect a calm cat, other options should be considered. Better measurements are often possible when the cat and owner are together in a quiet exam room. During future visits, when BP measurement is planned, it can be performed with the owner in the exam room at the beginning of the appointment, before the clinician arrives or tests or procedures are completed, to minimize anxiety. Another option is for the owner to hire a veterinarian or technician to make a house call. Simply scheduling a repeat visit on a separate day to allow the cat to rest from the hospital visit is also an option. Finally, sedation of fractious or anxious cats solely for the purposes of measuring BP is not recommended, since all sedatives can alter BP to a greater degree than is

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acceptable for clinical decision-making in systemic hypertension suspects.

Ancillary Tests: Clinical Pathology

Routinely, a complete blood count, serum biochemical profile, and urinalysis are indicated in cats being evaluated for, or known to have, systemic hypertension. Follow-up testing is performed based on results of previous tests and findings in the history and physical exam. No abnormalities are specific to systemic hypertension in cats, although proteinuria is a common finding (increased intraglomerular pressure, glomerular damage as part of chronic kidney disease). Azotemia with isosthenuria is consistent with kidney disease; hyperphosphatemia and/or anemia may also be present. Cats age 6 years old or older should have serum thyroxine levels measured to rule out hyperthyroidism. Retroviral serology is assessed as indicated by environmental exposure and clinical information.

Ancillary Tests: Thoracic Radiographs

There are no pathognomonic radiographic findings of systemic hypertension, and they are an insensitive test for this disorder. Nevertheless, some characteristic findings are associated with systemic hypertension and should be recognized. Undulation or tortuosity of the descending thoracic aorta has been associated with systemic hypertension (Nelson et al. 2002) (see Chapter 7, Figure 7.2). Cardiomegaly is not generally observed; the modest degree of left ventricular hypertrophy, and the concentric nature of that hypertrophy, probably explain the lack of difference in cardiac size in 15 hypertensive cats compared to 15 matched controls (Nelson et al. 2002).

Ancillary Tests: Echocardiography

Echocardiography is commonly performed in cats that are suspected or known to be hypertensive. In one study of 171 cats referred for BP measurement, a heart murmur was present in 117 (68%), potentially leading to a recommendation of echocardiography. Echocardiographic findings in hypertensive cats include left ventricular concentric hypertrophy (left ventricular thickening), which is generally mild. For example, 15 hypertensive cats had a median left ventricular free wall diastolic thickness of 5.1 mm, which was mildly but significantly ($P = 0.02$) greater than 4.2 mm in 15 normotensive cats (Nelson et al. 2002). Hypertension-associated left ventricular hypertrophy is reversible over months with adequate reduction in BP (target systolic BP < 160). Left ventricular hypertrophy is not a prognostic indicator in hypertensive cats.

Interestingly, this group of cats included some in which thickening of the left ventricle was noted to be asymmetrical. This finding is counterintuitive: a uniform increase in afterload (increased BP) should give rise to diffuse, symmetrical ventricular hypertrophy, but such asymmetry has been observed in human hypertensive patients. Regrettably, this study did not follow these cats through treatment and a prolonged normotensive period to document regression of hypertrophy. Without this information, hypertensive left ventricular hypertrophy with simultaneous hypertrophic cardiomyopathy cannot be excluded, and this combination occurs with some regularity in cats. With regards to other echocardiographic findings, hypertensive cats also show dilation of the proximal aortic root and adjoining segments of the proximalmost aorta. These changes are significantly different from equivalent measurements in normotensive cats (Nelson et al. 2002). Some hypertensive cats may develop eccentric left ventricular hypertrophy (dilation with preserved/enhanced contractility), and these cats may be younger and more hypertensive than their counterparts (Chetboul et al. 2002). More recent echocardiographic techniques (tissue Doppler imaging) have identified evidence of systolic and diastolic dysfunction of the longitudinal left ventricular myocardial fibers in hypertensive cats with left ventricular hypertrophy (Carlos Sampedrano et al. 2006)

Ancillary tests: Abdominal Ultrasonography

An abdominal ultrasound examination is warranted if elements of the physical exam and diagnostic testing to date suggest a case where chronic kidney disease is complicated (e.g., concurrent pyelonephritis, renal lymphoma, polycystic kidney disease, perirenal pseudocyst, hydronephrosis) or where adrenal disease is possible based on clinical features, mass effect in the adrenal region on physical exam, or radiographs (e.g., suspect pheochromocytoma because of intermittent or sustained ventricular tachycardia; intermittent disorientation, anxiety, or flushing; markedly fluctuating BP), or suspected primary aldosteronism based on profound, severe, refractory hypokalemia (serum K+ often <2.5 mEq/dl despite aggressive replacement therapy).

TREATMENT

General

An elevated arterial BP does not immediately warrant treatment. Environmental stressors that can transiently elevate BP must first be identified and abolished, and a true diagnosis of systemic hypertension can then be confirmed. Second, steps must be taken to control diseases that cause systemic hypertension. Third, antihy-

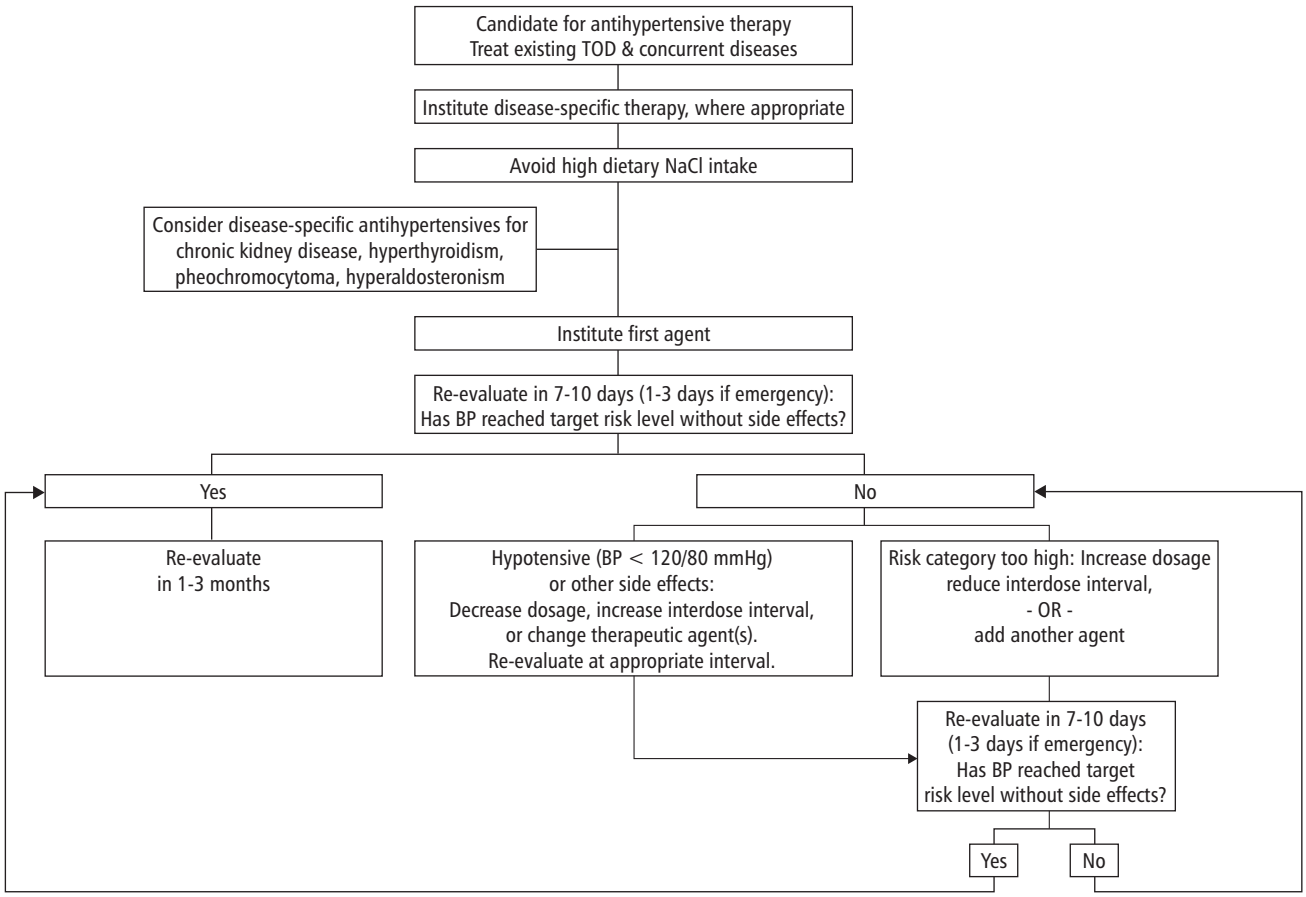


Figure 21.11. Algorithm demonstrating the process of treatment decision-making in animals with systemic hypertension. Reproduced with permission from ACVIM Consensus Statement.

pertensive medications may be initiated if systemic hypertension persists. Fourth, follow-up is undertaken and the approach is adjusted based on progress and subsequent results. Patients with successfully managed systemic hypertension rarely show dramatic, immediate improvements. Rather, the signs of success for treatment of hypertension include maintenance of the status quo if decompensation has never occurred, or if it has, stabilization and gradual improvement without relapse.

Systemic hypertension must be confirmed to be real (accurate measurement of BP) prior to initiation of BP-lowering drugs. While delayed implementation of antihypertensive therapy can allow life-threatening ocular or intracranial crises to develop, the reverse situation where patients who are not truly hypertensive are inadvertently given antihypertensive medications is equally troublesome and possibly more common. Hay was probably observing poor control of confounding factors, and resultant overdiagnosis of systemic hypertension, when writing, in 1930: "There is some truth in the saying that the greatest danger to a man with a high blood pressure lies in its discovery, because 'then some fool is certain to try and reduce it'" (Hay 1931). Accordingly, the first step in treating cats with systemic hypertension is to ensure that they are indeed truly and repeatably pathologically hypertensive (see "Differential Diagnosis," above) and that hypertensive diseases are optimally managed.

The optimal approach to treating systemic hypertension in cats is presented in Figure 21.11. Once extraneous artifacts that might have increased BP readings are eliminated and underlying diseases are properly managed, the drug of choice for treatment of persistent hypertension is amlodipine (Norvasc; available in 2.5 mg tablets). A typical initial dosage is 0.625 mg [1/4 tablet] PO q 24 h for most cats, and this is adjusted based on response. A mean decrease in systolic BP from 198 mm Hg to 155 mm Hg was noted in spontaneously hypertensive cats receiving amlodipine 0.08–0.23 mg/kg PO q 24 h, with some authors recommending up to double this amount if both warranted and clinically tolerated by the patient. Amlodipine has demonstrated efficacy in hypertensive cats, both with regard to direct blood pressure-lowering effects (Henik et al. 1997) and improvement in

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hypertension-related lesions (see Figures 21.5, 21.6). It is considered safe, with few reported adverse effects.

In humans and other species, beta blockers, ACE inhibitors, and diuretics commonly are used for treating systemic hypertension. In the cat, these are considered second-line therapies, if at all. ACE inhibition has provided convincing benefits in the experimental setting but does not lower arterial BP as consistently as amlodipine. An ACE inhibitor is not routinely used as monotherapy for systemic hypertension in cats, but it may have beneficial effects in hypertensive patients when its primary use is for the patient's proteinuric renal disease or congestive heart failure. Similarly, such beta blockers as atenolol are routinely and safely used in cats, but their efficacy for reducing an elevated blood pressure is inferior to that of amlodipine. Like ACE inhibitors, beta blockers are used in hypertensive patients only when a concurrent disorder primarily warrants their use (e.g., hyperthyroidism). Finally, diuretics recently have resurged in human hypertensive therapy, despite the activation of the renin-angiotensin-aldosterone system caused by their use. For this reason, and because many hypertensive cats have compromised renal function, diuretics have not been investigated extensively in management of feline systemic hypertension and are not recommended for this purpose.

Hypertensive Crisis

Management of severely hypertensive states has been reviewed recently (Brown 2009; Brown et al. 2007). These are cats in whom ocular or intracranial lesions are manifest or have previously been manifested in conjunction with systemic hypertension, and who have persistent arterial BP levels >180 mm Hg (and often much higher). The white coat effect must be reduced as much as possible for an accurate reading; failure to do so poses a risk of hypotension or hypotensive crisis during acute antihypertensive treatment. The goal of treatment is not normalization of the BP but rather an acceptable decrease that reduces the risk of target organ damage with minimal risk of overtreatment (hypotension causing renal, cerebral, or coronary ischemia). The current consensus in human medicine is a reduction in BP of at most 25% within minutes to 1 hour of identification of the emergency, and, if the patient is stable, subsequent reduction of BP to no lower than 160/100–160/110 over the next 2–6 hours (Labato 2009). Such guidelines seem appropriate for feline patients, pending species-specific data. Drugs used singly (virtually never in combination) for the management of hypertensive crisis include amlodipine 0.25 mg/kg PO q 24, with dosages up to 0.5 mg/kg being used in some cases with caution; hydralazine 2.5–5 mg/cat dissolved in water and given via syringe PO up to q 12 h; esmolol 50–75 µg/kg/min constant rate IV infusion (CRI); labetalol 0.25 mg/kg IV over 2 minutes, then repeated as needed up to total dosage ≤3.75 mg/kg followed by 25 µg/kg/min CRI; or enalaprilat 0.2 mg/kg as needed up to q 1–2 h (Brown et al. 2007).

MONITORING

Subsequent BP measurements follow the initial diagnosis. The interval is dictated by the presence or absence of signs of target organ damage; by the magnitude of hypertension; by the ability to control the inciting disease; and by client wishes and abilities (physical, financial, emotional, etc). Typical intervals range from a few days or 1 week for cats with severe target organ damage that are recovering and are being discharged after inpatient care, to 3–4 months for patients with clinically stable BP and well-controlled underlying disorders. Essentially all cats with confirmed systemic hypertension should have their BP measured whenever they come to medical attention, including when they seem well.

OUTCOME AND PROGNOSIS

The largest study of survival in cats with systemic hypertension to date assessed 141 hypertensive cats. Cats were treated with amlodipine in an open-label manner and followed; 89 died and were thus included in survival statistics. Of the variables studied, including age, serum creatinine, serum phosphorus, and degree of hypertension (BP measurements), only proteinuria was correlated with survival (Jepson et al. 2007). Hypertensive cats with lower urine protein:creatinine ratio (e.g., <0.2) before or after treatment with amlodipine lived longer than cats with higher urine protein:creatinine ratio (e.g., >0.4). The same study identified that treatment with amlodipine was associated with a significant reduction in urine protein:creatinine ratio.

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SECTION J

Pericardial Diseases

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22

Pericardial Effusion and Other Disorders of the Pericardium

Key points

- Pericardial disease is uncommon in the cat.
- The most common congenital pericardial disease is peritoneopericardial diaphragmatic hernia (PPDH); the most common acquired pericardial abnormality is pericardial effusion.
- Cardiac tamponade secondary to pericardial effusion is rare in cats.
- Congestive heart failure is the most common cause of feline pericardial effusion.

INTRODUCTION

The pericardium is the membrane, composed of two layers, which surrounds the heart. The outer layer is the fibrous "parietal" pericardium; the inner serous "visceral" pericardium is invaginated by the heart during embryogenesis and forms the epicardium. The pericardial cavity exists between these two layers and normally contains a small volume of serous fluid, which is an ultrafiltrate of serum. The pericardium functions to prevent cardiac overdilation, lubricate the myocardial surface, protect the heart from infections or adhesions, stabilize the heart within the chest, and regulate stroke volume between the ventricles (Miller 1994). Pericardial diseases make up approximately one percent of canine cardiac disease with pericardial effusion being most common (Miller 1994). Pericardial diseases are even more rare in the cat.

CONGENITAL PERICARDIAL DISEASES

Peritoneopericardial diaphragmatic hernia (PPDH) is the most frequently recognized congenital pericardial defect in the cat. There are several proposed theories regarding the embryologic mechanism (Frye and Taylor 1968); the end result is a persistent communication between the pericardial and peritoneal cavity. The defect allows cranial displacement of abdominal organs into the pericardial sac. Because there is normally no direct communication between these two spaces, a PPDH is never an acquired, traumatic defect. However, traumatic events can cause abdominal organs to move into the pericardial sac through a congenital PPDH. In one retrospective study evaluating feline PPDH cases, domestic longhair cats and Himalayans were over represented, and domestic shorthair cats were underrepresented (Reimer et al. 2004).

Clinical signs depend on the degree of herniation. Most affected cats show no clinical signs, and the defect is noted incidentally when thoracic radiographs are taken for other reasons. In a subset of affected cats, major organ herniation is present and clinical signs are noted by the owner, such as vomiting, diarrhea, anorexia, cough, dyspnea, or lethargy. The liver and gallbladder are the most often herniated organs followed by the small intestine, spleen, stomach, and omentum (Reed 1988). Therefore, the most common clinical signs are usually referable to the gastrointestinal or respiratory systems. On physical examination, a decreased or displaced cardiac apex beat may be noted and heart sounds are often muffled, particularly when

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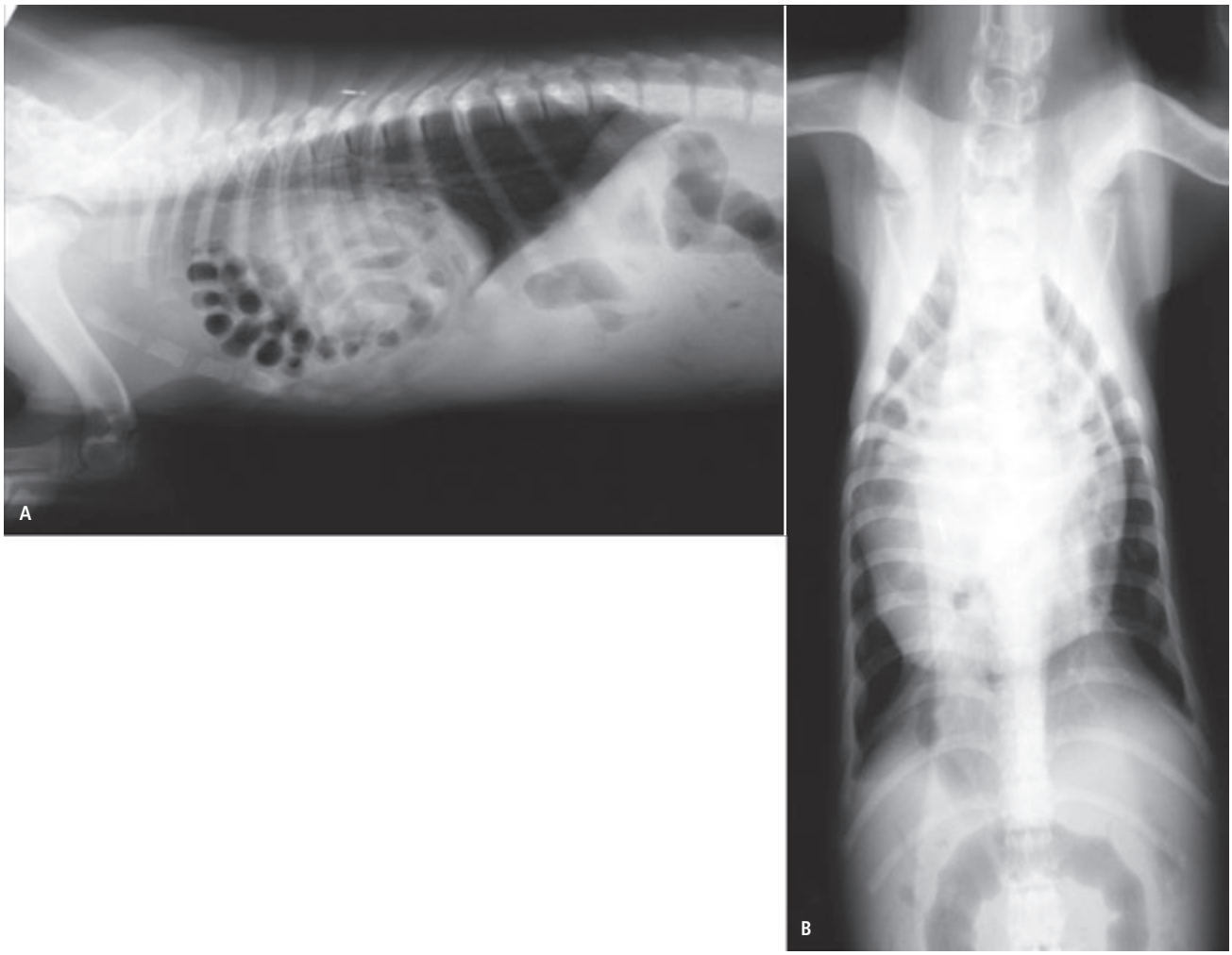


Figure 22.1. Lateral **(A)** and VD **(B)** radiographs from a cat with PPDH. Note the severely enlarged cardiac silhouette with overlap of the caudal heart border and diaphragm and the presence of bowel loops containing gas within the pericardial sac.

major organ herniation is present. Similarly, the abdomen may feel "empty." Other congenital defects may also be noted such as sternebral abnormalities (i.e., pectus excavatum).

Electrocardiography may show reduced QRS amplitude and/or axis deviation due to herniated abdominal contents and shifted cardiac position. Radiographs typically are diagnostic, with an enlarged cardiac silhouette and overlap of the caudal heart border and diaphragm when organ herniation is moderate or extensive (Figure 22.1). When only the omentum is herniated, thoracic radiographs may be unremarkable. Persistence of the dorsal mesothelial remnant, a meniscus-like connection between the caudal cardiac silhouette and the diaphragm, ventral to the caudal vena cava on a lateral radiograph, strongly suggests PPDH (O'Sullivan 2007). With herniation of one or more liver lobes, the gastric axis may be displaced cranially. Absence of cranial or midabdominal organs from the abdominal cavity may be noted and they may be visualized within the pericardial sac. Echocardiography is a straightforward diagnostic modality to confirm the diagnosis when abdominal organs are visible within the pericardium of affected cats (Figure 22.2). An important differential diagnosis is consolidation of the accessory lung lobe, because hepatization of the lung mimics herniated liver tissue adjacent to the heart; a radiologist should be consulted to clarify the diagnosis on radiographs if uncertainty exists.

Surgical correction is warranted if clinical signs are present, since the prognosis is excellent if the PPDH is uncomplicated and repaired. In one study, 60% of the 66 PPDH cases had clinical signs secondary to the PPDH, which prompted the owner to present the cat to a veterinarian (Reimer et al. 2004). Twenty-nine cats were treated conservatively and 37 were treated surgically (most often those with overt clinical signs related

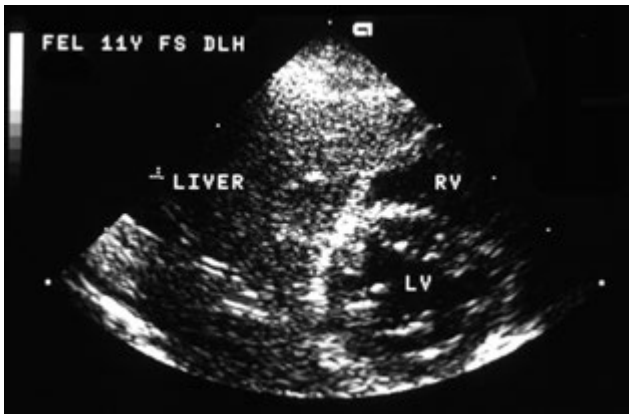


Figure 22.2. Right parasternal short-axis echocardiogram at the ventricular level. Note the presence of the liver within the pericardium. RV = right ventricle; LV = left ventricle.

to the PPDH), with a postoperative mortality rate of 14%. Cats that had historical signs attributable to the PPDH often continued to have intermittent clinical signs. At follow-up, approximately 75% of owners believed their cats were clinically normal whether their cat was treated surgically or conservatively (Reimer et al. 2004).

Congenital pericardial cysts are rare in dogs and have not been reported in cats; however, the physiologic implications are similar to those of pericardial effusion (see below). Thus, the expected history, clinical signs, and pathophysiology would be similar to those described below, but in a young animal. Diagnosis historically was made using pneumopericardiography in dogs; however, echocardiography has largely supplanted this technique. Surgical removal of the cyst and partial pericardiectomy results in an excellent prognosis.

ACQUIRED PERICARDIAL DISEASES

Pathophysiology

Pericardial effusion (PE) can develop for a variety of reasons and as it accumulates, intrapericardial pressure increases. If the pericardial pressure increases above right ventricular diastolic pressure, cardiac tamponade ensues, resulting in increased diastolic intracardiac pressures, reduced ventricular filling, and reduced cardiac output. As right atrial pressure increases, systemic venous pressure also becomes elevated. As fluid continues to accumulate in the pericardium, pericardial and right atrial and ventricular diastolic pressures rise together. Eventually, they can equalize with left ventricular diastolic pressure. At this stage, there is a marked decline in cardiac output, and compensatory measures such as activation of the sympathetic nervous system are initiated in a physiologic attempt to maintain cardiac output. Thus, sinus tachycardia, sodium and water retention, and venoconstriction help compensate for decreased cardiac output. However, increased systemic venous pressure leads to fluid transudation from systemic capillaries. Ascites accumulates once central venous pressure increases to ≥15 mmHg (normal ≤6 mmHg). Signs of right heart failure predominate because the right ventricle is thinner-walled and more influenced by high intrapericardial pressures. Pleural fluid accumulates secondary to venous hypertension (similar to ascites), and reduced absorption of subpleural pulmonary lymphatic vessels. However, pulmonary edema develops only when severe tamponade raises pulmonary venous pressure over 25 mmHg.

Clinical signs are determined by the rate of fluid accumulation and the ability of the pericardium to stretch. Typical historical signs include lethargy and weakness. Common physical exam findings include muffled heart sounds, a weaker than normal apex beat, generalized systemic venous congestion (i.e., jugular venous distension, hepatomegaly), and possibly right-sided CHF signs, such as tachypnea, dyspnea, pleural effusion ± ascites. Pulsus paradoxus may be noted on the physical examination, evidenced by an increased femoral arterial pulse strength during expiration and decreased pulse intensity on inspiration. It is defined by a drop of >10 mmHg in arterial pulse pressure with inspiration compared to expiration and occurs due to blood pooling within the great vessels in the thorax and away from the heart during inspiration when the intrathoracic pressure is most negative, which is subsequently pumped back into the heart during expiration. Most often arterial pulse strength is weak and pulses may be difficult to locate in severely affected, hypotensive patients. Hepatomegaly may be detected with abdominal palpation.

Pericardial effusion is the most common pericardial abnormality in cats, but it rarely causes cardiac tamponade or secondary right sided heart failure. However, the clinical signs described above should prompt astute clinicians to consider cardiac tamponade in their feline patients since there have been sporadic reports of feline patients with cardiac tamponade. In cats, PE is most often present in small volumes in conjunction with congestive heart failure. Congestive heart failure can lead to mild or moderate pericardial fluid accumulation, through a similar mechanism to the formation of pleural effusion, but tamponade due to heart failure-associated PE should not be possible. Unlike in dogs, CHF is the most common cause of PE in cats, followed by neoplasia (see Chapters 1 and 16). Contrary to the prevalence noted in dogs, chemodectomas have only been sporadically reported in cats (George and Steinberg 1989). However, a case of

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primary cardiac rhabdomyosarcoma with PE and cardiac tamponade has been reported (Venco et al. 2001). Pericardial effusion can also be infectious in origin. Feline infective pericarditis has been associated with *Escherichia coli, Staphylococus aureus, Streptococcus, Enterococcus*, and *Actinomyces* infections (Reed 1988). PE has been associated with feline infectious peritonitis (FIP) and with toxoplasmosis, although the fluid is usually a sterile inflammatory effusion. One case report describes a cat with presumptive disseminated toxoplasmosis presenting with myocarditis and PE (Simpson et al. 2004). FIP PE typically has a high protein content, which appears as a granular eosinophilic background on cytology. Finally, feline pericardial effusion has been recognized to occur secondary to uremia and coagulopathies.

Historically it was thought that FIP was the most common cause of PE in cats, but two retrospective studies later demonstrated that PE occurs most often secondary to congestive heart failure (36–75% of cases) (Davidson et al. 2008; Hall et al. 2007). The second most common cause of PE in both studies was neoplasia (5–19%) with lymphoma and adenocarcinoma occurring most frequently. Both studies were retrospective and did not assess the frequency of cardiac tamponade in these cases. One report included only those cats with an antemortem diagnosis (Hall et al. 2007), while the other included those cats with pericardial effusion diagnosed antemortem or on postmortem (Davidson et al. 2008). In the authors' experience, mild PE is a common finding in cats with severe structural cardiac changes associated with diseases such as cardiomyopathy. However, collapse of the RA or RV (echocardiographic evidence of cardiac tamponade) is rarely appreciated. This important observation highlights the difference between PE as an incidental finding (e.g., in congestive heart failure, uremia, others), where the volume of PE is usually small and no intervention specifically aims to quickly evacuate it, and PE as the principal cause of hemodynamic dysfunction (cardiac tamponade) requiring pericardiocentesis. PE alone is an insufficient descriptor for the clinician; the amount of effusion, and most importantly, its effect on the circulation, allow the clinician to decide whether conservative treatment is sufficient or whether pericardiocentesis is needed.

Electrocardiography will most often reveal a normal sinus rhythm or sinus tachycardia. If the volume of PE is significant, the QRS complexes are often low in amplitude. Electrical alternans, the beat-to-beat variation in amplitude of the QRS complexes, is rarely appreciated in cats because the volume of PE is almost never large enough to allow the swinging of the heart within the pericardial sac, which produces this finding, and because feline QRS complexes are often small even in health.

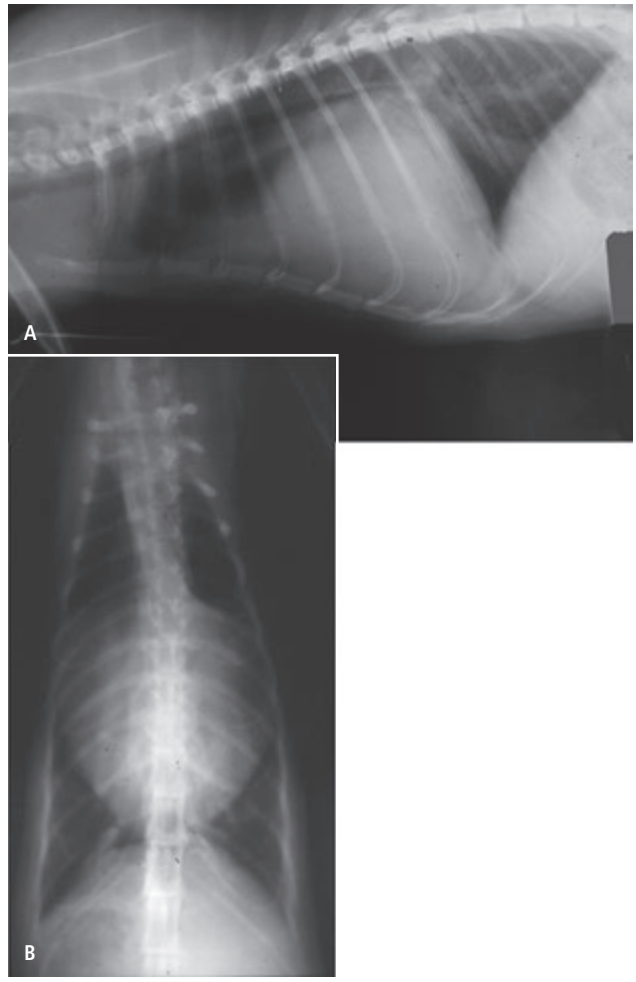


Figure 22.3. Lateral **(A)** and VD **(B)** radiographs from a cat with a moderate to marked amount of pericardial effusion. Note the round, globoid cardiac silhouette, especially on the VD view.

Findings on thoracic radiographs are also frequently less dramatic since the amount of effusion is often smaller in cats with PE compared to dogs (Rush et al. 1990). The cardiac silhouette may be generally enlarged and rounded and the edge of the cardiac silhouette is usually sharp owing to the lack of systolic and diastolic motion associated with a distended pericardial sac (Figure 22.3). The pulmonary vasculature and lung fields may be consistent with congestive heart failure since CHF is a common cause of PE in the cat.

Echocardiography is the most sensitive and noninvasive tool to confirm the presence of PE. With two-dimensional echocardiography, PE appears as anechoic (black) to hypoechoic (grey) space surrounding the heart (Figure 22.4). If the cat also has pleural effusion, the pericardial sac can be visualized as an echogenic (white) thin structure attaching to the base of the heart (see Figure 3.3). In most cats with PE, there will be evi-

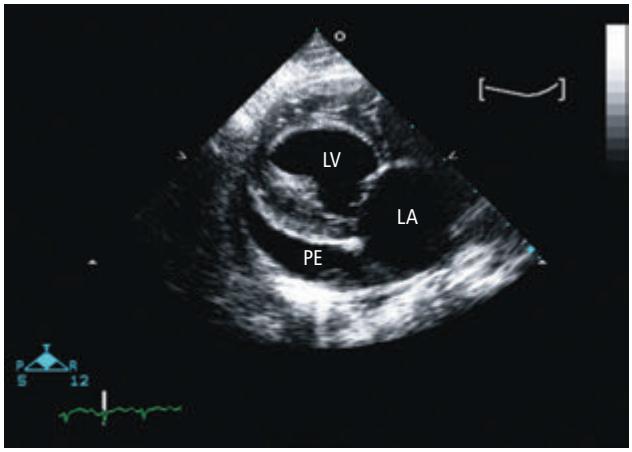


Figure 22.4. Long-axis echocardiogram obtained at the right parasternum of a cat with pericardial effusion (PE). Note the anechoic fluid surrounding the heart. LA = left atrium; LV = left ventricle.

dence of underlying primary heart disease, such as hypertrophic cardiomyopathy; however, in some individuals the heart is normal and another underlying cause may be found, such as neoplasia. With some neoplasms, the mass will be evident in association with the heart or great vessel(s); however, myocardial infiltration is a common presentation for cardiac lymphoma, the best-recognized cardiac tumor in the cat (Meurs et al. 1994). See Chapter 16 for further discussion regarding cardiac neoplasia.

Although rare, evidence of cardiac tamponade should be sought if PE is present on echocardiography. The right atrial free wall is normally rounded throughout the cardiac cycle. Evidence of right atrial inversion or collapse during the cardiac cycle suggests elevated intrapericardial pressure. If present, inversion usually occurs in late diastole and extends variably into ventricular systole. Similarly, if more advanced right ventricular tamponade is present, the right ventricular free wall will move inward or collapse during diastole.

When echocardiographic evidence of cardiac tamponade is noted, pericardiocentesis is essential for therapeutic purposes as well as diagnostic purposes. Tamponade rarely develops with PE secondary to congestive heart failure, but it has been recognized in several cases in which PE was caused by neoplasia (Zoia et al. 2004; Hall et al. 2007). Therefore, a subset of cats with pericardial effusion will have cardiac tamponade and require pericardiocentesis. Pericardiocentesis with cytologic fluid analysis is also important for the diagnosis of infectious etiologies. Pericardiocentesis can be achieved with an 18–20 gauge catheter or a butterfly needle connected to a three-way stop cock (depending on the size of the cat). Cardiologists may preferentially perform pericardiocentesis from the left or right precordium, but the ideal location can be best assessed via echocardiography (which allows one to choose the space with the largest fluid pocket). The patient should be restrained in lateral recumbency and the intercostal space should be blocked with 1 cc lidocaine using a 25–27 gauge needle. Some cats may need sedation in addition to the local lidocaine block. The catheter/butterfly should be attached to a 3-way stopcock as described for thoracocentesis (see discussion regarding pleural effusion removal in Chapter 3). An electrocardiogram should be placed to evaluate for new ventricular arrhythmias that may occur if the ventricle is contacted. Complications secondary to pericardiocentesis are rare, but they include cardiac puncture, cardiac arrhythmias, and/or laceration of the tumor or coronary artery. If the catheter is rapidly withdrawn and repositioned, the patient is often not clinically compromised by these possible problems (Gidlewski and Petrie 2005). See Box 22.1 for a more specific description of the pericardiocentesis procedure. The gross character of pericardial effusion in cats often differs from dogs; it rarely appears hemorrhagic in cats and can be difficult to differentiate from pleural effusion, which is also often concurrently present. If this dilemma arises, a few ml of agitated (microbubbled) sterile saline may be injected into the centesis catheter, and ultrasound is used for identifying whether the contrast appears in the pleural or pericardial fluid, confirming the location of the catheter tip. Cytologic analysis of PE should be performed if infectious or neoplastic etiologies are possible (i.e., most cases of PE causing cardiac tamponade in cats). Malignant lymphocytes generally exfoliate readily in feline PE caused by lymphoma (Brummer and Moïse 1989).

CONSTRICTIVE PERICARDITIS

Pericardial constrictive disease occurs when the visceral and parietal pericardial layers become fused or fibrotic (Figure 22.5). The pericardial space may be totally obliterated or may contain a small amount of PE. Constrictive pericarditis is a difficult diagnosis to make by echocardiography, but if clinical signs and echocardiographic findings are consistent with the diagnosis, cardiac catheterization for intracardiac pressure assessment is diagnostic. Since early ventricular relaxation is often normal, ventricular diastolic pressure drops normally; however, ventricular pressure rapidly increases with early filling because the limit of ventricular distensibility is met very early in diastole. This phenomenon will appear as a "square root sign" on a right ventricular pressure trace obtained through cardiac catheterization. Other hemodynamic abnormalities include elevation and

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Box 22.1. Procedure for pericardiocentesis in cats

1. Approach from the left or right side—each direction has advantages and drawbacks; in the example here, the cat is in right lateral recumbency, allowing an approach to the pericardium from the left side unless echocardiography suggests the fluid pocket is larger on the right side. Mild sedation can be achieved with 0.3 mg/kg butorphanol and 0.3 mg/kg midazolam IV or IM, if necessary. An electrocardiogram should be monitored during the procedure to monitor for ventricular ectopy (which can occur if the epicardium is abraded).

   Note: The direction of approach for pericardiocentesis is primarily driven by location of the largest fluid pocket and personal experience. Some clinicians prefer to perform the procedure from the right believing there is less risk of lacerating a coronary artery. Others prefer to approach from the left because deoxygenated blood in the right ventricle can easily be mistaken for the "port wine" appearance of the classic hemorrhagic pericardial effusion. Therefore, when performing the procedure from the left, the clinician knows quickly whether the sample is blood from the left ventricle (oxygenated and bright red in color), or pericardial fluid ("port wine" (dark red) in color). As long as the pericardiocentesis is performed from the apex of the heart and the needle is directed toward the opposite shoulder, the risk of coronary laceration is low, whether one performs the procedure from the right or left thorax.
2. Shave the left (or right) thorax after the ideal location for the procedure is determined by echocardiography. In many cats, the fluid pocket is small and echocardiographic guidance during the procedure is helpful.
3. Perform a sterile prep of the skin.

   Infiltrate the skin, intercostal muscles, and parietal pleura with local anesthetic (2% lidocaine, 1 ml) and repeat surgical preparation.
4. Use an 18–20 gauge over-the-needle catheter system or a 19 gauge butterfly needle in a cat. Make two small side holes near the tip of the catheter to avoid blockages during aspiration.
5. Attach the catheter to a 12–20 cc syringe via an extension tube and a three-way stopcock. If a butterfly needle is used, you can attach it directly to a three-way stopcock and syringe.
6. Slowly advance the catheter or butterfly needle through the skin toward the pericardium while maintaining slight negative pressure via the syringe. Once a flashback of fluid is noted, advance the catheter over the needle into the pericardial space and remove the needle while the extension tube is connected to the catheter (or advance the butterfly cautiously toward the opposite scapula). It is important to keep in mind that an initial flashback will be pleural effusion if the patient has both pleural and pericardial effusions present. Therefore, the needle/catheter will need to be advanced further for a second flashback, revealing fluid that often is different in appearance.
7. Pericardial fluid is often less sanguineous in cats compared to dogs, but if the appearance is bloody, place an aliquot of fluid in an activated clotting time tube to confirm that it is not blood. Pericardial effusion should not clot, whereas blood from a great vessel or cardiac puncture will clot.

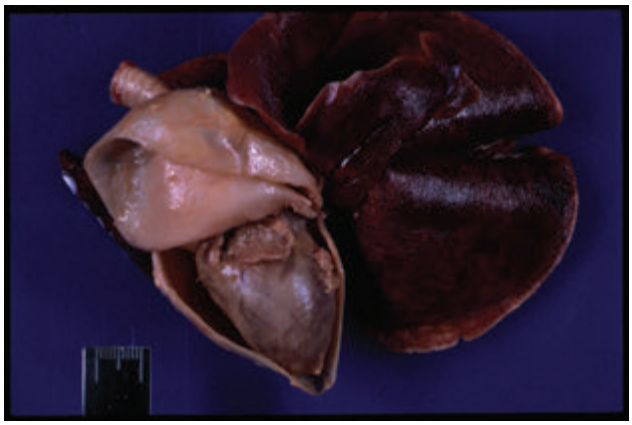


Figure 22.5. Postmortem specimen from a cat with constrictive pericarditis. Note the thick, opaque pericardium surrounding and reflected dorsal to the heart.

equilibration of atrial and ventricular diastolic pressures and loss of the normal reduction in caval pressure associated with inspiration. Right-sided heart failure is the most common abnormality noted on physical examination. This disease likely is extremely rare in the cat, and has not yet been reported.

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SECTION K

Heartworm Disease

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23

Heartworm Disease

Key points

- Feline heartworm disease causes more morbidity than previously believed and definitive diagnosis is often elusive.
- Extensive lesions can occur secondary to circulating larvae, even if the cat successfully clears the infection and no adult worms develop.
- Feline heartworm disease appears to be a primary factor in a subset of feline asthma cases.
- The acronym HARD (heartworm-associated respiratory disease) was coined to describe the pulmonary pathology resulting from the death of immature heartworms or the presence of adult heartworms in the lungs.

INTRODUCTION

Heartworm disease is a particularly common problem in tropical and subtropical regions; however, the disease has spread throughout most areas of the United States. Although the prevalence is still low at high elevations and in most northern states, evidence suggests that the disease is expanding throughout the United States (Nelson et al. 2007). Endemic foci frequently occur in regions with otherwise low prevalence and it is difficult to eliminate heartworms from a region once they have been established. Wild animal reservoirs include wolves, coyotes, foxes, California gray seals, sea lions, raccoons, and ferrets. Heartworm infection is an increasingly diagnosed entity in feline practice due to increased awareness of the disease in cats and improved diagnostic methods. In spite of these recent developments, diagnosis remains a challenge in cats and few cats are treated with heartworm preventative.

ETIOLOGY AND LIFE CYCLE

Heartworm infection is produced by the parasite *Dirofilaria immitis* and is transmitted to dogs mostly by 10–15 species of mosquitos. Although dogs are the usual definitive host, the life cycle of the parasite can be completed in cats, and feline infection rates in endemic regions are usually 10% to 20% of that of dogs within the same enzootic region. If the disease is present in a local canine population, it is occurring in local cats as well (Nelson 2008a). The infection rate is lower in cats compared to dogs for several reasons. Some mosquito species do not prefer to feed on cats. Additionally, cats are relatively resistant to infection due to immune clearance of infective larvae, so infected cats usually have fewer adult worms than infected dogs (usually six or less), and the lifespan of the worms is shorter in cats than dogs (2–3 years compared with 5–7). However, it is likely that the morbidity in cats associated with heartworm disease is underestimated for reasons that will be discussed later in this chapter. Additional evidence that cats are not the definitive host for the parasite include their typical low and transient microfilarial counts, and a longer average prepatent period (usually 1–2 months longer) in cats than in dogs. Finally, aberrant migration of the fourth-stage larvae (L_4) occurs more frequently in cats than in dogs (Nelson et al. 2005).

Female mosquitoes are the intermediate hosts and acquire the first-stage larvae (microfilariae) by feeding

Feline Cardiology, First Edition. Etienne Côté, Kristin A. MacDonald, Kathryn M. Meurs, Meg M. Sleeper.
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on an infected animal and ingesting the parasite. Two molts then occur to produce the infective L_3 stage. Larvae development to the third stage usually requires 1 to 2.5 weeks, depending on the ambient temperatures. Mosquitoes can survive the development of only low numbers (<10) of larvae. Larvae development within the mosquito requires an average daily temperature of at least 57°F (14°C) (Nelson et al. 2007). The cooler the temperature, the longer the time required for L_3 to develop and vice versa. Therefore, transmission is unlikely to occur during the cold months of the year, even in most southern regions of the U.S. Peak months of heartworm transmission in the northern hemisphere are July and August (Nelson et al. 2005). This is primarily because the time required for development from L_1 to L_3 may exceed the life span (30 days) of the mosquito when temperatures are moderately low.

Third-stage larvae (L_3) infect the cat via the bite wound created when an infected mosquito feeds. Larvae migrate through the subcutaneous tissues and vascular adventitial tissues. During this time, 2 molts occur. Once the larvae enter the bloodstream, they are swept with the circulation to the pulmonary arteries. There is very high mortality of the young adults (L_5) because they reach the feline lungs approximately 3 to 4 months postinfection, and only a subset of the larvae ever mature to the adult stage. Adult heartworms are typically sexually mature and able to reproduce by 7–8 months postnfection (which is 1–2 months longer than is seen in the dog) (McCall et al. 1994). However, microfilarial counts are usually very low and transient in the cat, seldom lasting for longer than 1–2 months (McCall et al. 1994). See Figure 23.1 for an illustration of the heartworm life cycle in the cat.

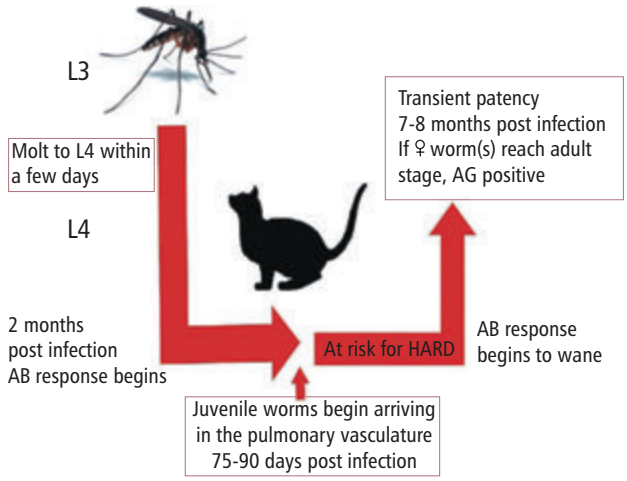


Figure 23.1. The life cycle of *Dirofilaria immitis* in the cat. The cycle is similar for dogs and cats until immature adults enter the pulmonary artery (approximately 100 days postinfection). In dogs, the majority of juvenile worms mature to adults and live 5 to 7 years. In cats, most juvenile worms die shortly after arriving at the pulmonary artery creating a significant inflammatory response. Antibody response begins at 60 days after infection (whether a dog or cat); however it begins to wane as juvenile worms die in the cat. Worms that survive to the adult stage require longer to mature in cats (7–8 months vs 6 months in the dog).

Prevalence

Heartworm infection is most common in tropical and subtropical climates. However, *D. immitis* infections have been reported in cats in many areas of the world, with the prevalence varying by geographic region. Most commonly it has been reported at 5–20% of the rate for the local dog population (Nelson 2008b). It has been suggested that this variation between the species reflects willingness of the local species of mosquitoes to feed on both dogs and cats. Indoor and outdoor cats are affected with heartworm disease and one retrospective study demonstrated that 25% of cats diagnosed with adult heartworms were classified as entirely indoor cats (Nelson et al. 2007). Some studies have suggested that male cats are at increased risk compared to females; however, this pattern has not been conclusively documented. In one necropsy-based report, the heartworm infection rate in cats was greater than that for FIV or FeLV, yet in the same report it was noted that fewer than 5% of cats in the United States are on preventative medications (Nelson 2008a). Another study determined seroprevalance of dirofilariasis, FeLV infection and FIV infection in cats exported from the Gulf Coast region following the 2005 hurricanes were 4.0%, 2.6%, and 3.6%, respectively (Levy et al. 2007).

Pathogenesis

Acute lung injury is the major contributing factor to the initiation of clinical signs. It is hypothesized that the arrival of fifth stage larvae in the lungs (typically 80–160 days postinfection) and the death of adult worms are the most likely stages of the life cycle to be associated with clinical signs in the cat. After an initial host response, the signs may disappear or become subclinical. Interestingly, recent research has shown that *D. immitis* has evolved various strategies to evade a host immune attack. These include dramatically different surface properties of the third and fourth larval stages and an acellular cuticle (Litster and Atwell 2008) and suppression of pulmonary intravascular macrophages by living heartworms (Dillon et al. 2008). It is hypothesized that these capabilities could account for the reduction of clinical signs after the initial, often marked, inflammatory response following arrival of the L_5 stage in the lungs, as well as the acute signs that follow death of the heartworm(s) in

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the cat (Dillon et al. 2008). Moreover, although cats may clear the infection so that no adult worms develop, pulmonary lesions can still be severe (Browne et al. 2005).

Thus, the disease process can be divided into 3 main stages of disease in cats, with the first being associated with the arrival of juvenile worms in the pulmonary arteries and an acute parenchymal inflammatory reaction. This stage is followed by a relatively symptom-free period after the worms mature to adults and the host immune response is suppressed. However, when the worm (or worms) die(s), the immune system is no longer suppressed and an intense inflammatory response follows (stage 2), with sudden death reported in 10–20% of affected cats (Nelson 2008a). Finally, if the cat survives, it enters the final stage of disease with permanent lung injury due to type II alveolar cell hyperplasia and chronic respiratory disease (Nelson 2008a).

A link between heartworm infection in cats and lower airway disease, such as feline asthma, has been hypothesized for a long time (Borgarelli et al. 1997). In fact, thoracic radiography performed in the first stage of heartworm disease often shows changes which may be misinterpreted as indicating allergic bronchitis or feline asthma (pulmonary bronchointerstitial pattern, hyperinflated pulmonary fields, etc). Furthermore, radiographic changes improve with glucocorticoid administration, further supporting the misdiagnosis (Nelson 2008a). Even if heartworm disease was suspected and tested for, cats in this stage of disease will not have a positive antigen test (because adult worms are not present) and a significant number of false negative results are possible with the various antibody tests (see the section "Differential Diagnosis" for further discussion).

This evidence has led to a proposed classification for heartworm disease, which reflects the difficulty of defining a heartworm-infected cat (Atkins 2007). In this recommended scheme, heartworm-exposed or infected cats would be divided into the following groups:

- Unexposed cats (antibody negative, antigen negative)
- Exposed cats treated with heartworm preventative (antibody positive, antigen negative, and free of clinical signs of heartworm disease)
- Exposed cats with subclinical disease in which the parasites developed to the immature L_5 stage in small numbers (antibody positive, antigen negative, and without radiographic lesions)
- Exposed, possibly clinically affected cats (parasites developed into immature L_5 with secondary pulmonary lesions, but parasites did not mature to adults (antibody positive, antigen negative, "pulmonary larval dirofilariasis")
- Exposed cats in which the parasite completed its life cycle to the mature L_5 stage with evidence of heartworm disease potentially involving multiple organs, particularly the lungs (antibody positive, ± antigen positive, dirofilariasis or heartworm disease)

Wolbachia are a vertically transmitted, gram-negative, intracellular bacterium that are harbored by *D. immitis* larvae and adults. *Wolbachia* are endosymbionts, which are also found in several other filarial species including *Onchocerca volvulus* and *Brugia malayi* (Simon et al. 2007). The metabolic products and surface proteins from *Wolbachia* can elicit an inflammatory response in the host dog or cat (Nelson et al. 2005), and exposure to *Wolbachia* occurs whenever larvae or adult worms die or are killed. A recent study showed a strong IgG response against the surface protein of *Wolbachia* in heartworm-infected cats (experimentally and naturally infected) leading to the hypothesis that the bacteria could play a large role in the feline inflammatory response to heartworm infection (Morchon et al. 2004). Moreover, the immune response to *Wolbachia* antigens was detected before antibodies against *D. immitis* further supporting this theory. A study evaluating pretreatment with doxycycline prior to adulticide administration in dogs showed there was a reduction in pathology associated with worm death (McCall et al. 2008; Nelson 2008b). No similar studies have been reported to date in cats; however, according to the American Heartworm Society, studies to determine the effects of suppressing *Wolbachia* populations with doxycycline in cats are in progress.

HISTORY, CHIEF COMPLAINT, PHYSICAL EXAMINATION

The owner-reported history is highly variable. The owner of an affected cat may report a wide range of clinical signs such as chronic coughing, sudden or episodic dyspnea, and/or vomiting (Atkins et al. 1998, 2000). Vomiting and coughing are common clinical signs in heartworm-infected cats, and the combination of these signs in a feline patient warrants a high level of suspicion for heartworm infection. Lethargy, decreased appetite and/or weight loss may also be reported. Occasionally central nervous system signs such as seizures or blindness may be present, particularly when aberrant migration has occurred. Cardiac abnormalities such as pulmonary hypertension, cor pulmonale, or congestive heart failure are uncommon. Asthmatic signs are common manifestations and often occur about 3 to 4 months postinfection. Less commonly, ascites, hydrothorax, chylothorax, pneumothorax, ataxia, and syncope have all been reported to be associated with feline heartworm

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disease. There are also rare reported cases of pneumothorax secondary to *D. immitis* (Smith et al. 1998).

In a subset of cats, severe respiratory distress ± collapse or sudden death may be the first clinical sign recognized by the owner (Nelson et al. 2005). It is a much more common presentation in feline heartworm disease than in canine heartworm disease. Acute death in affected cats has been attributed to pulmonary arterial infarction following spontaneous death of adult heartworms; however, filariae are not always present embolizing the main pulmonary arteries and the lung lobes are rarely ischemic (based on radioisotope studies). Recently, an experimental model of acute anaphylaxis using *D. immitis*–sensitized cats challenged with intravenous heartworm antigen demonstrated a similar shocklike reaction; the severity of response was influenced by the amount of exposure (Litster et al. 2008). Thus, it is theorized that damage to the heartworm cuticle causing release of large amounts of heartworm antigen (Ag) results in acute systemic anaphylaxis and death. See Table 23.1 for a list of clinical signs that may be associated with heartworm disease. On the other hand, approximately one third of affected cats will be asymptomatic, perhaps in part due to their sedentary lifestyle and variable immune response (Nelson 2008a).

Arterial intimal proliferation typical of canine heartworm arteritis develops in feline pulmonary arteries as well. However, because infections are usually light and short in duration, the lesions are often localized and less obstructive than in dogs. Therefore pulmonary hypertension with subsequent right ventricular hypertrophy and right heart failure occur less frequently than in the dog (Nelson et al. 2007). Caval syndrome is rare in cats because worm burdens are usually low; however, even single worm infections may cause tricuspid regurgitation and a right sided systolic murmur.

Table 23.1. Clinical signs associated with heartworm disease

Acute
Sudden death
Collapse
Shock
Dyspnea
Blindness
Seizures
Vomiting/diarrhea
Ataxia
Chronic
Vomiting
Cough
Dyspnea
Lethargy
Anorexia
Weight loss
Weakness

DIAGNOSIS

Diagnostic confirmation often requires a combination of tests. See Figure 23.2 for an algorithm of heartworm disease diagnosis in the feline patient that is suspected of having heartworm disease based on clinical signs. Affected cats usually lack circulating microfilariae (tests for microfilaremia are positive in less than 20% of infected cats), and the low worm burdens in this species result in light or absent antigen loads. Positive antigen test results are the result of the presence of adult female worms. The antigen is associated with the worm's reproductive tract. In cats, antigen tests have excellent specificity but false-negative results are common. False-negative test results are explained by low worm burdens with male-only infections, and infection with young (<7 months old) female worms that have immature reproductive tracts. The sensitivity of commercial Ag tests has improved dramatically in recent years and most are effective at detecting a singe adult female worm. In the cat, heartworm Ag is detectable about 5.5 to 8 months postinfection, and a positive Ag result generally indicates a current infection with at least 1 adult female worm.

Heartworm-associated antibody (Ab) tests are useful to rule out infections in cats when there is an index of suspicion for the disease; however, these tests also have significant limitations. Antibodies can appear as early as 2 months postinfection. Because these tests detect exposure to migrating heartworm larvae, they may be positive in cats with previous heartworm exposure or infection, so a positive antibody test indicates exposure but not necessarily active infection. Previously false negative results were thought to be rare, but recent studies suggest approximately 14–50% of infected cats are antibody negative (Atkins et al. 1998; Kalkstein et al. 2000; Nelson et al. 2007). This wide range is probably partly because the different antibody tests vary in their sensitivity to the various stages of larval development, and evidence suggests antibody levels in the cat decrease over time as the worm matures. Also, heartworm-infected cats with clinical signs are more likely to be positive than infected asymptomatic cats (Nelson et al. 2007). In a necropsy survey comparing 6 different Ab tests in an endemic region, Ab results varied greatly, with as many as 86 (26% of the cats) having positive results to as few as 9 (3% of the cats). This correlated with a positive predictive value ranging from 17.3 to 62.7% depending

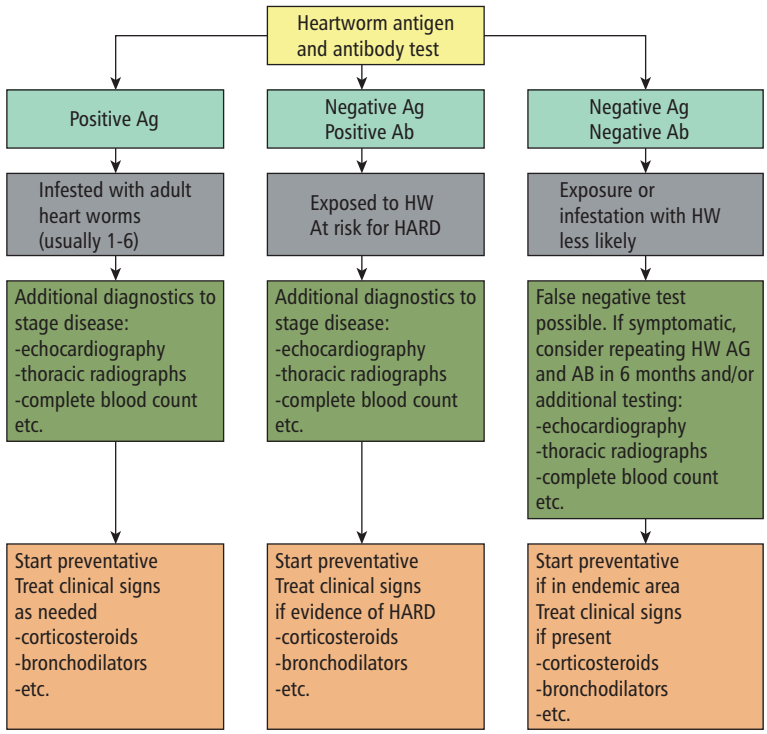


Figure 23.2. An algorithm for the diagnosis and basic treatment options of heartworm disease in cats in which heartworm disease is suspected.

on the test used (Snyder et al. 2000). Another study, which evaluated Ab and Ag performance in a large group of cats, also showed significant variation in diagnostic performance of the tests when compared to the gold standard of necropsy (which was imperfect because it was limited to the thorax) (Berdoulay et al. 2004). Because migrating L_4 and L_5 larvae and/or ectopic adult worms would not have been detected by necropsy yet could still produce clinical signs and abnormal serological results, the true number of infected cats was probably underestimated. Moreover, cats that have recovered from heartworm infection may have persistent Ag and Ab present for several months. In spite of these acknowledged shortcomings, the study illustrated the limitations of heartworm serology in cats and that combining Ag and Ab tests results in improved detection of heartworm infection compared to using either test alone (but it also resulted in more false-positive results). In this study, antigen tests detected 79.3% to 86.2% of heartworm infections and were highly specific, whereas antibody tests detected 62.1% to 72.4% of heartworm infections with 1.4% to 19.1% false-positive results (compared to 0.3% to 2% for antigen tests). Because both L_5 larvae and adult worms are capable of causing clinical disease in the cat, both antibody and antigen tests are useful tools, and the probability of making appropriate diagnostic decisions improves when they are used together.

Thoracic radiography and/or echocardiography are the two most useful diagnostic tests after serology in feline patients exhibiting evidence of heartworm disease. Thoracic radiography is useful for diagnosis as well as continued monitoring in cases of feline heartworm disease. The degree of caudal lobar arterial disease is best assessed by the dorsoventral radiographic projection (Nelson et al. 2005). The caudal lobar arteries, especially the right, are the first to enlarge and typically are the most severely diseased (Figure 23.3). The diameters of the caudal lobar arteries should not exceed that of the ninth rib at the point of their superimposition. Cardiomegaly with right ventricular enlargement is less common in heartworm-infected cats compared to heartworm-infected dogs. Patchy focal or diffuse pulmonary parenchymal changes, in particular a bronchointerstitial pattern, are suggestive of (but not unique to) feline heartworm disease. Less commonly associated pulmonary findings include: hyperinflation of the lungs with flattening of the diaphragm, consolidated lung lobes, pneumonitis (Figure 23.4), pleural effusion, and/or pneumothorax (Nelson et al. 2005). The radiographic picture often resembles feline asthma. However, radiographic changes occur less frequently in feline heartworm disease than in canine heartworm disease and the absence of radiographic abnormalities does not exclude a diagnosis of feline heartworm disease. In fact,

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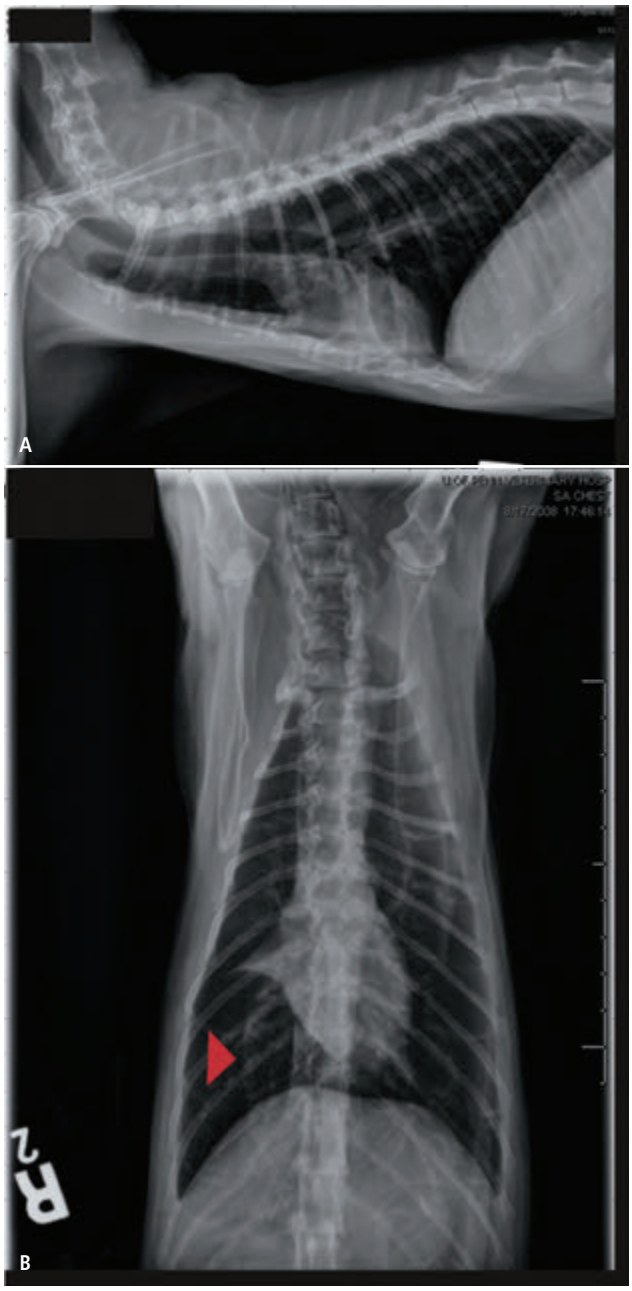


Figure 23.3. Left lateral **(A)** and ventrodorsal **(B)** radiographs from a heartworm positive cat. Note the diffuse bronchointerstitial pulmonary pattern and the prominent right caudal pulmonary artery (arrowhead). The cardiac silhouette is unremarkable.

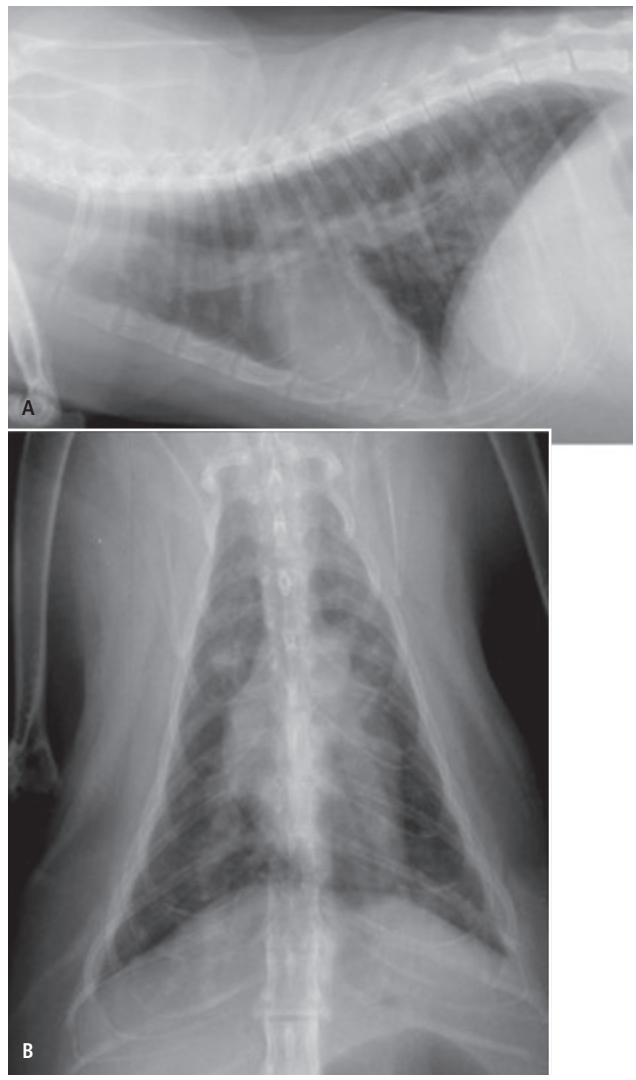


Figure 23.4. Thoracic radiographs (lateral and VD) from a cat presenting with an acute crisis and pneumonitis following adult worm death. Patchy interstitial infiltrates and severe pulmonary arterial enlargement are present.

radiographic changes consistent with heartworm disease are noted in only half of the cats suspected to have disease on physical examination (Atkins et al. 1998). In another study, only 55% of heartworm antigen-positive cats had radiographic signs consistent with heartworm disease (Nelson 2008b); another report showed normalization of peripheral pulmonary artery enlargement in experimentally exposed cats, in spite of active heartworm infection (Selcer et al. 1996). This finding was corroborated in a study that compared radiographic and serology findings with pulmonary histology in 120 shelter cats. The researchers demonstrated that radiographic pulmonary arterial lesions were heartworm stage-specific and inconsistent predictors of infection (Upchurch et al. 2010). Thus, radiographic findings in cats with heartworm disease are highly variable and dependent on the time postinfection when cats are presented.

Echocardiography is a particularly useful adjunctive test in cats in which there is a suspicion of heartworm disease despite negative Ag test results. One retrospective study reported that worms were visible echocardio-

graphically in 40% of heartworm positive cats, including 5 (of the 43 cats included) in which the Ag was negative (DeFrancesco et al. 2001). However, the sensitivity of echocardiography in these patients is highly operator-dependent and false positives are possible (Atwell et al. 2001; Atkins et al. 2008). Two-dimensional echocardiography allows interrogation of the right heart, the main pulmonary artery, and segments of the right and left pulmonary arteries. Methodical examination is important since cats have light infections and detection may be difficult. The worm cuticle is strongly echogenic and produces short segments of echogenic parallel lines on ultrasound imaging (Figure 23.5). From the right parasternal short-axis view at the heart base, the main pulmonary and central portions of the left and right main pulmonary arteries should be carefully evaluated for heartworms.

Eosinophilia and basophilia noted in the complete blood count are supportive findings, with eosinophilia being more common (in 63% and 10% of Ab-positive cats, respectively) (Dillon et al. 2000). However, in another study the eosiniphil and baosphil counts were not significantly different between cats with heartworm infection and cats unlikely to have disease (Atkins et al. 1998). Hyperglobulinemia may also occur in cats with chronic heartworm disease. Fecal testing for lungworms is useful to screen for lung parasites and to rule out this differential in the list of differential diagnoses for a cat presenting with clinical signs of lower airway disease (i.e., heartworm infection, feline-asthma, cardiomyopathy, bronchitis, pulmonary fibrosis, and lung parasites). A tracheal or bronchial wash may be useful for detecting lung parasitic lesions such as those produced by *Filaroides* spp. In heartworm-infected dogs, renal lesions associated with antigen-antibody glomerular deposition often lead to urine protein loss. Similarly, proteinuria occurs in experimental feline heartworm disease. However, it was detected only in cats with mature infections (1–10 adult worms) whereas none of the cats that resisted mature infection were microalbuminuric. Moreover it was more common in heavily infected, antigen-positive cats (Atkins et al. 2010).

The bottom line is that diagnosis of feline heartworm disease often requires multiple tests. The diagnosis is particularly difficult to confirm in the subset of cats that have mild disease. In these cats, immature worms may result in severe pulmonary damage, and yet be nearly impossible to diagnose because they are cleared prior to maturation (Browne et al. 2005). Since the antibody disappears quickly, the only remaining evidence of their presence may be pulmonary lesions which are virtually impossible to diagnose as having been caused by heartworm disease. The syndrome of vascular, airway, and

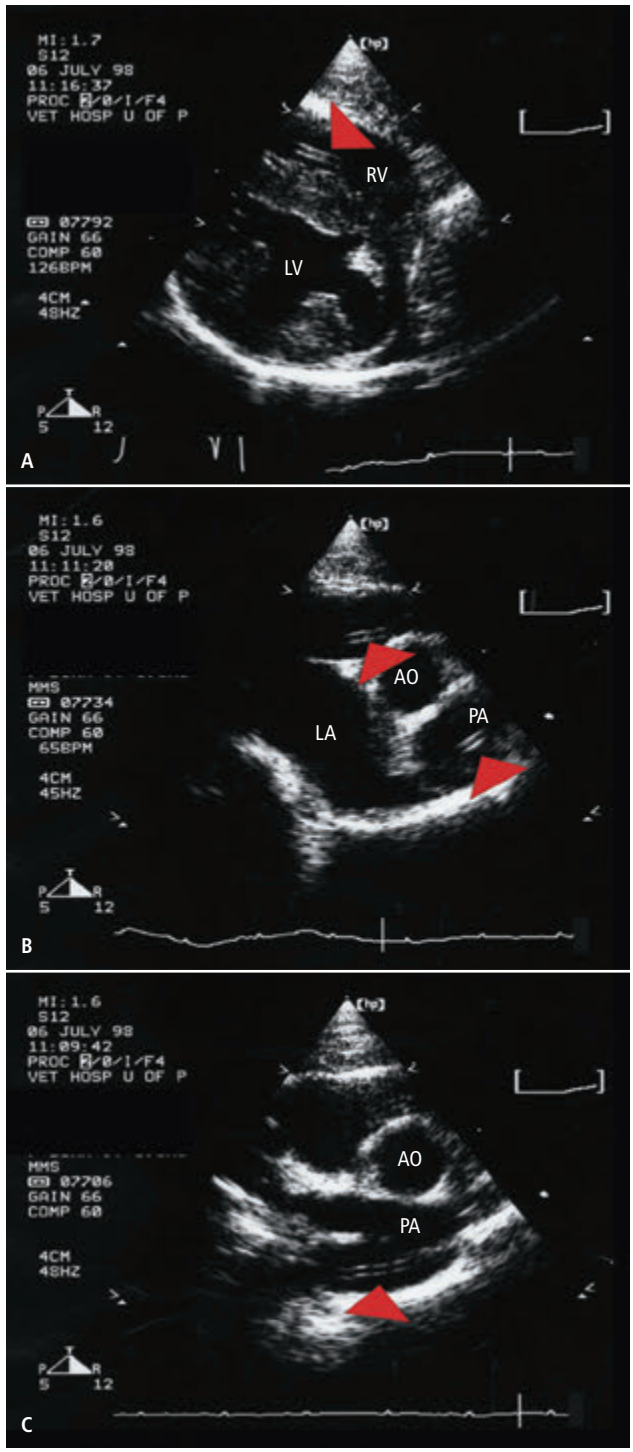


Figure 23.5. Right parasternal echocardiographic images obtained from a cat with heartworm disease. At least one worm is visible on echocardiography. **(A)** Image obtained at the ventricular level. **(B)** Image obtained at the heart base. **(C)** Image obtained at the bifurcation of the main pulmonary artery. In all images, the red arrowheads identify segments of adult heartworms, which appear as echogenic parallel lines. RV = right ventricle; LV = left ventricle; Ao = aorta; LA = left atrium; PA = pulmonary artery.

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interstitial lung lesions caused by the death of immature worms has been termed *HARD* (heartworm-associated respiratory disease) (Dillon 2007).

TREATMENT

Retrospective studies suggest that 10–20% of cats with adult heartworm infections die secondary to death of the worm (Nelson 2008b), but adulticide treatment itself is associated with significant risk in cats, as well. In addition to the toxicity and reported lack of efficacy of heartworm adulticide agents, killing of the heartworm(s) in a cat results in significant risk of fatal pulmonary thromboembolism and necrosis (McIntosh and Daniel 1999). For these reasons, and because the disease is often self limiting in cats, infected cats are usually managed with supportive treatment. Lifelong treatment for chronic bronchial disease may be necessary even after death of all heartworms in some cats due to residual, chronic pulmonary disease. Unfortunately, sudden death may still occur without premonitory signs until all adult worms have died. Some authors suggest providing the owner with injectable dexamethasone sodium phosphate so that the owner may administer it in a crisis (Nelson 2008b). Similarly a bronchodilator (i.e., injectable aminophylline, albuterol inhaler) may also be beneficial to dispense in case acute dyspnea occurs.

There is anecdotal evidence that antileukotrienes (i.e., montelukast, 2 mg/day) may prevent fatal lung injury when adult worms die, although thorough investigation of this drug and use has not been performed in the cat (Nelson 2008b). Similarly, it is possible that therapy with doxycycline will reduce lesions associated with eventual worm death (due to a reduction in *Wolbachia* antigens), but studies in cats are still lacking. These treatment options may be useful to consider at the time of diagnosis (prior to a crisis).

The following are general treatment recommendations for heartworm disease in cats:

- Treat asthmalike signs with prednisolone (2 mg/kg, daily for 10 days; gradually tapering to 0.5 mg/kg every other day by 2 weeks and discontinue in another 2 weeks). Repeat treatment as needed if recurrent clinical signs occur. Prednisolone is also warranted in cats without clinical signs if there is radiographic evidence of lung disease.
- Consider the addition of a bronchodilator if clinical signs persist despite anti-inflammatory treatment with corticosteroids (i.e., terbutaline, 0.625–1.25 mg/cat PO q 8–12 h; aminophylline, 4–6 mg/kg PO q 8–12 h; theophylline, 25 mg/kg PO q 24 h; albuterol sulfate inhaler, 1 actuation q 12 h).
- Canine data suggests that doxycycline treatment reduces damage associated with eventual worm death (due to a reduction in *Wolbachia* antigens). Although efficacy in cats remains unclear many clinicians recommend a course of doxycycline at the time of diagnosis.
- The monthly use of ivermectin at the prophylactic dose (24 mcg/kg) for 2 years has been reported to reduce worm burdens by 65% as compared to untreated cats (Nelson et al. 2005). Therefore, in cats suspected to have heartworm infection, prophylactic ivermectin therapy is recommended to both prevent superinfection and to slowly kill the current infection. However, the inflammatory response to worm death is likely to occur with ivermectin-treated worm death as well, and therefore owner education is important.

Acute crisis due to a dying worm(s) may require emergent therapy with supportive therapy for treating shock. Depending on the individual case, this may include

- Intravenous corticosteroids (dexamethasone sodium phosphate, up to 2.2 mg/kg IV or IM)
- Fluid therapy. The typical shock rate of crystalloid fluids is 60 ml/kg in cats; however, it is important to recognize that each animal is unique and will have a different response to fluid therapy. Generally, fluid therapy should be started at 1/3 to 1/4 of the calculated shock dose given rapidly. The patient should then be reassessed and fluid rate can be reduced if there is clinical improvement or continued at a high rate. Bronchodilator therapy is indicated (terbutaline, 0.01 mg/kg IV; or aminophylline, 4–6 mg/kg IV—inject slowly; or albuterol sulfate inhaler, 1 actuation). Intravenous medications would be preferable in a dyspneic cat; however, in a crisis the owner can administer albuterol with an inhaler while en route for emergency care.
- Oxygen supplementation
- Diuretics and nonsteroidal anti-inflammatory drugs such as aspirin are not recommended. Studies in cats with heartworm disease have shown only limited benefit to aspirin therapy at a dose that approached the feline toxic range (Rawlings 1990; Rawlings et al. 1990).

Use of injectable arsenicals has been associated with fatal thromboembolism or acute lung injury in cats, and is not recommended (Small et al. 2008). However, surgical removal of heartworms is feasible and effective in cats with echocardiographically visible worms in the right heart and/or main pulmonary arteries (when the

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worms are present in the distal pulmonary arteries, retrieval is much more difficult due to the complex three-dimension arborization of the distal arteries). Moreover, it makes theoretic sense that reducing worm biomass is preferential to adulticide therapy, particularly in cats that are predisposed to acute inflammatory reactions when worms die and degrade. Multiple worm retrieval approaches have been described in the literature and extraction of the worms often results in rapid and dramatic clinical improvement, including clinical signs secondary to right-sided congestive heart failure (Borgarelli et al. 1997; Atwell and Litster 2002; Small et al. 2008). While it is preferable to remove heartworms rather than destroy them in situ, damage to a worm during the retrieval process can result in shocklike signs and death (Nelson et al. 2005) and the clinician must take care to avoid damaging worms during the procedure. Additional challenges include the tenuous physiologic status of many of these patients (and associated anesthesia risk) and the small jugular size, which makes passage of the Ishihara flexible heartworm retrieval forceps difficult in small patients. Other devices that have been successfully implemented for retrieval include: basket-type retrieval forcepts (Borgarelli et al. 1997), nitinol gooseneck snare catheter (Small et al. 2008), horsehair brushes, endoscopic grasping forceps, and rigid alligator forceps (Litster et al. 2008).

MONITORING

Periodic monitoring at 6- to 12-month intervals with repeat Ag and Ab testing and thoracic radiography is warranted. After clearance of adult heartworms (iatrogenic or spontaneous), infected cats will usually become antigen negative within 4 or 5 months. However, it is important to review the results carefully for each individual case recognizing the inherent weaknesses of the available tests. The American Heartworm Society states that antibody testing becomes optional once the cat is antigen negative because antibody persists for an indefinite period after the worms are gone, and continued exposure (even when the cat is receiving preventative therapy) will result in a positive antibody test. Moreover, as already stated above, the performance of different brands of antibody tests is variable. At least regression of radiographic signs and seroconversion of a positive Ag test suggest the period of risk of an acute crisis following worm death and embolization is over. Follow-up CBC and/or echocardiography may lend further useful information in a small number of cases but rarely will alter therapeutic recommendations and are therefore not cost effective.

OUTCOME AND PROGNOSIS

In one field study, which followed 34 asymptomatic cats diagnosed with feline heartworm infection by antibody, antigen, and echocardiographic examination every 3 months until self-cure or death, over 80% of the cats self-cured and 21 of the 34 remained asymptomatic throughout the study. Six of the 34 cats (18%) died. Infections lasted over 3 years in most of the cats enrolled in the study (Venco et al. 2008). This study shows that a large proportion of heartworm-infected cats can survive the infection with supportive care. Moreover, many cats remain asymptomatic through the course of disease.

Prevention

Cat owners should be advised regarding the potential risk of heartworm infection in their community and the comparative ease of preventing the disease vs the difficulty of treatment. When monthly heartworm chemoprophylaxis is elected, it should be initiated at least 30 days following the estimated seasonal onset of transmission and continued for 30 days after that period has ended. Year-round administration has been recommended by some because 1) depending on the product chosen, the cat may also be protected from intestinal or external parasites; 2) studies suggest owner compliance is better; and 3) there is retroactive efficacy (reach-back) if doses are missed inadvertently. The reach–back effect covers the same age of heartworms as those killed under chemical prophylaxis (larvae 8 months postinfection and older) (McCall 2005). See Table 23.2 for a summarized comparison of the "reach-back" effect for the various preventatives. Currently four macrocytic lactone products are registered for feline heartworm chemoprophylaxis: ivermectin, moxidectin, milbemycin, and selamectin. All of these products are safe and effective options for cats living in areas where canine heartworm disease is considered endemic, and each is administered monthly. Ivermectin and milbemycin oxime are administered orally while moxidectin and selamectin are topical. All of these drugs can be safely administered in seropositive cats.

Ivermectin is an effective preventive drug with the most potent reach-back effect of the various prophylaxis options. This effect means that prolonged administration of the preventative can kill young larvae, older larvae, immature adults and/or older adult worms. This effect is particularly advantageous when the heartworm infection status is unknown at the time treatment is commenced or in cases of questionable owner compliance. A dose of 24 µg/kg administered monthly is an effective heartworm prophylaxis in cats, and it also controls hookworms. Milbemycin, at a dosage of 2 mg/kg,

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Table 23.2. Summary of reach-back effect of macrolytic lactones on *Dirofilaria immitis* (modified from McCall 2005)

Drug (%)	Age of Heartworms (Months)	# Treatments	Efficacy
Ivermectin	2	1	100
(6 mcg/kg, per os, monthly)	3	13	97.7
	4	14	95.1–97.8
	5	31	98.7
	5.5	12	52.2
	7	29	94.9
	8	16	56.3
Milbemycin	2	1	95.1
(500 mcg/kg, per os, monthly)	2	2	100
	3	13	96.7
	4	14	49.3
	4	12	41.4
	4.5	12	12.7
	5.5	12	1.1
	6.5	12	15.9
	8	16	0
Selamectin	2	1	100
(6 mg/kg, topically, monthly)	3	12	98.5
	Adult	18	39.0
Moxidectin	2	1	100
(0.5 mcg/kg, per os)			
Moxidectin	4	1	85.9
(0.17 mg/kg SC q 6 mo)	4/10	2	97.2
	6	1	25
	6/12/18	3	25

is an effective once-a-month preventive agent for heartworm disease in cats and it also controls roundworm infestations. It has the least reach-back effect of the macrocytic lactones. Selamectin (6–12 mg/kg) and moxidectin (1 mg/kg) are topical, once-a-month products, which lie somewhere between ivermectin and milbemycin in reach-back effect. These products are effective at controlling common fleas, ear mites, and roundworms in addition to heartworms.

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SECTION L

Comorbidities

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24

Comorbidities: Managing Cats That Have Coexistent Cardiac Disease and Extracardiac Disorders

Key Points

- Identification of acute, transient exacerbations of chronic conditions (cardiac, renal, or other), and differentiation of these from end-stage disease, are essential for accurate prognosis and treatment of cardiac and extracardiac disorders.
- The new onset of a gallop sound during intravenous fluid therapy in a hospitalized cat with heart disease should raise the concern of impending congestive heart failure, and fluid rate/type should be adjusted accordingly.
- Repositol glucocorticoid injections expand cats' plasma volume, possibly causing iatrogenic congestive heart failure if cats have pre-existing heart disease.
- Diuretic resistance may explain a persistence of congestive heart failure, and escalating dosages of diuretics should prompt an investigation for diuretic resistance, as well as a reassessment of the diagnosis of congestive heart failure if any uncertainty exists.
- Administration of diuretics and parenteral fluids simultaneously is self-defeating. The clinician should decide whether the patient needs more intravascular volume or less, and choose therapy accordingly (e.g., decrease diuretic dose rather than begin IV fluids).
- Triggers that may cause congestive heart failure in cats with previously compensated heart disease include acute salt ingestion (canned fish, other salty foods), overconsumption of commercial treats, repositol glucocorticoid injections, acute tachycardia-inducing events (general anesthesia, veterinary appointments), and parenteral fluids. Identifying such triggers is important because the long-term prognosis is likely better than when congestive heart failure occurs as a sole result of natural heart disease progression.

INTRODUCTION

In many feline patients, heart disease exists simultaneously with an extracardiac disorder and treatment of either one may be detrimental to the other. Common examples include disorders where fluid therapy may be required (e.g., chronic kidney disease, dehydration of any cause) or where glucocorticoids are the treatment of choice (e.g., inflammatory bowel disease, allergic airway disease, chronic dermatopathies). In both of these examples, the risk of precipitating congestive heart failure iatrogenically is a legitimate concern in the cat with coexisting heart disease. Another layer of this conundrum exists when treating congestive heart failure in a patient with concurrent illness where diuretic administration could be detrimental: what is the best way to manage a patient's heart failure without excessive impact on the extracardiac disorder? Perhaps the most common example of this dilemma is the cat with concurrent congestive heart failure and chronic kidney disease, where diuretic administration increases levels of blood urea nitrogen and creatinine to a level that raises concern, yet where the reduction or cessation of diuretics would trigger recurrence of pulmonary edema/pleural effusion. These difficult situations are discussed in this chapter, with recommendations and discussion of methods to find an appropriate balance between such commonly occurring, but often opposing, disorders.

Feline Cardiology, First Edition. Etienne Côté, Kristin A. MacDonald, Kathryn M. Meurs, Meg M. Sleeper.
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CONCURRENT HEART DISEASE AND KIDNEY DISEASE

The fundamental problem a clinician faces when managing a feline patient with both heart disease and kidney disease is one of vascular volume. Increasing a patient's circulating vascular volume, such as with administration of parenteral fluids, helps to maintain or increase glomerular filtration rate, but it also increases the risk of iatrogenically triggering congestive heart failure. Conversely, decreasing circulating volume, such as with administration of diuretics, is appropriate for eliminating fluid retention such as pulmonary edema, but doing so may exacerbate underlying kidney dysfunction.

In concert, coexisting heart disease and kidney disease can produce cumulatively detrimental effects (Schriffren et al. 2007; Sica 2006; Bonagura et al. 2006), and any or all of the following mechanisms may explain the observation that cats with hypertrophic cardiomyopathy are more likely to be azotemic than are normal cats (Gouni et al. 2008).

- Decreased renal perfusion due to renal afferent arteriolar constriction in heart disease
- Direct autonomic cardiac-renal interactions, where a decrease in distending volume of chronically distended atria may, via low-pressure cardiopulmonary baroreceptors, be perceived locally as "underfilling" and expressed through alterations in renal sympathetic tone (Weinfeld et al. 1999).
- Vasopressin/antidiuretic hormone release in advanced heart disease, contributing to intravascular volume overload
- Decreased renal perfusion in heart disease (due to decreased cardiac output, systemic hypotension, or hypovolemia secondary to diuretics), leading to sodium retention
- Systemic hypertension from chronic kidney disease increasing afterload and consequently end-systolic ventricular wall stress
- Tense ascites causing abdominal compartment syndrome, reducing renal perfusion
- Sympathetic and renin-angiotensin-aldosterone system activation as compensatory cardiac mechanisms worsening renal disease

Managing a patient with both disorders is challenging in the cat, in part due to restrictions imposed by small body stature and logistical/financial limitations in veterinary medicine. Optimal fluid or diuretic administration may be achieved in human beings through serial measurement of pulmonary capillary wedge pressure, for example, which helps guide the dose and frequency of diuretic or fluid administration (Gouni et al. 2008; Sharkey 1997). PCWP is a nearly exact measurement of pulmonary venous pressure, which is an important determinant of whether left-sided congestive heart failure (pulmonary edema and/or cardiogenic pleural effusion) occurs. The enormous clinical limitation that hinders PCWP measurement in the cat is the required placement of a Swan-Ganz catheter, which is large in diameter (e.g., 6 or 8 Fr) and challenging to place, although this can be done successfully in healthy, anesthetized cats (Lamont et al. 2001). Noninvasive surrogates for PCWP have been explored in other species, including Doppler echocardiographic estimates of left ventricular filling pressures (E/E') (Oyama et al. 2004; Schober et al. 2008a,b) but have not yet been validated for the cat. An alternative with limited uses is the measurement of central venous pressure (CVP) (Gouni et al. 2008; de Madron 2007). Placement of a jugular intravenous catheter is required for CVP measurement, which, with appropriate technical skill, is feasible in most cats barring severe dyspnea (Petrollini and Drobatz 2007). Measuring CVP provides information on the likelihood of right-sided congestive heart failure: CVP reflects the pressure of blood reaching the right ventricle (right ventricular end-diastolic pressure, barring tricuspid stenosis) and therefore the propensity for transudation of fluid through the walls of the systemic veins. The pulmonary capillary bed's action as pressure diffuser means that CVP cannot reliably identify increases in pulmonary venous pressure or the likelihood of left-sided congestive heart failure, yet a majority of heart diseases in cats are predominantly or exclusively left-sided. Therefore, jugular catheter placement and serial CVP measurements should be considered for optimal fluid therapy titration in hospitalized cats with echocardiographically confirmed heart disease that is predominantly or exclusively right-sided (uncommon). Normal CVP in the cat is 4.2 ± 1.1 mm Hg (Lamont et al. 2001). In cats, pleural effusion (of any origin) increases the CVP independent of right heart filling pressures (Gookin and Atkins 1999), and this important confounder is discussed below (see "Cardiac Disease and Unrelated Pleural Effusion").

Certain basic principles are essential for the optimal management of patients with concurrent cardiac and renal disorders. These principles include the following:

- Which disorder is predominant?
- Chronic versus acute decompensation
- Identification and management of contributing/additional factors
- Monitoring and treatment adjustments

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Which Disorder Is Predominant?

In a cat with concurrent heart disease (e.g., cardiomyopathy) and renal disease (e.g., chronic kidney disease), the initial approach depends on which one of the two disorders is the predominant clinical concern. Generally, patients are presented for management of decompensation of one disorder at a time. Two common scenarios are the patient with acute congestive heart failure whose renal function has previously been known to be compromised (cardiac dominant), and the patient with overt signs of kidney failure who has previously been documented to have asymptomatic heart disease (renal dominant). In these situations, treatment decisions should be strongly influenced by the history and physical examination. A patient presenting with overt signs of congestive heart failure, such as dyspnea, requires treatment for the dyspnea including diuretics for pulmonary edema or thoracocentesis for large-volume pleural effusion, regardless of renal values on a serum biochemistry profile. Conversely, a patient presenting with overt signs of renal failure such as anorexia, lethargy, signs of dehydration, halitosis, and uremic oral ulcers, requires intravenous fluid therapy regardless of abnormal echocardiographic measurements. It is very uncommon for a patient to present for the first time with concurrent spontaneous decompensation of both renal and cardiac abnormalities. That is, the cat with simultaneous dyspnea from pulmonary edema/cardiogenic pleural effusion and systemic signs of end-stage kidney failure is far less common than the cat with one of the two dysfunctions predominating, which allows the clinician to decide whether to implement treatments that judiciously increase, or decrease, intravascular volume. When both body systems decompensate simultaneously in the absence of any modifiable or correctable factors, the context is almost always a patient that has had an ongoing history of treatment for failure of one of the two body systems for some time (typically months to years). Therefore, the coexistence of concurrent heart and kidney disease with one of the two predominating is more common, and it warrants a guarded, but not poor, long-term prognosis because other aspects of the case can offer therapeutic opportunities (see below).

Another situation often occurs in practice: cats are presented much earlier in the disease processes, and the clinician must manage both kidney and cardiac problems when neither one is clinically overt. An example is the asymptomatic cat with hypertrophic cardiomyopathy identified based on an incidentally ausculted heart murmur and chronic kidney disease identified during routine abdominal palpation (small kidneys) and/or laboratory tests performed as part of preemptive or annual screening (concurrent isosthenuria and mild azotemia). When a cat shows no overt clinical signs referable to either the heart problem or the kidney problem, treatment of either one, or both, can be pursued as indicated in the absence of the other disorder. That is, prophylactic treatment of the kidney or heart disorder is administered as deemed appropriate for the isolated disorder irrespective of the other. Typically, such treatments could include beta blockade for hypertrophic obstructive cardiomyopathy and a protein-optimized diet for chronic kidney disease, for example. Although fluid therapy may be prescribed to be administered at home, subcutaneous fluids, like intravenous fluids, increase circulating blood volume and constitute an unproven but anecdotally well-recognized risk factor for iatrogenic congestive heart failure.

Occult/"early" chronic kidney disease in cats with isosthenuria is classified as International Renal Interest Society (IRIS) stage 1, where serum creatinine <1.6 mg/dl (<140 umol/l), or stage 2, where serum creatinine = 1.6 – 2.8 mg/dl (140–246 umol/l) (Polzin 2010). In both categories, the disease is usually found incidentally because no overt signs of uremia are apparent. Prophylactic subcutaneous fluid therapy for cats with IRIS stage 1 and 2 CKD is not universally accepted. Even in the absence of heart disease, the sodium load administered via such balanced electrolyte solutions as lactated Ringer's or 0.9% sodium chloride may be detrimental to the kidneys (Weir and Fink 2005). The intravenous route of fluid administration used in-hospital allows careful titration of fluid rate and modification of fluid type, as needed, but such changes are impractical in the home setting of subcutaneous fluid administration. Oral fluid supplementation for cats with chronic kidney disease may be considered, and an essential—but easily overlooked—approach is to instruct the cat's owner to ensure that the cat with kidney disease has copious, fresh drinking water available through sources that are attractive to a cat, including cat water fountains or slowly dripping faucets that allow the cat to consume moving water, in addition to water provided in bowls and changed at least daily. Some have advocated administration of water by syringe or via feeding tube to maintain the hydration of cats with CKD at home (Polzin 2010). Such an approach requires excellent tolerance on the part of both owner and patient and may be considered on an individual case basis. In summary, since no evidence exists that identifies a benefit of subcutaneous fluid administration at home in cats with IRIS stage 1 or 2 chronic kidney disease, such therapy should only be prescribed for these cats (with concurrent asymptomatic heart disease not requiring diuretics) in the following instances: the owner observes a clear-cut clinical improvement with treatment in the individual cat; the owner is aware and

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accepting of the importance of monitoring for signs of congestive heart failure should the patient's threshold for intravascular volume expansion be exceeded; and both the owner and the cat are tolerant of the treatments. Although 75–100 ml/cat can typically be administered q 24–72 hours (Polzin 2010) in cats that have chronic kidney disease but normal hearts, a more conservative volume is typically chosen when heart disease is present concurrently. For example, 50–75 ml can be administered q 24–48h if azotemia is substantial (e.g., serum creatinine >2.5 mg/dl [220 umol/l]), or q 48–72h if azotemia is less severe. With IRIS stage 3 (serum creatinine = 2.9 – 5 mg/dl [255–440 umol/l], clinical signs usually present) and stage 4 (serum creatinine >5 mg/dl [>440 umol/l], clinical signs essentially always present), subcutaneous fluid therapy administered at home may produce clinical improvements that are more substantial. Therefore, the benefit-to-risk ratio in such cases tilts further toward home fluid therapy. Such cats should not be receiving diuretics for heart disease, or if they are, the diuretic or the parenteral fluid administration should be discontinued (depending on whether the kidney or heart disorder is producing the most severe clinical signs, respectively) and the other treatment decreased accordingly, because diuretics and parenteral fluids are mutually antagonistic (see below). With advanced kidney disease patients, the administration of subcutaneous fluids is a palliative measure that is undertaken only when signs of overt illness are present and is pursued only if an appreciable improvement in the cat's quality of life is noted by owners as a result. In all cases, it is essential to discuss the divergence of renal and cardiac pathophysiology, and signs of decompensation of either one, with the owner and to obtain owner consent for instituting such treatment.

Chronic versus Acute Decompensation

Patients who present in an acute crisis (congestive heart failure or acute renal failure) may require in-hospital treatment for days, and the magnitude of treatment is substantially different than that of outpatient treatment once the patient is discharged. This important distinction means, for example, that much higher dosages of diuretics may be used in-hospital for 1 or 2 days, despite azotemia, if such dosages allow the patient to survive and recover rapidly from congestive heart failure. Similarly, a cardiac patient with acute worsening of chronic kidney disease may benefit from a short (24–48 hours) discontinuation of diuretics and/or a course of intravenous fluid therapy to restore hydration and in turn improve demeanor and appetite, even though such treatment would not be continued long-term. The use of these strategies requires ongoing monitoring to identify early signs of decompensation (overshooting) and identification of concurrent or complicating factors.

Specific management strategies for acute decompensation of cardiac or renal disease in a patient with disorders of both systems include the following (see also Table 24.1):

- Identify and address reversible causes (CHF: e.g., recent sodium-rich dietary indiscretion, glucocorticoid administration; uremia: e.g., pyelonephritis). Occasionally in cats with acute congestive heart failure, the underlying cardiac lesion is noted to be minimally worse, if at all, compared to the previous evaluation, especially echocardiographically. In such instances it is important to ask the owner about the possibility of acute precipitating factors such as acute salt ingestion, a stressful tachycardic event such as inter-cat conflict or being chased, or recent repositol corticosteroid administration. Inquiring whether a treat was given by a relative or friend, a food scrap or other indiscretion was found by the cat, or an extra meal was given by a neighbor, may identify a basis for a sudden but transient increase in intravascular volume due to ingestion of greater-than-normal quantities of sodium. Failure to investigate this aspect of the patient's history leads to the conclusion that heart failure was caused by worsening of the disease, and the clinician's response likely is to prescribe a higher dosage of diuretics indefinitely, rather than for only 48–72 hours to offset the sodium/fluid excess caused by the dietary indiscretion. Doing so would clearly not be in a cat's interest if he/she has concurrent renal disease. The worsened prognosis conveyed in this context is also not justified when heart failure was a temporary, sodium ingestion-related aberration.
- With uremia, identifying acute-on-chronic processes such as low-grade pyelonephritis is important. Pyelonephritis can produce few or no overt clinical signs and may not produce an active urine sediment; urine culture is warranted periodically (e.g., q 4–12 months) in cats with chronic kidney disease because identifying a bacterial infection offers the possibility of successful treatment and improvement in renal function. The alternative, if pyelonephritis is missed, can be deteriorating renal function and the need for additional therapies such as parenteral fluids, which would preferably be avoided if possible in any cat, particularly one with concurrent heart disease.
- Assess patient for onset of gallop heart sound during fluid therapy, suggesting iatrogenic CHF. Use IV fluid type that matches needs (e.g., no replacement fluids like lactated Ringer's solution/0.9% NaCl when patient is euvolemic [well-hydrated], but rather use maintenance fluids such as 0.45% NaCl in 2.5% dextrose). The importance of these concepts is

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explained further in the section on fluid therapy, below, and in Chapter 1.

- Manage coexistent electrolyte abnormalities, especially hypokalemia. Serum potassium levels should be measured from blood drawn into a green-top (lithium heparin) tube. Plain red-top vacuum tubes allow blood clotting, a process that releases potassium from activated platelets (Sevastos et al. 2008). Therefore, hypokalemia may be masked by this in vitro artifact (Sevastos et al. 2008). When hypokalemia is confirmed, treatment to correct it (e.g., with supplementation when the patient is receiving intravenous fluids) is important on two counts. First, hypokalemia causes skeletal muscle weakness, and may decrease appetite and general demeanor (DiBartola and de Morais 2006). All of these abnormalities can confer a negative prognosis to an owner and lead to an early decision for euthanasia. Second, normal serum potassium levels are necessary for the functioning of cellular sodium channels on which many intravenously administered antiarrhytmics, such as lidocaine and procainamide, act (Singh and Williams 1971). In hypokalemia, these drugs can be ineffective (DiBartola and de Morais 2006; Singh and Williams 1971). Since hypokalemia itself also increases the tendency to ventricular tachyarrhythmias, a synergistic negative sequence can easily occur where ventricular arrhythmias are more likely to occur and intravenous treatment is administered repeatedly in an attempt to convert the arrhythmia to normal sinus rhythm but is ineffective. Since hypokalemia abolishes only the antiarrhythmic effect, but not the neurotoxic effects of these drugs, patients whose hypokalemia escapes detection may develop ataxia and seizures iatrogenically as the clinician continues to administer increasing doses of antiarrhythmics that have reduced efficacy in patients with low serum potassium concentrations.
- Consider diuretic constant rate infusion instead of intermittent injections for superior natriuresis. In dogs, and likely in cats, calculating the total daily projected dosage of furosemide and administering it via syringe pump as a constant rate infusion produces superior diuresis (significantly more urine produced) than boluses (Adin et al. 2003).
- Change medications to injectable form (e.g., diuretic) while managing the crisis in-hospital, and temporarily (i.e., for 24 hours) suspend administration of oral medications with benefits that are long-term only, not short-term (e.g., oral ACE inhibitors, beta blockers, calcium channel blockers, and most drugs used for treating chronic kidney disease).
- Confirm suspicions. Is dyspnea from congestive heart failure? Thoracic radiographs are indicated regardless of pulmonary crackles or intensity of murmur. Radiographic results may be normal (e.g., pulmonary thromboembolism in patient with nephrotic syndrome), may confirm pulmonary edema, may identify large-volume pleural effusion rather than pulmonary edema (which can be immediately removed by centesis, reducing or avoiding acute doses of diuretics), or may reveal a third disorder such as airway disease as the cause of dyspnea.
- If radiographic findings are uncertain, have radiographs interpreted by radiologist/cardiologist. Both false-positive and false-negative results are common for pulmonary edema, cardiomegaly, and other relevant cardiovascular interpretations.
- In addition to characterizing the type of underlying heart disease, an echocardiogram may be useful simply to determine the likelihood of congestive heart failure in questionable cases. For example, if the left atrial size is normal, and there is no precipitating acute factor, then left-sided congestive heart failure is very unlikely.
- Removal of large-volume body cavity effusions in acute states: centesis is superior to diuretics for acute stabilization and efficacy, and based on human studies of cirrhotic ascites, centesis carries less potential for adverse effects (Ginès and Arroyo 1993). With centesis, the diuretic dose can be minimized since the patient has been acutely stabilized via fluid removal.

Chronic management strategies for cats with coexisting cardiac and renal problems can include the following:

- Verify client compliance with drug administration—both client diligence and patient cooperation. This is often overlooked, and a common mistaken impression when heart failure has recurred is that the dosage of diuretics must be inadequate. If the medication is not reaching the cat, the incorrect assumption is that the heart disease must be worsening, and the diuretic dosage is then increased. Over time, if compliance remains poor, the very high diuretic dosages lead to a belief that no higher a dosage may be given without severe risk of renal or electrolyte disturbances, and the client may decide to have the cat euthanized under such circumstances. Instead, if poor compliance is recognized as a problem, alternative medication strategies may be used. Specific points to address with the client include consistency of administration, monitoring for the cat's deglutition after a tablet is administered, and administration of tablets with a food treat or bolus of water to reduce the risk of midesophageal entrapment (German et al. 2005). Hollow treats ("Pill Pockets") are one way of disguising medication and many cats enjoy eating these. Having medications

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compounded into liquid form, with meat or fish flavors that many cats like, is another popular option. Transdermal preparations, on the other hand, have not proven to be reliable with cardiovascular drugs and are not recommended (MacGregor et al. 2005).

- Identify diuretic resistance.
  - Measure urine specific gravity, which should be <1.030 in any cat receiving diuretics. If it is ≥1.030, the diuretic effect is likely incomplete or absent. Discussion with the owner about compliance is then warranted, and if compliance is good, the possibility of the tablet not reaching the stomach should be considered and addressed with having the owner give a morsel of tasty food, or a 5 cc bolus of tap water by syringe, after diuretic administration. If this aspect of medication administration is satisfactory as well, then diuretic resistance may be present, and adding a second diuretic such as hydrochlorothiazide or torsemide (Uechi et al. 2003) may be beneficial (see Chapters 19 and 29).
- Identify systemic hypertension and treat if present and if attributed only to renal disease (i.e., rule out the "white coat effect" and obtain an accurate diagnosis of systemic hypertension, see Chapter 21). Uncontrolled systemic hypertension may lead to worsening renal lesions and further concentric left ventricular hypertrophy, which is undesirable, particularly if the cat's underlying heart disease is hypertrophic cardiomyopathy (see Chapter 21).
- With good client comprehension, taper diuretic to lowest effective dosage. This delicate balance mimics the titration that human congestive heart failure patients may undergo in order to achieve optimal drug dosage. A fundamental requirement is an astute owner who understands that gradually reducing diuretics carries risks and benefits. A reduction of 10–20% in diuretic dosage, no sooner than 2 weeks apart, and to as little as 1 mg/kg furosemide PO q 24h in cats with congestive heart failure caused by mild structural heart changes (e.g., moderate atrial enlargement), helps reduce prerenal azotemia and serum electrolyte changes; it also risks the recurrence of congestive heart failure. Thus, this measure can be considered when the cat is stable, comfortable, has a normal resting respiratory rate and effort, and appears overtly normal at home in the owner's opinion. It is preferably done in conjunction with transition to a low-sodium diet so that the reduced sodium intake requires a lesser quantity of sodium needed to be excreted through diuretic-induced natriuresis. During the tapering process, the owner can record daily or twice daily resting respiratory rate (should be <30/minute) and respiratory effort, which can be reviewed by phone consultation with the veterinarian or technician. This approach helps to identify congestive heart failure early if it recurs. When it does not recur, the patient is in an optimal situation: benefiting from being free of signs of congestion while also receiving lower dosages of diuretics and thus, a lower risk of adverse effects.
- For patients with a history of congestive heart failure, minimize diuretic need through low-sodium diets. These may be commercially prepared (e.g., Purina CV) or home-cooked provided the home cooking follows a recipe formulated by a veterinarian who is board certified in gastroenterology or nutrition (e.g., www.balanceit.com, www.petdiets.com, professional textbooks (Strombeck 1999; Hand et al. 2000)). Diets formulated for chronic kidney disease may be considered because they also are sodium-restricted and, in contrast to canine renal diets, renal diets for cats are generally not severely protein-restricted (Freeman et al. 1997). The protein content of a feline diet should contain a minimum of 6.5 g/100 kcal (Freeman et al. 1997). As a basic principle, sodium-restricted diets are only initiated gradually (the owner weans the cat onto the lower sodium diet over several days to weeks) and never at the expense of appetite. If the cat refuses to eat the low-sodium diet, then a different diet should be tried. Some cats find a low-sodium diet to be more palatable if it has been supplemented with a sprinkling of potassium chloride (e.g., "No Salt" salt substitute; 100% potassium chloride available in many supermarkets), but other cats dislike this taste.
- Differentiate between advanced chronic kidney disease and an acute-on-chronic process: anemia, hyperphosphatemia, and small kidneys (exceptions: polycystic kidney disease, lymphoma cause renomegaly) suggest chronic kidney disease. Their absence offers the possibility of an acute, potentially reversible superimposition on the chronic process, and therefore the potential to regain renal function with treatment of the acute disorder (e.g., pyelonephritis).
- Manage anemia (in cats, PCV <20%). With chronic kidney disease, anemia can arise due to chronic illness, erythropoietin deficiency, uremic gastrointestinal blood loss, or a combination of these factors. Correction of anemia when concurrent heart disease is present results in a lower risk of cardiac arrhythmias and improved tissue delivery of oxygen.
- Removal of large-volume, recurrent body cavity effusions in chronic states: periodic centesis/drainage may be superior to higher-dose diuretics for both efficacy and lesser degree of adverse effect. The limitation of frequency is dictated by client means (ability to return to the hospital, financial cost) and the cat's tolerance of the procedure. In some cats this approach provides

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an excellent quality of life for a year or more when performed as needed (up to biweekly or weekly if necessary), whereas for others repeated centesis is undesirable and declined by the owner.

- Avoid administering diuretics and intravenous or subcutaneous fluids simultaneously. Giving diuretics and parenteral fluids together is a common and easily made error. The reasoning appears to be aimed at decreasing diuretic-induced prerenal azotemia via fluid administration, or conversely, decreasing the risk of parenteral fluid-associated iatrogenic congestive heart failure by giving diuretics. The reasoning in both contexts is flawed: all commonly used diuretics (furosemide, thiazides, torsemide, spironolactone, etc.) act by increasing renal loss of electrolytes and water, while injectable crystalloid fluids consist mainly of electrolytes and water. The administration of both together serves the same purpose as administering a drug and its reversal agent at the same time. A more logical approach consists of reducing the dosage of one and not giving the other. Therefore, a patient receiving diuretics and requiring "protection" from prerenal azotemia does not need fluids simultaneously, but rather a lower dosage of diuretics. Similarly, a patient receiving parenteral fluids where a concern exists for intravascular volume overload should not receive both fluids and a low dose of diuretics, but simply a lower dosage of parenteral fluids. If such an approach is felt to be very likely to result in decompensation of the dominant problem (cardiac or renal), then the clinician should review the case with particular attention paid to the concurrent or associated factors listed in this chapter (Table 24.1) that could be corrected and thus reduce the need for diuretics or parenteral fluids. Two exceptions exist to the rule that diuretics and fluids should not be given together: fluids and diuretics may be coadministered if the fluids are a vehicle for other therapies (e.g., constant-rate infusion of potassium chloride in a severely hypokalemic cat, using low volume of fluids such as 1/4 to 1/6 maintenance rates), or if a patient has been dramatically overtreated and the effects of treatment need to be reversed. In the latter case, such as overzealous fluid administration warranting diuretic treatment, or overzealous diuretic administration warranting fluid therapy, both diuretics and fluids may be administered concurrently for a period of 12–24 hours, after which the treatment is adjusted and only one of the two continues to be given.

When a cat's serum creatinine and blood urea nitrogen concentrations increase over time in conjunction with higher diuretic dosages needed to control congestive heart failure, the clinician may justifiably give a more guarded prognosis. Ultimately, end-stage kidney and heart disease do occur simultaneously because in so many cases the underlying diseases are irreversible and progressive. However, such an outcome usually occurs only months to years after the initial diagnosis of the two disorders, and before giving a patient a guarded or poor prognosis, it is the clinician's responsibility to identify and correct complicating factors (see Table 24.1) to the fullest reasonable extent allowed by the client and patient.

CARDIAC DISEASE AND IDIOPATHIC CYSTITIS/ FELINE LOWER URINARY TRACT SIGNS

Although there is no known association between heart disease and lower urinary tract signs/disease (FLUTS) in cats, treatment of either disorder has been postulated to

Table 24.1. Complicating or concurrent factors to consider when managing cardiac and renal disorders simultaneously in a feline patient

Acute Management	Chronic Management
Identify and address reversible causes (sodium ingestion, glucocorticoids, acute tachycardia; pyelonephritis)	Verify client compliance: administering the medication
Assess for onset of gallop heart sound during fluid therapy	Verify patient compliance: accepting the medication
Identify and correct hypokalemia	Identify diuretic resistance: measure urine specific gravity
Diuretic as constant-rate IV infusion instead of boluses	Identify and treat systemic hypertension
Confirm diagnostic uncertainty, especially radiographic diagnosis of pulmonary edema	Decrease diuretic dosage to lowest effective level
Identify normal echocardiographic atrial size, lowering likelihood of congestive heart failure	Avoid dietary sodium excess and consider sodium-restricted diet
Centesis/drainage for large-volume body cavity effusions	Differentiate between advanced/end-stage disease and acute-on-chronic disease
Avoid administering parenteral fluids and diuretics simultaneously	Correct anemia if present
	Correct hypokalemia/hypomagnesemia, if present
	Periodic centesis/drainage for large-volume body cavity effusions
	Avoid administering parenteral fluids and diuretics simultaneously

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have impacts on the other. Specifically, diets for cats with lower urinary tract disease have historically been formulated to contain limited quantities of magnesium. Based on the experimental cardiomyopathies produced by hypomagnesemia in rats and dogs (Freeman et al. 1997), and the hypomagnesemia that can occur either with urinary acidification or with diuretic usage (Freeman et al. 1997), an association has been suggested between hypomagnesemia and feline heart disease. This association has been investigated and was not supported. Retrospective analysis has identified that a majority of cats (40/45, 89% in one study) (Freeman et al. 1997) with HCM are fed a low-magnesium diet, perhaps similar to the cat population at large. Yet a study comparing 10 cats with HCM to 10 healthy control cats demonstrated no difference in serum creatinine concentration, serum magnesium concentration, or urinary magnesium excretion, suggesting that in the cat, HCM is not associated with an alteration in magnesium balance (Freeman et al. 1997). Another study identified no benefit to magnesium supplementation: 15 cats with HCM who received placebo PO q 24h for 12 weeks showed no difference in magnesium status or echocardiographic parameters compared to 15 cats that received 210 mg MgCl (providing 25 mg elemental Mg) PO q 24 for 12 weeks (Freeman et al. 1997). Based on this limited but objective evidence, magnesium-restricted diets appear to be fed routinely to cats with heart disease without deleterious cardiovascular effects. Routine supplementation with dietary magnesium, or avoidance of magnesium-restricted diets when managing cats with concurrent heart disease and lower urinary tract disease, appears unjustified.

One of the cornerstones of preventing recurrence of feline lower urinary tract disease is the maintenance of a dilute urine (Westropp and Buffington 2010). Urinary dilution is theorized to be beneficial by decreasing the concentration of solutes (which could otherwise precipitate and allow formation of a urethral plug and/or uroliths), increasing the frequency of elimination and reducing the concentration of caustic substances in contact with the bladder mucosa. One time-honored method adopted for this effect has been to increase a food's sodium content in order to trigger thirst and greater water consumption. Because this sequence occurs via an increase in circulating blood volume, such an approach would not be recommended for a cat with concurrent heart disease. Modern diets designed and marketed for urolith prevention are variable in their sodium content compared to the equivalent maintenance diet (Table 24.2). For example, a diet designed to reduce the risk of urolith formation, Purina UR Urinary St/Ox Feline dry kibble, contains 1.17% sodium on a dry matter basis (DMB), while a nonprescription diet with similar indications, Purina ProPlan Urinary Tract Health Formula feline kibble, contains 0.26% sodium DMB; the latter compares favorably with 0.20% sodium DMB in the same company's feline cardiovascular diet kibble (Purina CV) whereas the former compares poorly (Purina Guide 2010). A typical maintenance diet (e.g., Purina ProPlan Chicken & Rice or Salmon & Rice feline kibble) contains 0.53–0.81% sodium DMB. Finally, feline diets also vary in sodium content when the canned formulation is compared to the dry kibble formulation. For example, the canned formulation of Purina UR Urinary St/Ox Feline diet contains approximately half as much sodium (0.62%) on a DMB as its kibble counterpart (1.17%), whereas canned formulations with gravy often have the reverse profile: Purina ProPlan Salmon & Rice Entrée contains 1.47% sodium DMB compared to

Table 24.2. Sodium content of diets designed for cats with recurrent lower urinary tract signs

Diet—Dry Kibble	[Na] DMB	Diet—Wet Canned	[Na] DMB
Hills c/d multicare	0.35%	Hills c/d multicare—seafood	0.33%
Hills c/d multicare—chicken	0.33%	Hills c/d multicare—chicken	0.32%
Hills s/d	0.40%	Hills s/d	0.37%
Iams low pH/S	0.49%	Iams low pH/S	0.43%
Iams mod pH/O	0.49%	Iams mod pH/O	0.43%
Purina UR St/Ox	1.17%	Purina UR St/Ox	0.62%
Waltham S/O control pH	1.4%	Waltham S/O control pH	1.05%

DMB = dry matter basis.
Sources: Purina Veterinary Diets: Purina Veterinary Product Guide, VET 0866H-0110; January 2010; www.walthamusa.com/newDiets.html; www.hillspet.com/products.html; www.iams.com. Websites accessed 6/23/10. Additional information provided courtesy of Dr. Sarah Miller, Cube Route Pty (Ltd).

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0.81% for the dry kibble formulation (Purina Guide 2010). Therefore, the clinician treating a cat that has both lower urinary tract disease and heart disease should recommend a specific diet that is suitably sodium balanced: mild or no sodium restriction is likely appropriate for cats with mild cardiovascular changes (e.g., no overt signs of heart failure, no diuretic treatment needed, no atrial enlargement, and normal arterial blood pressure) whereas moderate or marked sodium restriction should be considered for cats with advanced heart disease, particularly if they have experienced congestive heart failure and are receiving diuretics (Table 24.2).

CARDIAC DISEASE AND FELINE ASTHMA

Glucocorticoids have beneficial effects for inflammatory disorders such as feline lower airway disease (asthma) and are recommended as a mainstay of treatment when environmental modification alone is insufficient to control respiratory signs (Reneiro 2011). However, glucocorticoids are also recognized to have deleterious effects in cats with cardiac disease. Specifically, an association between glucocorticoid administration and the subsequent onset of congestive heart failure has been documented in some cats with heart disease (Smith et al. 2002). In this retrospective study of 29 cats, most (19/29, 68%) had echocardiographically identified left ventricular concentric hypertrophy (i.e. increased ventricular wall or septal thickness). Interestingly, follow-up echocardiography in 11 cats identified resolution of the ventricular hypertrophy in most (9/11; 82%) cases, suggesting pseudohypertrophy or a transient cause of ventricular hypertrophy. Most cats (22/29, 76%) had received long-acting repositol injections such as methylprednisolone acetate (Depo-Medrol) or triamcinolone acetonide, but 8 had received oral forms (prednisone, $n = 7$; methylprednisolone, $n = 1$; some cats received both injectable and oral forms). Generally, the injectable forms were associated with congestive heart failure signs much sooner after administration (mean = 4.4 ± 2.7 days) in contrast to the onset of signs after beginning oral administration (mean = 34.4 ± 30.7 days). The prognosis for survival was markedly, and favorably, influenced by glucocorticoid administration: compared to cats with spontaneously occurring congestive heart failure and no recent glucocorticoid administration history (median survival time = 65 days), cats with congestive heart failure that was associated with glucocorticoid administration had a median survival time of 439 days ($p = 0.0006$). These findings suggest that glucocorticoids can trigger congestive heart failure in cats with clinically silent/occult heart disease, and that recovery from the acute episode can lead to a better-than-expected prognosis in feline congestive heart failure. While several mechanisms could explain this phenomenon (Tobias et al. 2005), subsequent data identified hyperglycemia-associated hypervolemia as the most likely pathway (Ployngam et al. 2006). In a study of 12 cats given a standard injection (5 mg/kg IM) of methylprednisolone acetate, blood glucose levels rose from a mean of 136 ± 46 mg/dl to 187 ± 51 mg/dl ($p = 0.002$) (Ployngam et al. 2006). These cats' plasma volumes also increased (median 13%; up to 49% in one cat) 3–6 days after injection, but simultaneously calculated total body water content was unchanged or slightly lower. This interesting series of findings suggests that methylprednisolone injections cause a substantial shift in body fluid from the extravascular space (interstitium, intracellular) into the vascular space, likely as an osmotic shift due to hyperglycemia triggered by the corticosteroid (Ployngam et al. 2006). The clinical implications are that cats' responses to glucocorticoid administration are highly variable, that in some cats glucocorticoids may cause an excessive volume expansion that leads to congestive heart failure whereas other cats may tolerate a similar treatment, and that oral glucocorticoids may produce such events later after initiation of treatment than repositol injections.

There are several alternatives to oral or injectable glucocorticoids for cats with asthma. The most commonly used include inhaled beta-agonists (e.g., albuterol, terbutaline) and inhaled glucocorticoids (e.g., fluticasone) (Padrid 2008). These beta-agonists are beta-2 receptor selective and thus have minimal or no cardiac effect in aerosol form. There may be a crossover effect and some degree of beta-1 agonism with terbutaline (and other beta-2 agonists) when administered orally or by injection, likely as a function of dosage given, interindividual variation (such as beta-receptor polymorphisms observed in the cat) (Maran et al. 2010) and other factors. Fluticasone, similarly, does not undergo appreciable systemic absorption when administered by aerosol, and systemic glucocorticoid effects such as those described above are not expected. Recommendations typically include initiation with parenteral (short-acting injectable, or oral) glucocorticoids for a few days to one week, to allow systemic drug levels to reach the airways, followed by transition to aerosol administration (fluticasone one 110 mcg actuation ["puff"]/cat q 12–24 h PRN; 44 mcg actuations may be sufficient for some cats) (Reneiro 2011). In the acute setting, aerosol delivery is discouraged because the drug may not reach the target airways in acceptable concentrations during acute small airway narrowing or obstruction. Administration by aerosol at home is tolerated by most cats: 65% of cats accept this form of treatment from the very beginning, and an additional 15% can be coaxed to accept it over a

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few days to weeks; 20% of cats refuse it under any circumstance (Padrid 2006). A logical approach in a cat with concurrent asthma and heart disease is to attempt aerosolized treatment and determine whether the cat will tolerate it, in which case it can be continued, or resists it, causing patient and client stress and warranting discontinuation.

Additional methods to manage feline asthma without corticosteroids should be an integral part of optimal treatment. A cornerstone of such treatment is the reduction of environmental triggers and exposures. Methods for decreasing allergic stimuli include elimination of volatile-scented products from the cat's immediate environment, such as carpet-fresheners, scented kitty litter, and strong perfumes; reduction or elimination of airborne particulates, including tobacco smoke, house dust, and clay-based kitty litter; and nonspecific reduction of airborne irritants through installation of an air purifier system.

Other medications may be considered (Padrid 2008). Cyproheptadine (2–4 mg/cat PO q 12h), an antihistamine used for appetite stimulation in cats, decreases serotonin release in bronchial smooth muscle and may be beneficial in cats already receiving aerosol fluticasone and albuterol or other beta-2 agonist. Aminophylline or theophylline (10 mg/kg PO q 8–12h) may provide mild bronchodilation, and trivial diuretic effects. The sustained-release preparations (e.g., Theo-Dur) are not absorbed as predictably as the plain (anhydrous) forms and are not recommended. Zafirlukast and other leukotriene inhibitors have not demonstrated dramatic efficacy and are not widely recommended in feline asthma. Empirical antibiotic therapy also is not routinely recommended due to the scarcity of clinically significant bacterial infection in asthmatic cats.

Finally, where geographically appropriate, cats suspected of having asthma should be tested for heartworm disease (see Chapter 23) because clinical signs may be identical, and treatment of heartworm infection has both respiratory and cardiovascular benefits.

In cats with concurrent asthma and heart disease, it is important to choose a beta-1 selective blocker if beta blockade is instituted for the heart disease. Nonselective beta blockers such as propranolol and carvedilol by definition also antagonize beta-2 receptors, which are prominent in bronchial smooth muscle and which cause bronchodilation. Therefore, antagonism of beta-2 receptors may trigger asthmatic decompensation and should always be avoided. Even selective beta-1 blockers may exert some beta-2 blocking effects at higher dosages, so an asthmatic feline patient should be carefully monitored for exacerbation of lower airway disease when starting even a selective beta blocker.

Cats that have both asthma and heart disease may pose a diagnostic dilemma to their owners when signs of respiratory compromise occur and it is unclear whether bronchoconstriction or congestive heart failure is at fault. Some owners develop a very accurate ability to discern between the two after several crises and resolutions, but a wide range of signs, including wheezing, retching/cough, respiratory noise, discomfort, vocalizing, gasping, and obvious distress may occur with similar frequency in individual cats with congestive heart failure and asthmatic airway disease. Therefore, a cat in this condition should be brought to the veterinary hospital promptly and given supplemental oxygen and an opportunity to rest, and a radiographic diagnosis can be made when proper radiographs can be obtained quickly and safely. Nonspecific, blanket treatment such as the simultaneous administration of both a diuretic (e.g., furosemide 3 mg/kg IV) and a bronchodilator (e.g., terbutaline 0.01 mg/kg IM) may be provided initially in cats with such severe dyspnea when they have a documented previous history of both disorders, and when this temporary measure is felt to be necessary to allow the patient to survive long enough for radiographs to confirm the diagnosis and focus the treatment plan.

CONCURRENT CARDIAC DISEASE AND OTHER DISORDERS TREATED WITH GLUCOCORTICOIDS

The adverse effects of injectable or oral glucocorticoids, as described above, are relevant to many other important feline diseases that are immune-mediated or neoplastic. In general, oral and parenteral glucocorticoids are not strictly contraindicated in feline heart disease, but the risk they carry of triggering congestive heart failure means an alternative form of treatment should be sought if available. If no other option exists, glucocorticoids should be prescribed (because a majority of cats with heart disease likely tolerate such treatments), preferably oral rather than repositol injectable, along with a basic discussion with the owner about signs of congestive heart failure that would warrant an immediate recheck—the same discussion that takes place at discharge of any cat with substantial structural heart disease.

Inflammatory Bowel Disease

Since glucocorticoids are an inexpensive and often-effective treatment for inflammatory bowel disease (IBD), management of cats that have concurrent heart disease and inflammatory bowel disease involves two important approaches: search for and treatment of possible underlying causes (to create a true diagnosis of idiopathic IBD), and use of treatments other than glucocorticoids for palliation of intestinal inflammation.

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Dietary, parasitic, and other inciting causes of intestinal inflammation may produce clinical signs and histologic lesions suggestive of IBD. Such disorders require proper and comprehensive diagnostic investigation, and correction if a disorder is found, before a diagnosis of idiopathic IBD can be made. Many clinicians advocate empirical deworming regardless of fecal cytology results prior to endoscopy, and certainly prior to administration of immunosuppressive agents. When idiopathic IBD has been identified in a cat with concurrent heart disease, there are several alternatives to prednisolone (the active form, which is more likely to be effective in cats that cannot hepatically transform prednisone) or sustained-release/repositol glucocorticoid injections. Budesonide is a corticosteroid with marked first-pass hepatic elimination and therefore reduced systemic corticosteroid effects. It may be given orally (0.5 mg/cat; compounding is necessary because the product is available only as a 3 mg capsule), or as an enema (0.5–1 mg/cat; enemas are 2 mg each) if the intestinal lesion predominantly affects the large bowel. Alternatively, cyclosporine (e.g., Atopica, Neoral; 2–5 mg/kg PO q 12h) may be effective and anecdotal reports of a positive response have been noted. Chlorambucil (2 mg/cat PO q 48h) is routinely used in cats with severe inflammatory bowel disease and/or histologic changes consistent with low-grade intestinal lymphoma. Results have been variable, with some cats demonstrating a good response and others responding minimally (Richter 2003). Any of these treatments can be used, with minimal cardiovascular effect compared to oral or parenteral glucocorticoids.

Immune-mediated Liver Disease, Lymphocytic-Plasmacytic Cholangiohepatitis

The principles and recommendations listed for IBD (above) may also be applied to immune-mediated cholangiohepatitis. As an alternative to immune suppression with cyclosporine or chlorambucil, methotrexate 2.5 mg/m^2 PO q 48–72h has been advocated for lymphocytic-plasmacytic cholangiohepatitis.

Inflammatory or Immune-mediated Skin Disease

Glucocorticoids are perhaps used more for skin disease than diseases of any other organ in small animal medicine. In cats with concurrent heart disease, seeking underlying causes of skin disorders and choosing other options for treatment becomes especially important. Empirical and vigilant antiparasitic (anti-flea) treatment is essential, and many dermatologists advocate early empirical treatment for other ectoparasites (e.g., *Cheyletiella, Notoedres*) when consistent with clinical signs.

Instead of inflammatory skin disease, cats may show hair loss due to behavioral disorders or to internal discomfort including anal sac impaction (Waisglass et al. 2006) or ureteral obstruction (Polzin 2010). Therefore, such disorders must be considered, identified, and corrected to avoid misdiagnosis and mistreatment with glucocorticoids, particularly when a cat also has concurrent heart disease and may not tolerate such therapy.

Topical treatments, such as shampoos, rinses, sprays, and topical wipes can be helpful for cats with inflammatory skin disease and concurrent heart disease, and barring a cat's dislike of a particular treatment (e.g., bathing), this approach carries minimal risk of cardiovascular detriment. However, topical therapies that contain glucocorticoids also may exert systemic glucocorticoid effects and should be used sparingly if at all.

CARDIAC DISEASE AND UNRELATED PLEURAL EFFUSION

When pleural effusion is caused by a noncardiac disorder (e.g., mediastinal lymphoma, idiopathic chylothorax, etc.) but the patient also has concurrent, unrelated heart disease, it may be difficult to feel certain that the pleural effusion is—or is not—caused by cardiac disease. Certain guidelines are helpful: in the absence of atrial enlargement on an echocardiogram, it is unlikely that pleural effusion is cardiogenic. Lack of cardiomegaly on thoracic radiographs likewise makes a cardiogenic cause of pleural effusion less likely, but the conclusion is less definitive than the echocardiographic absence of atrial enlargement. Echocardiographic measurements of left ventricular or right ventricular wall thickness are unlikely to provide information that is more useful than atrial dimensions because substantial differences in ventricular wall compliance (degrees of restrictive physiology) may be present with only minimal difference in wall thickness. For example, there may be increased ventricular wall thickness but normal diastolic filling pressures and a low likelihood of heart failure, or the ventricle may be minimally thick but very stiff in cases of restrictive cardiomyopathy. The character of the pleural effusion may be helpful: purulent effusions are not cardiogenic, and hemorrhagic effusions are also not cardiogenic unless the patient has marked atrial enlargement and the thoracocentesis needle has inadvertently punctured an atrium. Milky/chylous effusions and modified transudates are nonspecific and may be caused by heart disease or extracardiac disorders. Definitive confirmation may be obtained via measurement of central venous pressure (CVP) which, if above 8 cm H_2O postcentesis, is consistent with right-sided congestive heart failure and a cardiogenic source of the effusion. As

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mentioned previously, a normal CVP measurement does not exclude left-sided congestive heart failure, which can cause pleural effusion in the cat (see Chapter 19). An important limitation is that pleural effusion itself may alter CVP readings: removal of effusion via thoracocentesis decreases CVP by 0–7 (mean 4.5) cm H_2O in cats with naturally occurring pleural effusion of various causes (Gookin and Atkins 1999). Therefore, measuring CVP on a cat with pleural effusion prior to thoracocentesis may produce a falsely elevated reading and an erroneous diagnosis of cardiogenic effusion and right heart failure. To avoid this pitfall, CVP measurements should be made after thoracocentesis in cats.

CRITICAL CARE REQUIRING FLUID THERAPY IN THE CAT WITH HEART DISEASE

A patient that has sustained large fluid losses may require immediate intravenous fluid resuscitation. Examples include cats that are hit by cars and suffer massive blood loss, cats with severe fluid losses due to gastrointestinal disease, and various others. When these patients also have underlying heart disease, a dilemma exists because fluid administration should be sufficient to benefit the patient, but not excessive such that it triggers congestive heart failure. Some guidelines for optimizing acute fluid therapy in the feline cardiac patient are as follows:

The time frame of fluid loss is important, because it is correlated to the appropriate time frame of fluid replacement. For example, a large volume of blood lost over the span of two hours can be replaced with blood (or crystalloids or colloids) over an equally rapid period of time, with minimal likelihood of fluid overload. By contrast, a patient with debilitating illness lasting several weeks that presents severely dehydrated likely has activated several mechanisms, including renal sodium retention and translocation of intracellular fluid to the extracellular compartment, to compensate for such losses. In this case, a gradual (24–48 hour) replacement of fluid is indicated. Under either circumstance, an accurate calculation of fluid deficits is essential for approximating the proper fluid dose. Administration of fluids consists of replacing deficits, replacing ongoing overt losses, and offsetting insensible losses. Calculations are based on the simple principle that 1 liter of water (or body tissues) weighs 1 kg. Therefore, 10% dehydration of a 5 kg cat means 10% of 5 liters, or 1/2 liter (500 ml), must be administered to correct the deficit. Added to this are ongoing overt losses (e.g., loss of 50 ml in vomitus or diarrhea), and daily insensible losses (approximately 45 ml/kg/day normally lost in breath, urine, feces, etc.). The sum total of these three categories outlines the volume that is to be administered in a time frame that considers the rate of loss and patient's hemodynamic stability.

The fluid type is chosen based on the patient's requirement: either replacement or maintenance. Replacement fluids, such as lactated Ringer's solution (LRS), Plasmalyte 146, Normosol R, and 0.9% sodium chloride, are isotonic crystalloid solutions that are indicated for replacing fluid deficits. Their sodium content approximates the sodium content of blood (140–150 mEg/l). Examples of indications include acute blood loss and dehydration. Once a patient is euvolemic/hydrated, however, ongoing losses are sodium-poor because sodium conservation is one of the most important functions of the kidney. Indeed, daily losses in urine, breath, and other normal routes contain a total sodium concentration of only 30–40 mEq/l. Therefore, when a patient is euvolemic, administration of replacement-type fluids like LRS constitutes an excessive administration of sodium. When cats have a normal cardiovascular system, this excess (and resultant expansion of intravascular volume) goes unnoticed while renal natriuresis increases and a normal state is restored. However, in cats with cardiovascular disease such as cardiomyopathy or systemic hypertension, these high concentrations of sodium may be poorly tolerated, and iatrogenic congestive heart failure is possible. Therefore, in any cat (with or without cardiovascular disease) that is euvolemic, parenteral fluid therapy should be changed when euvolemia is reached, not only in terms of rate of fluid administration, but also fluid type, to minimize the risk of causing decompensation of an otherwise compensated cardiac disorder. Maintenance-type fluids are also isotonic crystalloid solutions, but they are lower in sodium concentration and contain other solutes to reach isotonicity. Examples include Normosol M + 5% dextrose (sodium concentration is 40 mEq/l), Plasmalyte 56 + 5% dextrose (56 refers to the concentration of sodium in mEq/l), and 0.45% sodium chloride in 2.5% dextrose. Many of these solutions have high levels of potassium (e.g., 10–20 mEq/l), which means they are ideal for maintaining anorexic and/or hypokalemic patients but must never be bolused.

Individual cats have highly variable tolerances for intravascular volume expansion, and certain essential factors such as ventricular stiffness in the face of increasing diastolic ventricular volumes are difficult or impossible to assess accurately in a clinical setting. Therefore, monitoring the response to fluid administration is essential for preventing or minimizing negative outcomes in cats with cardiovascular disease.

Assessment of the respiratory rate and character are important and should be done in a regular and consistent fashion during fluid administration. An increase in either,

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if not caused by other factors such as pain or anxiety, may mark the onset of pulmonary edema or pleural effusion and warrant a repeated chest radiograph.

The onset of a gallop heart sound during fluid therapy is also an important clue suggesting intravascular volume overload. A true gallop sound is a low-frequency, thud-like sound that occurs in addition to the two normal sounds (see Chapter 1). If a new gallop heart sound has emerged when it was not present at the time of admission/before fluid therapy, then congestive heart failure can be considered to be imminent and the fluid rate should be decreased; a single dose of furosemide, typically 1–3 mg/kg IV, may be given if mild dyspnea is also apparent. Disappearance of the gallop is expected with normalization of intravascular volume and end-diastolic left ventricular pressure. In this way, the presence and disappearance of a gallop heart sound can act as a gauge of intraventricular pressures and therefore imminence of congestive heart failure. Importantly, many other extra heart sounds that are not gallop sounds occur in the cat (i.e., midsystolic click, split heart sound), and the mere presence of an extra heart sound with each heartbeat does not automatically indicate congestive heart failure. The practical utility of gallop sounds during fluid administration lies in their new onset, and their diagnosis requires recognizing the characteristic low frequency (audible better with the stethoscope's bell than the diaphragm) of the extra sound.

Finally, the principle of cardiac pseudohypertrophy is recognized in cats, and cats that require fluid therapy due to dehydration must not be diagnosed with cardiac hypertrophy prematurely. When 10 normal cats were given furosemide at standard dosages, echocardiography identified that the interventricular septum and left ventricular free wall thicknesses increased significantly, including a thickness >6 mm (a generally agreed-upon cutoff for left ventricular hypertrophy) in 4/10 cats (Campbell and Kittleson 2007). Therefore, when a patient is dehydrated, the diagnosis of left ventricular hypertrophy is questionable if an echocardiogram was performed prior to rehydration. This is particularly important if the pseudohypertrophy is interpreted as a reason to administer fluids cautiously, or more slowly, when in fact the patient has a normal heart and may require vigorous fluid resuscitation.

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SECTION M

Pulmonary Arterial Disorders

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25

Pulmonary Thromboembolism and Pulmonary Hypertension

Key Points

- Pulmonary thromboembolism (PTE) affects cats without sex, age, or breed predisposition, including several cases in cats <2 years old.
- A variety of associated disorders are thought to contribute to PTE, notably heart disease and neoplasia. It is rare for PTE to occur without a concurrent or predisposing disorder. Clinical signs are most commonly constitutional (e.g., lethargy, anorexia) or respiratory (e.g., dyspnea) and are subtle or nonspecific, because in virtually all feline cases, pulmonary thromboembolism was not suspected at admission or during treatment.
- Pulmonary hypertension is a rare disorder in cats, and when it occurs, it is typically associated with (and likely caused by) congenital heart disease, heartworm disease, pulmonary thromboembolism, or pleural effusion of any cause.
- Management of cats with pulmonary hypertension revolves around identification and treatment of the associated/inciting cause.

PULMONARY THROMBOEMBOLISM

Introduction

In both human and veterinary medicine, pulmonary thromboembolism is an underrecognized, potentially life-threatening disorder. It is characterized by in situ formation of a thrombus (a clump of red and white blood cells, platelets, fibrin, and possibly foreign material, bacteria, fungi, or neoplastic cells; or air, fat, or amniotic fluid) within a pulmonary artery, embolization (detachment of a distant thrombus from the venous system to a pulmonary artery); or a combination of the two.

Pulmonary thromboembolism is an uncommon disorder in cats, but it is likely underrecognized. One necropsy survey identified a prevalence rate of 0.06% in the feline population of accessions to a university pathology service (Schermerhorn et al. 2004).

There are three crucial elements that dominate the diagnosis and treatment of pulmonary thromboembolism. First, there is a need for early suspicion of the diagnosis; second, there must be confirmation through diagnostic imaging or thorough diagnostic testing to exclude other causes of dyspnea (pulmonary thromboembolism often is a clinical diagnosis of exclusion); and third, effective treatment requires therapy directed at both the clot and the underlying process that almost always accompanies it and likely predisposed to its formation.

Etiology and Pathophysiology

In pulmonary thromboembolism cases, pulmonary arterial or arteriolar obstruction is caused by a clot of blood and possibly other substances. Pulmonary arterial resistance is increased due to this mechanical obstruction of blood flow and also due to reflex vasoconstriction from release of vasoactive mediators (serotonin, thromboxane) from the thrombus. Low output ("forward") heart failure and shock may occur with acute, massive pulmonary thromboembolism (Whitley and Stepien 2001). Factors that cause hypoxemia in cases of pulmonary thromboembolism include ventilation : perfusion mismatch, alveolar dead space, intrapulmonary or intracardiac right-to-left shunting, pulmonary

Feline Cardiology, First Edition. Etienne Côté, Kristin A. MacDonald, Kathryn M. Meurs, Meg M. Sleeper.
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edema from overperfusion of the nonthrombosed lung, atelectasis and decreased lung compliance due to reduced surfactant, and humoral factors causing bronchoconstriction and increased airway resistance.

The concept of Virchow's triad, consisting of sluggish blood flow, endothelial disruption, and hypercoagulability of the blood, evolved specifically from a search for understanding the origin of pulmonary thromboembolism (Dickson 2004). It describes the three mechanisms by which thrombus formation may occur. In cats, an underlying disorder almost invariably seems to be present when pulmonary thromboembolism occurs (see Table 25.1). For example, in the two largest case series, 45/46 cats had identifiable concurrent illness associated with pulmonary thromboembolism (Norris et al. 1999; Schermerhorn et al. 2004). Cause-and-effect relationships have not been formally established, but if concurrent disorders contribute to thromboembolism, the exact mechanism by which the original thrombus forms is likely dependent on the trigger. For example, neoplasms have been documented to cause platelet hyperaggregability (Thomas and Rogers, 1999), and heart disease associated with cardiac chamber enlargement can cause blood flow stasis, as evidenced by spontaneous echogenic contrast seen in cats with enlarged atria (Schober and Maerz 2006). Of 29 cats with pulmonary thromboembolism in one series, 21 (72%) had intravenous catheters, potentially providing a surface for platelet aggregation within the venous system where thrombi could form and embolize to the pulmonary arteries (Norris et al. 1999). A case of defecation-associated syncope was speculated to have been fatal due to dislodgement of a thrombus by changes in abdominal pressure (Valsalva maneuver), resulting in massive pulmonary thromboembolism documented at necropsy (Whitley and Stepien 2001).

Signalment

Cats of any age may suffer from pulmonary thromboembolism. Affected cats have ranged in age from 10 months to 16 years (Schermerhorn et al. 2004; Norris et al. 1999), with a bimodal age distribution noted in one group (6 cases in cats aged 4 years or less; none between 4 and 8 years; and 11 cases in cats aged >8 years) (Schermerhorn et al. 2004). There is no apparent gender (23 male, 23 female in 2 large case series) (Schermerhorn et al. 2004; et al.; Norris et al. 1999) or breed predilection.

History and Chief Complaint

Historical findings and presenting complaints of cats later found to have pulmonary thromboembolism appear to fall into two categories: respiratory abnormali-

Table 25.1. Conditions identified in association with naturally occurring pulmonary thromboembolism in 52 cats*

Intravenous catheters	**21**
Peripheral venous	17
Jugular venous	2
Hemodialysis (both with clot sonographically apparent at tip)	2
Neoplasia	**17**
Lymphoma	3
Bronchiolar carcinoma	2
Metastatic carcinoma (pancreatic [n = 1])	2
Type of neoplasm not specified	10
Heart disease	**16**
Hypertrophic cardiomyopathy	5
Endocarditis	3
Restrictive cardiomyopathy	2
Heartworm disease**	2
Infiltrative lymphoma	1
Dilated cardiomyopathy	1
Toxoplasma myocarditis	1
Tricuspid regurgitation	1
Corticosteroid administration	**9**
Disseminated intravascular coagulation	**5**
Protein-losing nephropathy	**4**
Protein-losing enteropathy	**4**
Pancreatitis	**2**
Nonhemolytic anemia	**2**
Immune-mediated hemolytic anemia	**2**
Sepsis	**2**
Other	**7**
Glomerulonephritis	1
Bacterial pneumonia	1
Hepatic lipidosis	1
Feline infectious peritonitis	1
Encephalitis	1
Humeral fracture repair (fat embolism)	1
Dorsolumbar abscess and feline leukemia infection	1

*numbers exceed a total of 52 because 1 case series (Norris) described multiple associated conditions for each case, as applicable, totaling 68 associated conditions in 29 cats
**and numerous additional cases of pulmonary thromboembolism described in experimental feline heartworm infections
Refs: Norris et al. 1999; Schermerhorn et al. 2004; Davidson et al. 2006; Dvorak et al. 2000; Pouchelon et al. 1997; Sottiaux and Franck 1999; Schwartz et al. 2001; Whitley and Stepien 2001.

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ties (22/50, 44%), nonspecific signs of ill thrift such as lethargy (19/50, 38%), and loss of appetite (16/50 [32%]) (Norris et al. 1999; Schermerhorn et al. 2004; Davidson et al. 2006; Dvorak et al. 2000; Pouchelon et al. 1997; Sottiaux and Franck 1999; Schwartz et al. 2001; Whitley and Stepien 2001). The combination of lethargy, anorexia, and respiratory distress appears to be common. Unfortunately, such signs also are nonspecific and overlap in clinical presentation exists with congestive heart failure, systemic disease causing metabolic acidosis and compensatory efforts that trigger tachypnea or dyspnea and primary pulmonary parenchymal diseases. In specific contexts, such as fat embolism due to intramedullar bone pinning under general anesthesia in one cat or acute increases in abdominal pressure in a cat with heart disease and pancreatic malignancy, embolism appears to be so fulminant as to produce no premonitory signs (Schwartz et al. 2001; Whitley and Stepien 2001).

Physical Examination

Respiratory abnormalities are the most commonly noted physical abnormality during examination, but pulmonary thromboembolism rarely is considered as the cause. For example, of 46 cats with necropsy-confirmed pulmonary thromboembolism, this diagnosis was suspected only during the antemortem period in 4 (9%) (Norris et al. 1999; Schermerhorn et al. 2004). This fact substantiates the claim that pulmonary thromboembolism in general, and in the feline species specifically, is an underdiagnosed disorder.

Physical examination may reveal respiratory abnormalities, and/or signs that are related to the concurrent disorder rather than to pulmonary thromboembolism. For example, in 29 cats examined while suffering from pulmonary thromboembolism, 21 (72%) were lethargic, 16 (55%) were tachypneic or dyspneic, 13 (45%) were felt to show signs of dehydration, 8 (28%) were hypothermic, and 5 (17%) were icteric (Norris et al. 1999). Findings potentially associated with critical or near-moribund states (bradycardia, weak or absent pulse) are described in a few cases, but specific cardiac abnormalities are conspicuously absent from most reports. Such abnormalities either are not mentioned (Norris et al. 1999; Schermerhorn et al. 2004; Dvorak 2000) or specifically are described as having been absent (Davidson et al. 2006). One cat with pulmonary thromboembolism associated with hypertrophic cardiomyopathy had a left apical systolic murmur (Pouchelon et al. 1997). A split second heart sound, which could emerge as a physical manifestation of delayed pulmonic valve closure as a result of thromboembolism-induced pulmonary hypertension, has not been described in any cat with pulmonary thromboembolism. Loud breath sounds (Sottiaux and Franck 1999), a rapid heart rate, and soft heart sounds may mask such a finding in the cat with pulmonary thromboembolism.

Differential Diagnosis

The main differential diagnoses to consider are primary intrathoracic disorders and systemic diseases, depending on whether clinical abnormalities are mainly respiratory or nonspecific, respectively. Pulmonary edema, pneumonia, pulmonary contusions due to trauma, heartworm disease, malignancy or other pulmonary infiltrative processes, pneumothorax, and pleural effusion of any cause are important differential diagnoses for respiratory signs, and many may cause systemic signs of illness such as lethargy and anorexia. Lethargy and anorexia alone may be caused by virtually any severe illness in cats. Therefore, these retrospectively identified chief complaints of cats with pulmonary thromboembolism confirmed at necropsy illustrate the lack of specificity of such signs and the diagnostic challenge presented by many cases of pulmonary thromboembolism in cats.

Diagnostic Testing

Given the frequency of overlooking this diagnosis, diagnostic testing may occur as a general investigation assessing nonspecific signs, or on occasion, to specifically evaluate for pulmonary thromboembolism. Confirming the diagnosis revolves around diagnostic imaging, and even so, pulmonary thromboembolism in cats is reasonably described as a diagnosis of exclusion in most cases.

Initial Tests

All cats with suspected pulmonary thromboembolism should undergo routine heartworm testing including a heartworm antigen test and a heartworm antibody test if geographically relevant (see Chapter 23). A minimum database including complete blood count, serum chemistry, urinalysis, and, if clinically applicable, thyroxine level should be done. If proteinuria is present, a urine protein creatinine ratio should be done to further evaluate the presence and severity of proteinuria, as protein-losing nephropathy may lead to a hypercoagulable state via loss of antithrombin III. Antithrombin III level may be measured in cats with significant proteinuria (Cornell University), to further evaluate for the potential of prothrombotic state as a precipitating factor for development of pulmonary thromboembolism.

As in the dog, cats that have pulmonary thromboembolism are disadvantaged by the absence of specific diagnostic tests that may reasonably be performed on a distressed animal while also being sufficiently sensitive

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to detect thromboemboli. Thoracic radiographs are routinely performed when respiratory signs or severe debility are present. In cats with pulmonary thromboembolism, radiographic abnormalities may include pleural effusion (n = 11/20), alveolar opacification (n = 8/20), conspicuous lucency of circumscribed areas of the lungs suggesting hypoperfusion (n = 5/20), circumscribed mass (n = 3/20), and peribronchial and interstitial markings (n = 2/20) (Schermerhorn et al. 2004; Norris et al. 1999; Sottiaux and Franck 1999). Vascular changes may coexist or may occur independent of pulmonary parenchymal lesions, and the vascular changes may include asymmetrical enlargement in vascular size or distribution (n = 6/15), proximal vascular enlargement coupled with disproportionate tapering of central or peripheral pulmonary arteries ("pruning") (n = 5/15), or both (Norris et al. 1999; Sottiaux and Franck 1999). Some cats with pulmonary thromboembolism have normal thoracic radiographic findings, despite clinically evident dyspnea (Norris et al. 1999). The presence or absence of thoracic radiographic abnormalities is both poorly sensitive (as evidenced by the lack of suspicion of thromboembolism antemortem) and nonspecific (since no single radiographic finding pinpoints pulmonary thromboembolism). However, severe dyspnea that is not seemingly related to upper airway obstruction, in a cat with normal thoracic radiographs, should prompt a strong suspicion of pulmonary thromboembolism.

Echocardiography may rarely reveal a thrombus that extends to the pulmonary trunk and pulmonic valve. Such a finding may occur in cats with overt clinical signs such as respiratory distress (Pouchelon et al. 1997) or as an incidental finding, as in the 6-year-old female spayed domestic shorthaired cat whose thoracic radiograph is shown in Figure 25.1. This cat had a history of occult/"asymptomatic" hypertrophic cardiomyopathy, which was treated daily with atenolol 12.5 mg PO; on routine echocardiographic follow-up 1 year later, a large thrombus occupied the entire right pulmonary artery to the level of the right and left main pulmonary artery bifurcation without producing any associated clinical manifestations of illness (Etienne Côté, unpublished observation, 2004).

Arterial blood gas measurement may provide useful information that helps increase the suspicion of pulmonary thromboembolism. Hypoxemia and hypocapnia have been documented in some cases in other species, with hypercapnia in severe cases. An elevated alveolar-arterial oxygen difference can occur with pulmonary thromboembolism. The alveolar-arterial oxygen difference (A-a gradient) is the step in oxygen content between the alveoli of the lungs and the arterial circulation. A

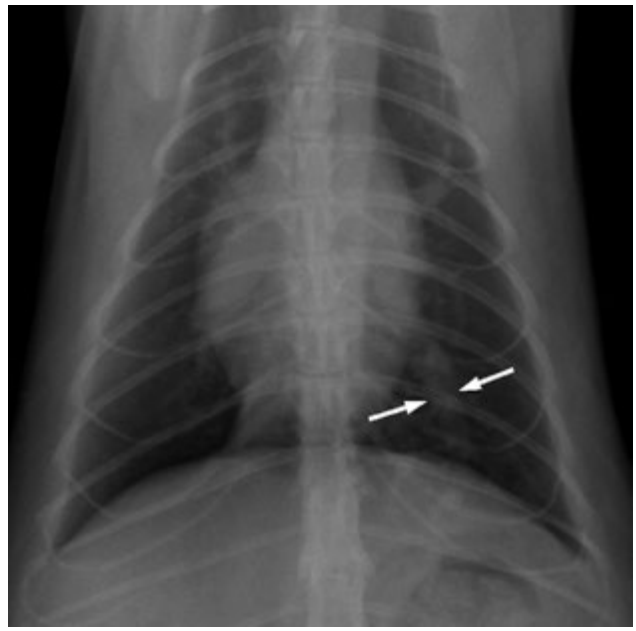


Figure 25.1. Thoracic radiograph of an adult cat with pulmonary thromboembolism, dorsoventral view. Note the markedly enlarged left caudal pulmonary artery (arrows). Paradoxically, the thromboembolus was best seen in the right pulmonary artery on echocardiography.

normal value is <15 mm Hg, indicating adequate lung perfusion and diffusion of oxygen into blood. Values >15 mm Hg may occur with many pulmonary disorders; in the presence of radiographic pulmonary abnormalities, an elevated A-a gradient adds little diagnostic information. However, in the absence of radiographic abnormalities, an elevated A-a gradient is strongly suggestive of pulmonary thromboembolism. The A-a gradient is calculated as follows:

$$\text{A} - \text{a gradient (mm Hg)} = \text{FIO}_2(\text{P}_\text{b} - \text{P}_{\text{H}_2\text{O}}) - (\text{PaCO}_2/\text{R}) - \text{PaO}_2$$

where FIO_2 is the fraction of inhaled oxygen (e.g., 0.21 for room air, or 0.4 for 40% oxygen), P_b is barometric pressure (627–643 mm Hg; instantaneous values for any location in the U.S. may be found at www.weather.com), P_{H2O} = 47 mm Hg, R= 0.8, and PaO_2 and $PaCO_2$ are obtained from the arterial blood gas measurement.

Advanced Testing

Confirmatory tests for pulmonary thromboembolism in humans include radiographic or computed tomographic angiography, and nuclear scintigraphy. Given the limited availability of such modalities and hemodynamically fragile state of many cats with pulmonary thromboembolism, confirmatory testing is undertaken in very few suspected cases. One cat that underwent

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pulmonary scintigraphy (perfusion scan with technetium-99m-labeled macroaggregated albumin) demonstrated perfusion defects consistent with pulmonary thromboembolism, and although a ventilation scan was not performed concurrently, the diagnosis was supported because a thrombus had been visualized echocardiographically in the right pulmonary artery (Pouchelon et al. 1997). Presence of a perfusion defect on nuclear scintigraphy in the absence of radiographic pulmonary abnormalities of that lung segment are highly suggestive of pulmonary thromboembolism. However, for most cats with pulmonary thromboembolism, the standard of care for diagnostic imaging at the present time should include thoracic radiography, echocardiography, and arterial blood gas analysis.

Plasma D-dimer is a breakdown product of cross-linked fibrin, which is produced when fibrin is degraded by plasmin. Measurement of plasma D-dimer concentrations in humans with pulmonary thromboembolism is a highly sensitive (approaching 100%), poorly specific test, meaning that a negative result rules out pulmonary thromboembolism in most cases, but a positive result may or may not be the result of pulmonary thromboembolism (Fedullo and Tapson 2003). D-dimer measurement for assessment of thrombotic states in cats is not routinely done, but results of a study of cats suffering from arterial thromboembolism indicate that D-dimers are not effective at detecting the disorder (poor sensitivity). D-dimer concentration was elevated in only half of cats with arterial thromboembolism, and there was no difference in D-dimer concentration between normal cats and cats suffering from arterial thromboembolism (Stokol et al. 2008). No studies have evaluated the utility of D-dimer to screen for pulmonary thromboembolism in cats.

Treatment

Optimal management of pulmonary thromboembolism involves three aspects of treatment: identification and correction of the underlying cause whenever possible, anticoagulation to prevent growth of the thrombus and formation of additional thrombi, and supportive care. Thrombolysis is controversial, and active dissolution of thrombi is currently reserved for patients with severe clinical signs (hypotension, cardiogenic shock, and severe dyspnea) and a high index of suspicion (if not confirmation) of pulmonary thrombosis.

Anticoagulation can be achieved with heparin or low molecular weight heparin in hospital, followed by low molecular weight heparin daily injections, oral clopidogrel (18.75 mg PO q 24 hr with food), oral warfarin (0.25–0.6 mg PO q 24h), or oral aspirin (5–81 mg PO q 3 days) if the inciting cause has not been eliminated (see Chapter 20). The heparins require adequate plasma antithrombin (AT) levels to be effective, and for this reason, significantly hypoproteinemic patients (particularly those that are hypoalbuminemic, since albumin and AT are similar in molecular weight) should be anticoagulated with drugs other than heparin or low molecular weight heparin. Anticoagulant treatment approaches and options are identical to those for aortic thromboembolism, and the reader is referred to Chapter 20 for this information.

Outcome and Prognosis

The prognosis for cats with pulmonary thromboembolism varies depending on cause, extent, and response to treatment. Subjective experience and extrapolation from other species suggest that a better prognosis exists when respiratory signs are minimal or absent, when a precipitating cause can be identified and treated, and when hypoxemia is mild (e.g., A-a gradient <20 mm Hg). In turn, these elements likely depend mainly on the promptness of suspicion of pulmonary thromboembolism and initiation of tests and treatment based on reasonable clinical suspicion. The late onset of clinical signs and lack of specificity of signs for pulmonary thromboembolism translate to typically a guarded to poor prognosis of this disease in cats.

PULMONARY ARTERIAL HYPERTENSION

Introduction

Pulmonary hypertension is an uncommon, poorly described disease in cats. It is defined as an elevated pulmonary artery systolic, diastolic, or mean arterial pressure. In order to define an abnormally elevated pulmonary artery pressure, normal pressures must first be defined. The normal systolic and mean pulmonary arterial pressures in healthy cats are 15–22 mm Hg (average = 18; right ventricular pressure) [Lord et al. 1974] and 15.1 ± 4.29 mm Hg [Nadeau and Colebatch 1965] in cats anesthetized with surital/nitrous oxide/halothane, and chloralose, respectively. Systolic right ventricular—and therefore, pulmonary arterial—pressures of 36 ± 10 mm Hg have been reported in healthy cats anesthetized with surital when evaluations took place at 5200 feet (1600 m) altitude (Reeves et al. 1963). Systolic, diastolic, and mean pulmonary arterial pressures for cats and dogs under pentobarbital anesthesia are reported as 25 ± 5, 10 ± 3, and 15 ± 5 mm Hg, respectively (Thomas and Sisson 1999) and 15–30, 5–15, and 8–20 mmHg for "cats and dogs under general anesthesia" (Kittleson and Kienle 1998). A mean pulmonary

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arterial pressure of 16.0 ± 0.9 mm Hg was recorded in 7 cats anesthetized with isoflurane, and this value did not change with administration of medetomidine (Lamont et al. 2001).

Pulmonary hypertension is an abnormally high systolic, diastolic, and/or mean pulmonary arterial pressure. A practical clinical definition is systolic pulmonary arterial pressure >25 mm Hg.

The main potential cardiovascular complication of pulmonary hypertension is *cor pulmonale*, a Latin term meaning "lung-influenced heart" that describes the process of right ventricular concentric hypertrophy resulting from acquired pressure overload (pulmonary hypertension), and right-sided heart failure. Severe acute pulmonary hypertension could conceivably produce reflex bradycardia, hypotension, and possibly cardiac arrest, although this mechanism has not been clearly illustrated in clinical feline medicine cases.

Etiology, Pathophysiology, and Gross Pathology

Mean pulmonary artery pressure (MPAP) is related to pulmonary blood flow (PBF) and pulmonary vascular resistance (PVR) by the equation MPAP = (PVR × PBF) + pulmonary capillary wedge pressure (PCWP). An increase in any component of this equation can cause pulmonary hypertension.

Pulmonary hypertension may occur acutely or chronically, with chronic pulmonary hypertension appearing to occur more frequently that acute disease. A cause-and-effect relationship is rarely identified, but congenital heart disease, heartworm disease, pulmonary thromboembolism, or pleural effusion of any cause are typically found concurrently with chronic pulmonary hypertension and are thought to contribute to its occurrence. Experimental heartworm infections in cats (with much higher worm burdens than in naturally occurring disease) have caused pulmonary hypertension (Rawlings et al. 1990), but natural infections rarely appear to do so (www.heartwormsociety.org). Acute-onset pulmonary hypertension typically involves pulmonary thromboembolism or an acute respiratory insult (such as smoke inhalation) with or without acute respiratory distress syndrome.

Conceptually, pulmonary hypertension may be categorized hemodynamically as follows, and this grouping offers future possibilities for applying specific treatments and obtaining a clearer prognosis:

1. *Pre-capillary* pulmonary hypertension occurs due to abnormalities of the pulmonary arterial vascular bed and is characterized by increased systolic, mean, and diastolic pulmonary arterial pressure; increased pulmonary vascular resistance; and normal pulmonary capillary wedge pressure. Examples of diseases that cause pre-capillary PH include primary pulmonary hypertension (PPH), Eisenmenger physiology (Connolly et al. 2003), chronic pulmonary disorders, pulmonary thromboembolism, heartworm disease (Rawlings et al. 1990), and peripheral pulmonary artery branch stenosis (Schrope and Kelch 2007). In otherwise healthy lungs, more than half of the pulmonary vasculature must be nonpatent in order to produce pulmonary hypertension.
2. With *post-capillary* pulmonary hypertension, pulmonary arterial pressure passively increases due to increased pulmonary venous hydrostatic pressure (elevated pulmonary capillary wedge pressure). Diastolic pulmonary arterial pressure is within 5 mm Hg of pulmonary venous pressure (pulmonary capillary wedge pressure), and pulmonary vascular resistance is normal. Left-sided congestive heart failure is the most common cause of this form of pulmonary hypertension and may result from any form of cardiomyopathy or severe mitral regurgitation.
3. *Mixed hemodynamic response* may be seen with chronic elevations in pulmonary venous pressure (pulmonary capillary wedge pressure). A mixed hemodynamic response consists of a disproportionate elevation in pulmonary arterial pressures in comparison to elevated pulmonary venous pressure—a combination of forms 1) and 2) listed above. The mechanism for this form of pulmonary hypertension requires further elucidation and likely involves endothelin-1 release, endothelial dysfunction and abnormal pulmonary vasodilatory reserve.
4. *Pulmonary blood flow (PBF)-associated* pulmonary hypertension. Here, pulmonary vascular resistance is normal, and pulmonary arterial pressure is increased mainly or solely due to increased pulmonary blood flow. Examples include large-volume left-to-right shunting congenital heart defects such as ventricular septal defect and, less commonly in the cat, atrial septal defect, patent ductus arteriosus, atrioventricular canal, and others. Some patients with large excesses in pulmonary blood flow due to these shunts are at risk for development of Eisenmenger's physiology. There is a window of time in these patients in which the increased pulmonary blood flow (without pathologic pulmonary arteriolar changes) causes pulmonary hypertension that is reversible with correction of the left-to-right shunt. However, if left untreated and with chronicity, Eisenmenger's physiology develops secondary to irreversible pulmonary arteriolar vascular remodeling and permanent pul-

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monary hypertension (likely forms 1 or 3, above), leading to reversal of the shunt (right-to-left). Eisenmenger's physiology typically occurs early on, often by 6 months of age, depending on the size of the left-to-right shunt and response of the pulmonary vasculature.

Signalment

Cats of any age and either sex may have pulmonary hypertension. The signalment of affected cats likely reflects the signalment associated with the inciting cause; for example, pulmonary hypertension that coexists with congenital heart disease likely is more prevalent in younger patients.

History, Chief Complaint, and Physical Examination

Pulmonary hypertension alone is not conclusively associated with specific clinical manifestations in cats. Based on clinical signs observed in patients of other species, such signs as dyspnea, decreased stamina, lethargy, syncopal episodes and inappetence could be expected especially in severe cases; often, such signs are difficult to separate from signs caused by the concurrent disorder. For example, cats with post-capillary pulmonary hypertension caused by congestive heart failure likely are dyspneic from the congestion, with an uncertain contribution to clinical signs from the pulmonary hypertension.

Physical examination abnormalities likewise could be expected to reflect those caused by the predisposing disorder. Additionally, a split second heart sound (delayed closure of the pulmonic valve) is classically noted in dogs and humans with pulmonary hypertension. Such a finding has not been reported in cats, possibly because the faster heart rate and softer or obscured heart sounds in a dyspneic cat make such sounds difficult to hear. Abdominal enlargement due to ascites, jugular venous distension, dyspnea due to pleural effusion, and other manifestations of right-sided congestive heart failure stemming from cor pulmonale were not reported in a cat with a pulmonary arterial systolic pressure of 56 mm Hg (Sottiaux and Franck 1999) and appear to be infrequent compared to such signs in dogs with severe pulmonary hypertension.

Differential Diagnosis

On physical examination, dyspnea must be differentiated from primary airway or pulmonary disease (e.g., allergic airway disease, airway obstruction, pneumonia, neoplasia), metabolic disease (notably those causing metabolic acidosis), secondary pulmonary disease (e.g., cardiogenic or noncardiogenic edema, pulmonary hemorrhage from bleeding disorder), and pleural diseases (e.g., idiopathic chylothorax). Often split heart sounds may be misdiagnosed as extra heart sounds such as systolic clicks and gallop sounds. Echocardiographic right ventricular enlargement (often with concentric and eccentric hypertrophy) must be differentiated from concentric right ventricular hypertrophy caused by pulmonic stenosis or branch pulmonary arterial stenosis.

Diagnostic Testing

Thoracic radiographs are indicated for evaluation of any patient suspected of having pulmonary hypertension, since dyspnea is the main clinical abnormality being pursued. Pulmonary arterial dilation, pulmonary parenchymal abnormalities, and signs of right heart enlargement are possible. Lobar pulmonary artery dilation seems to be one of the more prominent abnormalities in cats with pulmonary hypertension. Identification of prominent central portions of the pulmonary arteries that rapidly taper, in conjunction with right heart enlargement should raise the suspicion of pulmonary hypertension.

The electrocardiogram (ECG) is insensitive for the detection of mean electrical axis shifts in general in cats, and is not a reliable test for assessing cor pulmonale.

Echocardiography

Practically speaking, pulmonary hypertension and cor pulmonale is best identified, albeit indirectly, through echocardiography. Pulmonary hypertension is consistent with the following pair of findings: absence of pulmonic stenosis, plus elevated tricuspid regurgitation velocity (>2.5 m/s), elevated pulmonic insufficiency velocity (>2 m/s), or both. Right ventricular and right atrial enlargement, and flattening of the interventricular septum, have been documented in chronic feline pulmonary hypertension associated with pulmonary thromboembolism (Sottiaux and Franck 1999). Other findings could include a rapid decrease in right ventricular outflow velocity in midsystole due to the increased resistance to flow imposed by pulmonary hypertension and a decreased time to peak right ventricular outflow tract velocity. Tissue Doppler imaging is an emerging application in other species to evaluate for elevated pulmonary artery pressure, which appeared to be superior to standard techniques for identifying even mild elevations in pulmonary arterial pressure in dogs (Serres et al. 2007). Finally, echocardiography is also useful for identifying underlying causes such as heartworms, a pulmonary thrombus, or significant left heart disease.

The gold standard for documenting pulmonary hypertension is direct measurement of pulmonary

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arterial pressures using a cardiac catheter introduced through the jugular vein. Such measurements are not routinely undertaken in cats both because diagnosis and treatment of an underlying cause appears to be more clinically applicable and rewarding, and because performing such measurements may create a risk of substantial iatrogenic problems (particularly as general anesthesia is generally needed for catheterizing the pulmonary arteries of cats).

Treatment

When pulmonary hypertension exists in association with a contributory or inciting cause, treatment of the cause is indicated first. A common example is congestive heart failure, where treatment of cardiogenic pulmonary edema with diuretics and an ACE inhibitor may bring improvement or resolution of the pulmonary hypertension.

In the normal cat, pulmonary vasculature tone is maintained as a balance between locally acting vasodilators prostaglandin I_2 and nitric oxide (NO), countered by vasoconstricting substances including thromboxane, endothelin-I (ET-I), and angiotensin II (ATII). Endothelial dysfunction in pulmonary hypertension contributes to smooth muscle cell proliferation (increased ET-I, AT-II, reduced NO), increased production of vasoconstrictor mediators including ET-1 and AT-II, and decreased synthesis of vasodilating substances including PGI_2 and NO. Thus, treatment of pulmonary hypertension can address either of these two arms if pulmonary hypertension persists despite control of its inciting cause. In the cat, such treatment applications are speculative; published reports of the outcomes of these treatments are absent in the feline species, likely due to the rarity of this disorder in the cat and the limited efficacy of treatment of pulmonary hypertension in many cases. Candidate drugs for treatment of pulmonary hypertension that persists beyond the treatment of its associated or underlying causes may include phosphodiesterase inhibitors such as sildenafil (extrapolated dose of 1 mg/kg PO q 8 h) or tadalafil, calcium channel blockers such as amlodipine, angiotensin converting enzyme inhibitors such as enalapril or benazepril, endothelin antagonists such as bosentan, and prostaglandin analogs such as beraprost and treprostinil. These treatments represent future possibilities, because reported use in feline pulmonary hypertension is absent from the veterinary literature.

Outcome and Prognosis

The natural history of pulmonary hypertension in the cat has not been properly documented. Based on information from other species, identification of a treatable or reversible cause, positive response to such treatment, and milder degrees of pulmonary hypertension should be associated with a more favorable prognosis. Since this is a syndrome comprised of many different causes, the expected outcomes are likewise varied. In human patients with pulmonary hypertension, mean pulmonary arterial pressure, right atrial pressure, and pulmonary vascular resistance are inversely proportional to survival.

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SECTION N

Endocrine Diseases Affecting the Heart

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26

Endocrine Diseases Affecting the Heart

Key Points

- In cats, hyperthyroidism produces concentric ventricular hypertrophy (thickening) and systemic hypertension as its primary cardiovascular effects.
- Reversion to euthyroidism can cause complete or partial reversal of these changes in many cases. Initial reports of feline hyperthyroidism (1980s) described lesions that were often more dramatic and severe than those observed today; possible explanations include earlier recognition of cases at present and the emergence of milder forms of feline hyperthyroidism.
- A small proportion of hyperthyroid cats may be affected with idiopathic hypertrophic cardiomyopathy simultaneously. The presence of the two concurrent disorders is confirmed retrospectively, when antithyroid treatment brings long-term euthyroidism but cardiovascular abnormalities (e.g., left ventricular hypertrophy) persist.
- The cardiovascular implications of hyperthyroidism are mild for the most part, and with the exception of acute severe decompensation ("thyroid storm"), are infrequently responsible for morbidity or mortality in affected cats.

HYPERTHYROIDISM

Introduction

The seminal report that first detailed cardiovascular changes in spontaneously hyperthyroid cats appeared in 1984 (Liu et al. 1984). Additional milestones have included investigation of electrocardiographic features of feline hyperthyroidism (Peterson et al. 1982), echocardiographic features (Bond et al. 1988; Peterson et al. 1993), the cardiac effects of a return to the euthyroid state (Peterson et al. 1993; Weichselbaum et al. 2005), the evolution of hyperthyroidism itself over time (Broussard et al. 1995; Edinboro et al. 2004), and an exploration of etiologic factors (Kass et al. 1999; Edinboro et al. 2004; Martin et al. 2000).

Although much of our current understanding of hyperthyroidism can be traced back to early reports (Liu et al. 1984; Holzworth et al. 1980), some confusion occasionally persists regarding nomenclature. Original descriptions of "hypertrophic cardiomyopathy caused by hyperthyroidism" (Liu et al. 1984) are no longer accurate and may seem misleading, because hypertrophic cardiomyopathy is now known to be a type of idiopathic or inherited myocardial protein defect that causes ventricular thickening in the absence of any intracardiac or systemic causes. Therefore, the cardiac changes caused by hyperthyroidism are correctly referred to as *thyrotoxic heart disease* or *hyperthyroid heart disease*, not hypertrophic cardiomyopathy. The distinction is a clinically important one, since thyrotoxic heart disease presents the opportunity for normalization of cardiovascular structure and function with antithyroid treatment, whereas with hypertrophic cardiomyopathy, no treatment is available that returns cardiac structure to normal.

Prevalence of Cardiovascular Abnormalities in Hyperthyroid Cats

The recognition that elevated circulating thyroid hormone levels in cats cause structural cardiac changes predates the emergence of clinical feline hyperthyroidism by several years. Experimental hyperthyroidism induced in cats in the early 1970s via daily intraperitoneal injections of *l*-thyroxine for 10 months produced massive biventricular hypertrophy, with near-doubling of cardiac

Feline Cardiology, First Edition. Etienne Côté, Kristin A. MacDonald, Kathryn M. Meurs, Meg M. Sleeper.
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mass (Skelton and Sonnenblink 1974). The reversibility of such changes was also appreciated at this time, with complete regression of thickening in cats allowed to recover for 12 months. When naturally occurring feline hyperthyroidism first was documented in the early 1980s, left ventricular thickening was a prominent feature of the disease (Liu et al. 1984) but prevalence information was not available. Shortly thereafter, an echocardiographic study identified left ventricular free wall hypertrophy in 72% of hyperthyroid cats and interventricular septal hypertrophy in 40% (Bond 1988). A more recent study of 91 hyperthyroid cats has shown that 37% of hyperthyroid cats have an echocardiographically demonstrable cardiac lesion, and for the most part these are mild lesions. Therefore, while the prevalence of gross cardiac changes approaches 40% in the current population of hyperthyroid cats, the clinical impact of these changes appears to be minimal and, in many cases, negligible.

The prevalence of systemic hypertension in hyperthyroid cats ranges widely. One study has documented 19% of hyperthyroid cats with systolic blood pressure measurements ≥160 mm Hg when assessed with standard Doppler ultrasonic sphygmomanometry (Stepien et al. 2003) whereas another study also using Doppler measurements identified 85% of hyperthyroid cats as having systolic blood pressure >2 standard deviations above control subjects (Kobayashi et al. 1990). This extremely broad range can be better understood based on the chronology of the studies: the higher prevalence was identified in a study of 39 cats evaluated in a report published in 1990, whereas the lower prevalence was identified in an abstract published 13 years later. As will be discussed below, newer case series of feline hyperthyroidism describe abnormalities that are less severe, likely due to an earlier recognition of the disease compared to original reports from the first decade of emergence of feline hyperthyroidism (1980s). Furthermore, the lower prevalence noted in the more recent study identified higher blood pressure readings in another group of hyperthyroid cats that was no different clinically, but in which blood pressure was measured in a busy clinical environment by operators with varying amounts of training. Therefore, at the present time, if the blood pressure of hyperthyroid cats is measured by an experienced operator using the Doppler technique in an environment that minimizes external stressors, the true prevalence of systemic hypertension in feline hyperthyroidism likely approaches the lower value of 19%.

The prevalence of systemic hypertension in feline hyperthyroidism may or may not change with antithyroid treatment. An early report identified a significant change from pre- to 2–3-month post-treatment values in 7 hyperthyroid cats (from 159.5 ± 15.4 mm Hg to 132.0 ± 1.62 mm Hg, respectively) (Kobayashi et al. 1990). More recently, a study of 39 cats examined before and 30–60 days after treatment did not identify a significant difference in systolic blood pressure values (Stepien et al. 2003). A small but significant decrease (from 144.9 ± 16.8 mm Hg to 139.8 ± 21.3 mm Hg) did occur in 100 hyperthyroid cats treated with carbimazole or thyroidectomy, but euthyroidism was then associated with the appearance of systemic hypertension in 9/40 (22.5%) previously normotensive cats (Syme and Elliott 2003). This change suggested an unmasking of concurrent chronic kidney disease or other hypertensive factors. Overall, while few hyperthyroid cats appear to experience a dramatic lowering of blood pressure with the return of euthyroidism, some experience a new onset of systemic hypertension. This finding justifies the ongoing measurement of blood pressure in hyperthyroid cats that are receiving or have received antithyroid therapy.

Etiology, Pathophysiology, and Gross Pathology

Mechanism of Hyperthyroidism

In cats, hyperthyroidism is caused by primary hypersecretion of thyroid hormone from the thyroid gland. The cause of excessive hormone synthesis and secretion is a functional neoplasm of the thyroid gland that has been given many different names (adenoma, thyroid adenomatous goiter, adenomatous hyperplasia, and others) and that affects both thyroid lobes in most (70%) feline cases.

Thyroid hormone is not indispensable for cardiac function, but its presence—and its excess—can greatly influence the cardiovascular system (Dillman 2002). The actions of thyroid hormone on the cardiovascular system are manyfold, and thyroid hormone excess can exert at least four broad categories of effects: 1) myocardial hypertrophy, 2) increased systolic and diastolic function, 3) vasodilation and increased circulating blood volume, and 4) alterations in heart rate and rhythm (Figure 26.1). The clinical repercussions of hyperthyroidism on the heart and vasculature are the result of the interplay of these actions and other factors, a process that can change frequently from day to day and over the extended course of the disease.

Myocardial hypertrophy is likely mediated at least in part by an increase in the synthesis of myosin. Triiodothyronine (T3, the metabolically active form of thyroid hormone in all cells that is created from mainly hepatic monodeiodination of thyroxine, T4) activates transcription of the α-myosin heavy chain (V1) (Klein and Ojamaa 2001; Dillman 2002). This mechanism has a greater impact in animals, where the α-myosin (V1)

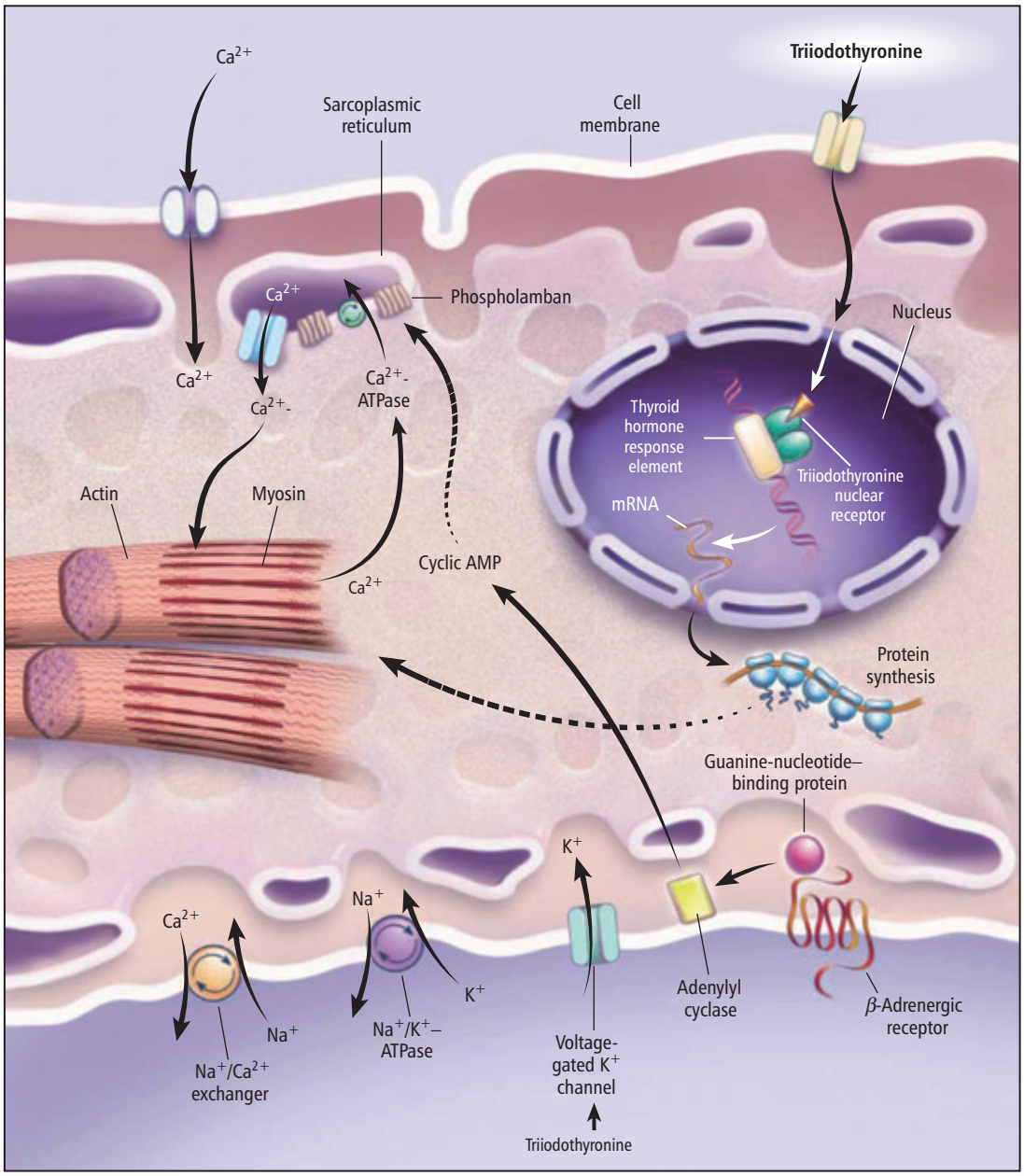


Figure 26.1. Intracellular actions of thyroid hormone. Reproduced with permission from the New England Journal of Medicine. Copyright 2001, Massachusetts Medical Society.

heavy chain predominates, making up more than 70% of a euthyroid rat's cardiac myosin, for example. Conversely, the human heart contains mainly β-myosin heavy chain and the α-myosin heavy chain (V1) comprises only 2.5% of cardiac myosin (Klein and Ojamaa 2001; Dillman 2002). Accordingly, in human hyperthyroidism, few if any changes in expression of these cardiac myosin isoforms is noted as compared to euthyroid humans (Klein 2008). Such interspecies differences may help to explain the routine occurrence of concentric myocardial hypertrophy in hyperthyroid cats, in contrast to the general documentation of hyperfunctional but not prominently hypertrophied ventricles in human hyperthyroidism (Klein and Ojamaa 2001; Klein 2008). As will be discussed below, an alternative explanation could be the late recognition, with very dramatic lesions, of hyperthyroid patients in initial feline reports from the early 1980s; by contrast, earlier recognition of hyperthyroidism in cats at the present time coincides with very modest cardiac structural changes in these cats, as in humans. Finally, additional factors exist in hyperthyroidism that are likely to further contribute to left

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ventricular concentric hypertrophy, including systemic hypertension, increased erythropoietin release, activation of the renin-angiotensin-aldosterone system, and chronic sympathetic stimulation (Kittleson and Kienle 1998; Klein and Ojamaa 2001).

Increased systolic and diastolic function are the result of several factors. An increase in myosin ATPase activity occurs due to the binding of T3 to the α-myosin heavy chain (V1) gene's regulatory region. Greater α-myosin heavy chain (V1) activity increases systolic function because myosin ATPase serves the essential function of hydrolysis of ATP to ADP and Pi, generating energy in the process that fuels the power stroke of actin-myosin interaction (Opie 2004). Triiodothyronine also increases influx of calcium into the myocyte cytosol through L-type sarcolemmal calcium channels and ryanodine channels in the sarcoplasmic reticulum, both of which are T3-responsive, and this increase in cytosolic calcium increases inotropic function. Venoconstriction is observed in hyperthyroidism, increasing return of blood to the heart and raising stroke volume according to Starling's law (Dillman 2002). An increase in beta-adrenergic receptor density identified in hyperthyroid hearts also can be expected to contribute to increased systolic function (Dillman 2002). Diastolic function is enhanced via T3-mediated phosphorylation (disinhibition) of phospholamban, the protein that otherwise blocks sarcoplasmic reticulum calcium ATPase (SERCa2, the pump that evacuates intracytoplasmic calcium and thus initiates diastole) (Dillman 2002; Klein and Ojamaa 2001). Finally, T3 alters the function of various cardiac sodium and potassium channels, an interplay that contributes to inotropy and lusitropy (see Figure 26.1). These systolic and diastolic effects are mediated by T3 directly and not via the autonomic nervous system, as evidenced by the decrease in heart rate, but not in systolic or diastolic function, when a beta-blocking drug is administered to hyperthyroid patients (Klein 2008).

The vascular effects of thyroid hormone mainly lead to vasodilation, and thus emerges a paradox: despite the direct vasodilatory effect of thyroid hormone (mediated by direct action of T3 on vascular smooth muscle cells) (Ojamaa et al. 1996), the most common blood pressure abnormality in hyperthyroid patients is systemic hypertension. The explanation lies in the greater degrees of increased systolic function and blood volume increase, which surpass the effect of arterial dilation. Hyperthyroid patients, through vasodilation, also have activation of the renin-angiotensin-aldosterone system, and thus a larger circulating plasma volume that limits the blood pressure effects of vasodilation; increased erythropoietin synthesis in hyperthyroidism results in a larger overall blood volume.

Hyperthyroid patients of many species commonly have sinus tachycardia (Klein and Ojamaa 2001; Peterson 1982; Feldman and Nelson 2004). There are several factors that contribute to increases in heart rate and potentially to arrhythmogenesis in hyperthyroidism, including a greater density of beta-adrenergic receptors as noted above, increased peripheral tissue demand, increased myocardial oxygen consumption as found in cats with experimentally induced hyperthyroidism (Skelton et al. 1970), atrial and ventricular enlargement, and actions on several membrane pumps and channels (see Figure 26.1).

Causes of Hyperthyroidism

Although a causative relationship has not yet been proven between specific etiologies and naturally occurring feline hyperthyroidism, associations with goitrogenic substances have been found through epidemiologic investigations. One exhaustive environmental study identified a threefold increase in risk of hyperthyroidism in cats that used litter compared to those that did not. A proposed explanation is that litter-using cats tend to be indoor cats, and a previous study identified an elevenfold greater risk of hyperthyroidism in indoor cats compared to outdoor cats (Scarlett et al. 1988), and thus either are exposed to hyperthyroid-inducing substances or simply are more closely cared for and thus more likely to live to the age at which hyperthyroidism occurs and to have owners take note of clinical signs and seek veterinary care.

For over 2 decades, the consumption of canned food has been associated with a higher risk of hyperthyroidism in cats. Scarlett et al. (1988) and Feldman and Nelson (2004) point out that the appearance of commercial canned cat food in North America the late 1960s coincides with the emergence of hyperthyroidism in cats beginning some 10 years later, when cats having consumed such food for several years would have begun to reach the age at which hyperthyroidism most commonly occurs. Several studies have identified an association between diet and hyperthyroidism, with hyperthyroidism being 2–3 times more likely to occur in cats eating canned food (Kass et al. 1999), threefold more likely in cats specifically eating canned food from pop-top cans (Edinboro et al. 2004), fourfold more likely in cats in which baby food was part of the diet (Edinboro et al. 2004), and a 1.9-fold to 2.4-fold increased risk in cats that specifically ate fish or liver and giblets flavors of food as opposed to 11 other flavor types (Martin et al. 2000). It is theorized that goitrogenic substances (substances which elicit greater synthesis and release of thyroid hormones) may be concentrated in certain ingredients within canned foods, such as fish, liver, and giblets, or that the cans themselves may be of a composi-

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tion that releases goitrogenic substances into the food (specifically, the plastic lining of pop-top cans).

Other possible causes, such as exposure to cigarette smoke, pesticides, herbicides, insecticides, and lawn fertilizers, have been variously implicated and then discounted (Kass et al. 1999; Scarlett et al. 1988).

Cardiovascular Pathologic Findings of Hyperthyroidism

The characteristic gross pathologic finding of thyrotoxic heart disease is diffuse left ventricular concentric hypertrophy/thickening. Such thickening may be marked in severe cases of hyperthyroidism, but the left ventricle of the average hyperthyroid cat is significantly less thick than the left ventricle of the average cat with hypertrophic cardiomyopathy. For example, a comparative gross pathologic study of cats with different forms of myocardial disease identified mean septal and free wall thicknesses, respectively, of 7.0 ± 0.4 mm and 7.1 ± 0.3 mm in hyperthyroidism, 8.3 ± 0.2 mm and 8.7 ± 0.2 mm in symmetric hypertrophic cardiomyopathy, and 9.8 ± 0.3 and 7.7 ± 0.2 mm in asymmetric hypertrophic cardiomyopathy affecting the interventricular septum more than the free wall (Liu et al. 1984). These postmortem dimensions should not be compared to diastolic measurements obtained echocardiographically, since the heart remains in end-systole after death.

The evolution of hyperthyroidism as a clinical entity over time has led to less dramatic clinical expression of the disease, likely because it is recognized routinely now in the early stages of the disease as opposed to in its latest stages when the disease was still new (Broussard et al. 1995; Scarlett et al. 1988; Edinboro et al. 2004). Cardiovascular implications are that the sometimes dramatic gross pathologic lesions, and general extent of thyrotoxic cardiovascular lesions, are less frequent and milder now compared to those reported in the 1980s, for example. This observation helps to explain the lower prevalence of marked left ventricular thickening, congestive heart failure (12% in 1979–1983 versus 2% in 1993 [Broussard et al. 1995]), and systemic hypertension described above.

Concurrent Thyrotoxic Heart Disease and Hypertrophic Cardiomyopathy

Because thyroid hormones (principally triiodothyronine, T3) exert their effects throughout the myocardium, left ventricular concentric hypertrophy in hyperthyroidism should be a diffuse process. Yet certain cases of hyperthyroidism are characterized by thickening that is asymmetrical, such as those where the interventricular septum is thicker than the left ventricular free wall (Liu et al. 1984). It is also worth noting that in some hyperthyroid cats, successful treatment leading to prolonged euthyroidism is not accompanied by complete normalization of left ventricular wall dimensions (Weichselbaum et al. 2005). These two observations, together with the recognition of the high prevalence of hypertrophic cardiomyopathy in the cat population (16% of overtly healthy cats in one echocardiographic study) (Paige et al. 2009), have led to the understanding that some cats may be afflicted with thyrotoxic heart disease and hypertrophic cardiomyopathy simultaneously (Liu et al. 1984). Such an observation is supported histologically: in a study of 23 cats with thyrotoxic heart disease, 20 had symmetrical left ventricular thickening and 3 had disproportionate septal hypertrophy. These 3 cats also had myocardial fiber disarray on microscopic examination, the hallmark finding of idiopathic hypertrophic cardiomyopathy. Therefore, the identification of an asymmetrically thickened left ventricle, or of ventricular thickening that has not resolved despite an otherwise effective antithyroid treatment, should lead to the clinical suspicion of concurrent hypertrophic cardiomyopathy. Such suspicion forms the clinical diagnosis of the 2 conditions occurring simultaneously, since confirmation requires histologic evaluation of the myocardium. An echocardiographically apparent finding that can occur with hypertrophic cardiomyopathy but that is uncommonly seen with thyrotoxic heart disease is systolic anterior motion of the mitral valve, and this feature may further strengthen the suspicion of concurrent hyperthyroidism and (idiopathic) hypertrophic cardiomyopathy in the same cat.

Signalment

Hyperthyroidism affects adult cats of any breed and both sexes. The mean age is approximately 13 years (range: 4–22 years), with fewer than 5% of cases occurring in cats less than 8 years old (Feldman and Nelson 2004). Males and females are affected in similar proportions, which stands in contrast to the prevalence of hypertrophic cardiomyopathy and its 3:1 or 4:1 predilection for male cats (Rush et al. 2002). No breed predisposition is known to exist; Siamese and Himalayan cats are less likely to be affected (odds ratios: 0.44 [0.26–0.74] and 0.29 [0.093–0.89], respectively) (Kass et al. 1999; Scarlett et al. 1988). Case series and epidemiologic studies have not reported the specific cardiovascular effects of hyperthyroidism to be of greater or lesser importance in any subgroup.

History and Chief Complaint

The presenting signs caused by hyperthyroidism reflect an inappropriate increase in metabolic activity. Weight

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loss (87%), polyphagia (49%), vomiting (44%), polydipsia/polyuria (36%), and increased activity/restlessness (31%) are some of the most common historical signs identified in the medical histories of hyperthyroid cats (Broussard et al. 1995). Many of these signs occur less dramatically, and less frequently, than the classically described initial reports of feline hyperthyroidism, and some authors have theorized that routine recognition of and testing for hyperthyroidism in cats has led to earlier recognition of the disorder in a larger number of more mildly affected cats. A small proportion of affected cats present with so-called "apathetic hyperthyroidism" characterized by weakness and anorexia. It appears that many or most of these cats have concurrent nonthyroidal illness, with chronic kidney disease, primary heart disease, and neoplasia most commonly implicated (Feldman and Nelson 2004).

Overt signs attributable to cardiovascular dysfunction are uncommon as chief complaints in cats with hyperthyroidism. Rather, cardiovascular effects often are identified incidentally during subsequent diagnostic evaluation of the hyperthyroid patient. Congestive heart failure, manifesting with dyspnea and anorexia, is a well-recognized complication of hyperthyroidism in cats, but it occurs in a small proportion of hyperthyroid cats (as high as 4/23 [17%] in one early, small case series, but subjectively far fewer cats in current practice) (Jacobs et al. 1992; Liu et al. 1984). Clinical signs of aortic thromboembolism are rarely reported, and this syndrome appears to be less common with thyrotoxic cardiovascular disease than with other forms of heart disease in the cat, possibly due to the hyperdynamic state and arterial dilation associated with this endocrinopathy.

Physical Examination

General physical findings in hyperthyroid cats can include palpable thyroid gland enlargement (83–90% of cases, with bilateral involvement palpable in about 2/3 of these), a thin body condition (65% of cases), nervous, hyperactive, or aggressive behavior, an unkempt hair coat, and ocular lesions (Feldman and Nelson 2004; Broussard et al. 1995).

Cardiovascular abnormalities are noted frequently on physical examination, often as incidental findings. Heart murmurs were present in 54% of 202 hyperthyroid cats in 1 study and 53% of 131 cats in another study at the same institution (Broussard et al. 1995). The source of these murmurs may include a combination of hyperdynamic inotropic/systolic and lusitropic/diastolic function with dynamic right ventricular outflow obstruction (Rishniw and Thomas 2002) or left ventricular outflow tract obstruction due to left ventricular concentric hypertrophy, heightened by the greater audibility of heart sounds through a thin body wall if the patient has a thin body condition.

A gallop sound is commonly heard, although such a finding is not necessarily as strongly suggestive of congestive heart failure in the cat as it is in other species. By definition, a gallop sound/"gallop rhythm" is a low-frequency third heart sound, usually S_4 rather than S_3, although this distinction is difficult or impossible to make when ausculting a tachycardic cat (see Chapter 1).

The pulse of hyperthyroid cats is typically normal to increased in strength, the latter due to a greater pulse pressure caused by increased left ventricular systolic function and normal diastolic arterial pressure.

A variety of cardiac arrhythmias is possible with hyperthyroidism, and these may be apparent on physical examination. Tachycardia is often present (42% of cases [Broussard et al. 1995]), although such a finding does not separate the hyperthyroid cat population from the healthy cat population in a hospital setting (Côté 2004). Premature beats may be noted during the physical examination. Typically, the postextrasystolic pause that follows the premature beat is most striking, such that on physical exam in cats, premature beats stand out by this pause and are often misinterpreted as atrioventricular block or other causes of "dropped beats." An electrocardiogram provides the correct diagnosis and is indicated in any hyperthyroid patient with an arrhythmia noted on examination.

Differential Diagnosis and Disease Variants

Differential diagnosis

The systemic signs of hyperthyroidism classically may be confused for diabetes mellitus, infiltrative or inflammatory bowel disease, chronic kidney disease, and various forms of neoplastic disease. From a cardiovascular standpoint, the main differential diagnoses revolve around left ventricular concentric hypertrophy and systemic hypertension. Disorders that cause left ventricular concentric hypertrophy include hypertrophic cardiomyopathy, systemic hypertension, valvular aortic stenosis, acromegaly, and hyperviscosity. History, physical examination, laboratory blood and urine tests, blood pressure measurement, and echocardiography help to differentiate hyperthyroidism from these conditions. Disorders that cause systemic hypertension include chronic kidney disease, pheochromocytoma, and other uncommon entities.

Cases of equivocal or mild hyperthyroidism may be confusing diagnostically if the level of circulating thyroxine seems inconsistent with the severity of clinical

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signs. Given their adult or advanced age, such cats often have concurrent diseases contributing to the observed clinical signs. Comprehensive diagnostic testing is indicated to rule in or rule out the disorders mentioned above because nonthyroidal illness is known to reduce circulating thyroxine concentrations ("euthyroid sick syndrome") and could explain a serum thyroxine level that is only minimally elevated despite prominent clinical signs of hyperthyroidism. If uncertainty continues to persist, diagnostic tests that help to confirm or refute hyperthyroidism may be indicated (see "Advanced Testing," below). From a cardiovascular perspective, cats that have mildly elevated serum thyroxine levels and equivocal, if any, systemic signs of hyperthyroidism almost never have deleterious cardiovascular effects of hyperthyroidism; the heart and circulation seem to be affected later in the disease process. Therefore, a patient with mild hyperthyroidism and substantial cardiovascular abnormalities (e.g., target organ damage from persistent, severe systemic hypertension, or marked left ventricular thickening) should be suspected of having a concurrent, unrelated problem as the cause of these abnormalities.

Complication of Hyperthyroidism: Thyroid Storm

"Thyroid storm" refers to an acute exacerbation of thyrotoxicosis in hyperthyroid cats. It may be triggered by the cat's presence in a stressful environment such as the veterinary clinical setting, restraint for diagnostic procedures, or other environmental factors, the intensity of which is potentiated by the effects of excess thyroid hormone. Four factors are thought to contribute to its pathogenesis (Ward 2009): high levels of circulating thyroid hormones; rapid, acute further increases in circulating thyroid hormones; hyperactivity of the sympathetic nervous system; and an increased intracellular response to thyroid hormones. Thyroid storm occurs variably and may cause cardiovascular abnormalities that can be fatal. Such abnormalities include sinus tachycardia, premature ventricular complexes and ventricular tachycardia, systemic hypertension, acute cardiogenic pulmonary edema/congestive heart failure, and cardiac arrest. Diagnosis is circumstantial: signs of acute onset of these abnormalities occur in a hyperthyroid cat, typically in the context of a triggering event. Treatment is generally conservative because the rapidly fluctuating thyroid hormone and sympathetic effects make pharmaceutical choices and dosage selection challenging. For example, while a hypertensive crisis or hemodynamically destabilizing arrhythmia may be treated with drugs, administering and monitoring the effects of the drugs may in fact worsen thyroid storm simply through handling of the patient, through incomplete monitoring, or both. Therefore, cats experiencing thyroid storm should be allowed to ambulate freely in a cage if they were previously being manually restrained, should be moved to a quiet and nonthreatening location if such was not already present, and should be monitored closely but in a manner that the cats tolerate and that does not antagonize or worsen the signs of thyroid storm. Although data are lacking to confirm this observation, prevention of thyroid storm is likely the best strategy, and such prevention begins with awareness that this complication occurs in hyperthyroidism. Specific precautions should include careful and conscientious handling of all hyperthyroid cats with attention paid to surroundings (e.g., presence of dogs or other cats should be avoided) and adjustment of one's handling and restraint of the patient based on signs of tolerance.

Other Complications of Hyperthyroidism

Reversion to euthyroidism is known to reveal chronic kidney disease in a proportion of the hyperthyroid cat population, and complications related to antithyroid treatment are well-recognized. These aspects of hyperthyroidism have been reviewed elsewhere (Feldman and Nelson 2004).

Diagnostic Testing

Initial Tests

The diagnosis of hyperthyroidism is established by identifying a high concentration of circulating thyroxine (T4). Although exact normal ranges are laboratory- and population-dependent, a typical range of normal serum T4 is 0.8–2 µg/dl (Feldman and Nelson 2004).

In hyperthyroid cats, cardiovascular diagnostic testing is inconsistently pursued and specific guidelines for which tests to perform under which conditions do not exist at present.

At a minimum, all cats with hyperthyroidism should have blood pressure measured via Doppler ultrasonic sphygmomanometry (Syme and Elliott 2003) initially and then throughout antithyroid treatment and periodically thereafter (see Chapter 21 for technique). Additional testing in the form of electrocardiography (Chapter 9), radiography (Chapter 6), and echocardiography (Chapter 7) may be implemented as dictated by clinical findings. Specifically, hyperthyroid cats with a heart murmur, gallop sound, or cardiomegaly on radiographs should undergo echocardiography to rule in or rule out concurrent forms of heart disease; cats with an arrhythmia or persistent tachycardia should undergo an electrocardiogram; and cats with dyspnea, auscultatory

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abnormalities of the heart and/or lungs, or other respiratory signs should be evaluated with thoracic radiographs.

Historically, hyperthyroidism has produced radiographic cardiomegaly, increased QRS amplitude and other ECG changes, and thickening of the left ventricle on echocardiography (Moïse and Dietze 1986; Moïse et al. 1986). Radiographic changes are limited in their sensitivity and specificity; that is, radiographs are poor screening tools and poor confirmatory tools for hyperthyroidism, respectively, because radiographic changes are only noted when cardiac changes are very substantial, and there is much overlap between such changes with other nonthyroid diseases such as hypertrophic cardiomyopathy. Radiographic cardiomegaly was noted in 8/20 (40%) (Moïse et al. 1986) and 5/11 (45%) (Liu et al. 1984) of hyperthyroid cats in 2 studies published in the mid-1980s, and even this prevalence of cardiomegaly is likely much lower now given our earlier consideration of hyperthyroidism in the differential diagnosis of cats with compatible clinical signs (Broussard et al. 1995). However, in cats showing overt clinical signs of respiratory embarrassment (mainly dyspnea), thoracic radiographs remain the diagnostic test of choice for ruling in or ruling out pulmonary edema, for identifying pleural effusion, and for identifying other causes of respiratory signs that might be unrelated to hyperthyroidism. The current standard of care should include radiographs of the thorax in all cats with suspected or confirmed hyperthyroidism, not principally for assessing the heart but for identifying other intrathoracic abnormalities that could be responsible for clinical signs otherwise attributed to hyperthyroidism (e.g., metastatic neoplasia, primary respiratory disease).

Sinus tachycardia has been recognized as the most common arrhythmia in cats with hyperthyroidism, occurring in 29–70% of cases (Broussard et al. 1995; Peterson et al. 1982; Liu et al. 1984). However, a newer study identified sinus tachycardia in only 14/202 cats (14%) (Broussard et al. 1995). Electrocardiographic evidence of left ventricular enlargement consists mainly of increased QRS amplitude in the left-sided and caudal ECG leads (II, III, aVF, V2). Historically, such evidence was apparent in 22% (Liu et al. 1984), 49% (Peterson et al. 1982), 65% (Moïse 1986), and 66% (Broussard et al. 1995) of hyperthyroid cats; a more recent comparative study revealed a lower prevalence (34% [Broussard et al. 1995]). Overall, this decreasing trend in radiographic and ECG abnormalities is consistent with the general decrease in the severity of lesions in feline hyperthyroidism over time (Broussard et al. 1995). Therefore, the current role of electrocardiography in feline hyperthyroidism is reserved for identifying arrhythmias in patients known or suspected to have them based on history and physical examination. Arrhythmias and conduction disturbances noted in hyperthyroid cats historically have included prolonged QRS complex duration (7/45 cats, 16%) (Peterson et al. 1982), atrial premature complexes (5/45, 11%; Peterson et al. 1982), short QT interval (5/45, 11%) (Peterson et al. 1982), left anterior fascicular block (2/45, 4%) (Peterson et al. 1982), premature ventricular complexes (2/45, 4%; Peterson et al. 1982), 2 cases of ventricular preexcitation (Peterson et al. 1982; Riesen and Lombard 2005) and one case each of ventricular tachycardia and bigeminy, right bundle branch block, atrial tachycardia (all Peterson et al. 1982), second-degree atrioventricular block with right bundle-branch block (Rishniw et al. 1982), and third-degree AV block (Jacobs and Otto 1988). The AV block and bundle branch block cases may have been caused by ossification of the central fibrous body and fibrosis and degeneration of conduction fibers in and around the atrioventricular node, as was found in 3 hyperthyroid cats (Liu et al. 1984).

Echocardiography is the diagnostic test of choice for assessing myocardial structure and function clinically in the cat. An echocardiogram is indicated in any cat with suspected or confirmed hyperthyroidism if a history of syncope, presyncope (self-resolving ataxia and disorientation of a few seconds' duration), or respiratory distress is present; if physical examination reveals a heart murmur, gallop sound, dyspnea, an arrhythmia, or pulselessness of a limb; if radiography identifies cardiomegaly and/or pulmonary infiltrates or pleural effusion; or if an electrocardiogram demonstrates a cardiac arrhythmia. In the absence of all of these signs, the diagnostic yield of echocardiography is low and unlikely to alter treatment or prognosis.

The first report of echocardiography in hyperthyroid cats described structural changes in a majority of them: hypertrophy of the left ventricular free wall in 74/103 cats (72%), and interventricular septal hypertrophy in 41/103 cats (40%). Such changes resolved in 30–50% of cats after antithyroid treatment (Bond et al. 1988). A more recent survey of 91 hyperthyroid cats, published 20 years after the report mentioned above, identified one or more abnormal echocardiographic measurements in only 37% of cases (Weichselbaum et al. 2005). Even with this lower prevalence of echocardiographic changes, the abnormalities mostly appeared to be trivial: for example, the mean interventricular septal thickness in diastole in the hyperthyroid cats was 4.4 ± 0.7 mm compared to 4.2 ± 0.7 mm in healthy controls, and mean left ventricular free wall thickness in diastole was 4.7 ± 1 mm compared to 4.1 ± 0.7 mm. By comparison, the pre- and

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posttreatment values in 24 of the cats from the earlier study were: 5.5 ± 13.2 mm and 4.8 ± 10.1 mm (left ventricular free wall in systole and diastole, respectively) and 5.2 ± 10.4 mm and 4.5 ± 8.9 mm (interventricular septum in systole and diastole, respectively). Such substantial differences, especially with large standard deviations, suggest a wide range of ventricular concentric hypertrophy historically. By comparison, at the present time the structural cardiac changes induced by hyperthyroidism in cats appear to be modest. Reversion toward normal of even these small changes can occur in some cats after treatment, and a decrease in mean septal thickness of 0.2 mm and left ventricular free wall thickness of 0.5 mm occurred in 91 hyperthyroid cats treated with radioiodine (Weichselbaum et al. 2005). Other reports have described resolution of cardiac enlargement radiographically and electrocardiographically but not echocardiographically (Moïse and Dietze 1986).

Additional abnormal findings, including enlargement of the left atrium, aortic root, end-diastolic left ventricular diameter, and increased fractional shortening, have been noted in some hyperthyroid cats (Bond et al. 1988).

Mitral regurgitation due to systolic anterior motion of the mitral valve may be identified echocardiographically. This finding is rarely due to thyrotoxic heart disease alone, and finding this abnormality in a hyperthyroid cat should raise the possibility of unrelated, concurrent hypertrophic cardiomyopathy.

Advanced Testing

In 2–10% of cats with subsequently confirmed hyperthyroidism, serum T4 concentration is within the normal range or in an equivocal zone (e.g., 2–5 µg/dl) at the time of first examination for signs of hyperthyroidism (Feldman and Nelson 2004). Possible explanations for this paradox include measurement of T4 early during the course of the disease, diurnal variation, and concurrent nonthyroidal illness. In this situation, additional measurement of serum free T4 concentration (by equilibrium dialysis) provides diagnostically useful information: of 26 cats with mild hyperthyroidism, where the cats later developed unmistakable signs of hyperthyroidism and elevated serum T4 concentrations, initial serum T4 concentration was elevated in 16/26 cats (60%), but initial serum free T4 concentration was elevated above the normal range of 3–10.5 ng/dl in 25/26 cats (96%).

Advanced cardiovascular tests are rarely pursued or necessary in feline hyperthyroidism. An intriguing development is the investigation of circulating levels of a cardiac biomarker, cardiac troponin-I (cTn-I) in hyperthyroid cats on initial presentation compared to levels measured again after treatment. On initial evaluation, 11/23 (48%) of hyperthyroid cats had detectable circulating levels of cTn-I, whereas after radioiodine treatment only 3/18 (17%) of cats had detectable circulating levels of cTn-I. While not statistically significantly different with a small study population, these results may have identified that myocardial damage both exists as part of thyrotoxic heart disease, and is reduced when euthyroidism is restored (Connolly et al. 2005). A large, prospective, single-institution study of circulating cardiac biomarkers in 425 cats did not reveal a linear relationship between serum thyroxine levels and plasma NT-proBNP levels; hyperthyroid cats had a mean plasma NTpro-BNP level that was somewhat higher than euthyroid cats, but there was a large degree of overlap between hyperthyroid and euthyroid groups (Ettinger 2010). Therefore, hyperthyroidism may affect plasma NT-proBNP results in the cat, generally by increasing them.

Treatment

Antithyroid Therapy

The treatment of choice for hyperthyroidism is radioiodine therapy, often preceded by a period of oral antithyroid drug treatment (see below) to assess renal function during euthyroidism and decide whether to permanently eliminate the hyperthyroid state. Treatment with 3–5 mCi ^{131}I (dosage based on clinical signs, size of the thyroid gland, and serum T4 concentration) successfully lowered the serum T4 concentration to normal or below normal in 516/524 (98.5%) of treated cats (Peterson and Becker 1995) with few complications (2.1% hypothyroidism; 2% persistent or recurrent hyperthyroidism). Alternatively, surgical thyroidectomy was preferred prior to the advent of radioiodine therapy and it remains an acceptable option when radioiodine therapy is not possible and an owner does not wish to, or cannot, administer daily antithyroid drugs. A substantial drawback is the occurrence of thyroid adenoma bilaterally in 70% of cases, requiring either bilateral adrenalectomy (and daily thyroid supplementation, whereas the avoidance of daily medication administration often was the factor that led to the decision to perform thyroidectomy instead of administering oral antithyroid drugs) or only partial resolution due to removal of only one thyroid lobe. Oral antithyroid drugs are a third treatment option, and while advantages include being able to adjust treatment based on clinical signs or appearance of comorbid conditions (e.g., chronic kidney disease) and lower initial cost to the client, drawbacks include daily pilling, lack of eradication of the problem, and the possibility of adverse drug reactions. Methimazole (Tapazole) 2.5 mg PO q 12 h is a typical starting dosage, and every-12-hour dosing has been shown to be necessary where previously

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once daily was thought by some to be adequate (Trepanier et al. 2003). The dosage may be titrated up to better control persistence of the hyperthyroid state, or titrated down if chronic kidney disease with or without systemic hypertension are unmasked by the euthyroid state. Methimazole treatment is generally effective and safe; reported adverse effects include thrombocytopenia, gastrointestinal signs such as acute vomiting, transient hepatopathy, and facial pruritus causing self-mutilation. Such effects may prompt the use of alternative drugs, such as carbimazole (not available in the United States) 2.5 mg PO q 12 h for 7 days, then 5 mg PO q 12 h with further dosage adjustments made based on serum thyroxine levels and clinical signs (Feldman and Nelson 2004).

Cardiovascular Drugs

Cardiac-specific drugs given to hyperthyroid cats aim to offset the effects of excess thyroid hormone indirectly. Beta blockers such as atenolol (6.25 mg PO q 12 h) are most widely used in this respect. Beta blockers may be considered in hyperthyroid cats that have sinus tachycardia with atrial or ventricular premature complexes, with or without systemic hypertension. Such drugs aim to blunt sympathetically mediated increases in heart rate and inotropy, both of which may be detrimental or life-threatening in severely hyperthyroid cats (see "Thyroid Storm," above). It is essential, however, that such prescriptions be given only if the cat is fully cooperative and willing to receive oral medications at home. An owner's perception of the critical importance of giving heart medication, together with a cat's resistance to pilling, may trigger a struggle that initiates a thyroid storm in the home setting, and such a complication can and must be avoided through clear communication with the owner proactively.

It is worth noting that no difference was observed in 91 hyperthyroid cats with respect to echocardiographic dimensions when cats who received prior oral medications (methimazole, beta blocker, calcium-channel blocker, angiotensin converting enzyme inhibitor) were compared to normal controls (Weichselbaum et al. 2005).

Antihypertensive drugs are indicated in cats showing target-organ damage resulting from the hypertension (see Chapter 21), in cats with severe hypertension (e.g., persistent systolic arterial blood pressure >180 mm Hg in calmest environment) that has not responded to antithyroid medication, and in cats with a new onset of systemic hypertension during antithyroid treatment (Syme and Elliott 2003). The drug of choice is amlodipine begun at 0.625 mg per cat PO q 24 h, with dosage adjusted based on clinical signs of hypertensive damage and follow-up blood pressure measurements.

Outcome and Prognosis

Natural Evolution of Hyperthyroidism in Cats

Untreated hyperthyroidism in the cat leads to prominent externally observable clinical signs, with extracardiac signs such as weight loss and ravenous appetite almost invariably preceding cardiovascular signs.

When treated, hyperthyroid cats survive for a period of time that appears to be related at least in part to treatment type. In a retrospective study that addressed this question, 47 cats treated with methimazole survived for a median of 2.0 years (interquartile range: 1–3.9 years), which was significantly shorter than the median survival time for 55 cats treated with radioiodine alone (4.0 years; interquartile range = 3.0–4.8 years) or the median survival time for 65 cats treated with methimazole for a median 88 days followed by radioiodine therapy (5.3 years; interquartile range = 2.2–6.5 years).

OTHER ENDOCRINOPATHIES

Acromegaly

Acromegaly is a syndrome caused by an excess in circulating growth hormone, usually a result of a functional tumor of the somatotropic cells of the pituitary pars distalis in cats (Feldman and Nelson 2000). After hyperthyroidism, acromegaly is the most common feline endocrinopathy that produces clinically relevant cardiovascular effects. It is a rare disorder, however, with between 100 and 200 feline cases reported worldwide to date (Niessen et al. 2007).

Measurement of serum growth hormone concentrations revealed a higher than normal concentration in one study of cats with hypertrophic cardiomyopathy, raising the possibility that a sizable subset of cats with what was thought to be hypertrophic cardiomyopathy would in fact have cardiac manifestations of acromegaly, and therefore the opportunity for reversal of heart lesions with control of the endocrinopathy (Kittleson 1992). Unfortunately, the serum growth hormone level elevations were modest, unlike those of acromegalic cats with pituitary tumors, and of the 8 cats who died and were examined at necropsy, none had a pituitary tumor. Therefore, in some cats with idiopathic hypertrophic cardiomyopathy, serum growth hormone levels appear to be modestly elevated, and the way in which this finding is associated with heart disease—if there is an association at all—is unclear.

Clinical signs of acromegaly in cats typically are those of diabetes mellitus (polyuria, polydipsia, polyphagia), because of the insulin antagonizing effects of growth hormone, but the anabolic effects of growth hormone may cause weight gain in contrast to the weight loss of

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the typical diabetic patient (Peterson et al. 1990). Abdominal organomegaly, stertor due to excess growth of pharyngeal tissues, and broadening and flattening of the forehead are other physical features of acromegaly in cats (Peterson et al. 1990; Feldman and Nelson 2000; Berg et al. 2007; Niessen et al. 2007). Other anabolic effects of growth hormone may explain cardiovascular physical examination abnormalities, notably systolic heart murmurs in 9/14 (64%) of cats and signs of congestive heart failure in 6/14 (43%) (Peterson et al. 1990). In one case series of acromegalic cats, congestive heart failure manifested with ascites in 2/6 cats, in addition to pulmonary edema (5/6) and pleural effusion (1/6) (Peterson et al. 1990). Thoracic radiographs revealed mild to moderate cardiomegaly in a majority (12/14, 86%) of cats, and echocardiography demonstrated left ventricular concentric hypertrophy, with septal thickening in 7/8 cats and left ventricular free wall thickening in 5/8 cats (Peterson et al. 1990). Systemic hypertension and electrocardiographic abnormalities do not appear to be a common feature of feline acromegaly (Niessen et al. 2007), both having been detected in zero of 17 acromegalic cats. Despite treatment with pituitary gland irradiation and/or the somatostatin analog octreotide, 5/14 cats in one series developed congestive heart failure, which contributed to euthanasia or death in 4. Necropsy results in 10 cats included "hypertrophic cardiomyopathy" (likely left ventricular concentric hypertrophy) in 7 and "dilated cardiomyopathy" (possibly growth hormone–associated myocardial failure) in 1. Nevertheless, the clinical relevance of acromegaly in feline cardiology remains that it may cause left ventricular concentric hypertrophy and subsequent congestive heart failure, and that such disorders may be addressed most effectively through therapies that treat the endocrinopathy, in addition to treatment for congestive heart failure should it be present.

Diabetes Mellitus

Diabetes mellitus in humans is an important risk factor for heart disease, but this association does not hold true in cats. Most likely this difference is due to the different underlying substrate of heart disease: the most common heart disease of humans in industrialized nations is coronary artery atherosclerosis, and this disease is potentiated by diabetes mellitus. Fortunately for cats, the feline species does not sustain coronary artery atherosclerosis to any clinically meaningful degree, either in diabetic or nondiabetic states.

Diabetic humans also have an increased incidence of systemic hypertension. This cardiovascular problem, likewise, is virtually unknown in diabetic cats: 2 cases of systemic hypertension have been recorded in cats with diabetes mellitus (Maggio et al. 2000) and diabetes is therefore considered to not be a clinically significant cause of systemic hypertension in cats (Brown et al. 2007).

Hyperadrenocorticism

Hyperadrenocorticism, a disease of glucocorticoid excess, is rare in the cat. Feline hyperadrenocorticism is caused by a functional pituitary tumor in approximately 50% of cases and a functional adrenal tumor in the remaining 50% (Feldman and Nelson 2000). Due to the insulin-antagonistic effects of glucocorticoids, the clinical presentation is typically that of insulin-resistant diabetes mellitus. Historical, physical exam findings, and diagnostic test results are not remarkable with respect to the cardiovascular system. Abnormalities should be viewed with skepticism in terms of causality, and common, independent disorders (e.g., hypertrophic cardiomyopathy if left ventricular concentric hypertrophy is noted echocardiographically, or chronic kidney disease or the white coat effect if the patient is hypertensive) occurring concurrently with hyperadrenocorticism should be considered a likely explanation for such findings.

Hyperaldosteronism

Excessive synthesis and systemic release of mineralocorticoids produces the syndrome of hyperaldosteronism, a rare endocrinopathy of cats. The cause is almost invariably a primary adrenal neoplasm (Ash et al. 2005). The pathophysiologic nexus is systemic sodium retention and severe potassium wasting caused by excessive activity of the aldosterone-driven sodium-potassium exchanger pump in the distal renal tubule. Accordingly, history and physical exam typically describe weakness due to hypokalemia-associated decreased skeletal muscle tone, inappetence, and other nonspecific signs. A minority of patients (2/13 in one case series) presents with acute vision loss due to intraocular hemorrhage and retinal detachment. Diagnostic testing typically reveals profound hypokalemia (may be <2.5 mEq/l) that is typically refractory to standard supplementation alone. This hypokalemia predisposes hyperaldosteronemic cats to ventricular ectopy, which may resolve with correction of serum potassium concentration. However, the feline ECG is notable for the rare occurrence of U waves with profound hypokalemia, in contrast to humans. Systemic hypertension due to aldosterone-mediated sodium retention is present in many cats, including some with target-organ damage (e.g., fundic lesions) that may or may not have led to overt organ dysfunction (i.e., some cats with hypertensive fundic lesions are still visual, while others present due to acute blindness) (Ash et al.

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2005). The confirmatory test of choice is immunohistochemical staining of an excisional biopsy of the affected adrenal gland(s); a high index of suspicion can be formed from the combination of an adrenal mass identified on abdominal sonography in a patient with severe hypokalemia where the hypokalemia has no other identifiable cause and is partially or fully resistant to IV potassium infusions of up to 0.25 mEq/kg/hour. Treatment initially involves correction of hypokalemia (with intravenous infusion of KCl-supplemented fluids, spironolactone, angiotensin-converting enzyme inhibitor drugs, or combinations of these), and definitive treatment is possible with adrenalectomy to remove the affected gland; barring local invasion, such treatment can be curative.

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SECTION O

Anesthesia in the Patient with Cardiac Disease

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27

Anesthesia in the Patient with Cardiac Disease

Bruno H. Pypendop

Key Points

- Anesthetic management of cats with heart disorders is based on the underlying heart structure, which can be divided into five functional categories:
  - Systolic myocardial failure (e.g., dilated cardiomyopathy)
  - Diastolic dysfunction (increased ventricular wall thickness or other forms of ventricular wall stiffening, e.g., hypertrophic cardiomyopathy [HCM], restrictive cardiomyopathy [RCM])
  - Ventricular volume overload (e.g., ventricular septal defect)
  - Ventricular volume underload (e.g., dehydration)
  - Structurally normal heart (e.g., physiologic heart murmur)
- Preanesthetic preparation includes assessment of the state of cardiac disease with a minimum database (CBC, serum chemistry profile, urinalysis), thoracic radiographs, electrocardiogram, blood pressure, and optimally an echocardiogram.
- Cardiac medications, with the exception of angiotensin converting enzyme (ACE) inhibitors, should be administered the morning of anesthesia.
- Correction of anemia and electrolyte disturbances prior to anesthesia is recommended as an important step toward minimizing anesthetic risk.
- An anesthetic induction protocol with minimal cardiovascular adverse effects in most stable, asymptomatic cats is propofol and a benzodiazepine (diazepam or midazolam) for induction, and isoflurane or sevoflurane for maintenance. For cats with symptomatic disease, the preferred technique is induction with etomidate and a benzodiazepine and maintenance with isoflurane or sevoflurane.
- In cats with significant heart disease (e.g., cardiac enlargement on thoracic radiographs or echocardiogram), lower IV fluid rates of 3–5 ml/kg/hr are recommended to avoid fluid overload and precipitation of congestive heart failure.
- Intra-anesthetic hypotension is initially managed by reducing the anesthetic concentration to as low as possible and careful intravenous fluid resuscitation (3–5 ml/kg IV with additional volume titrated if necessary) if hypovolemia is present.
- Persistent hypotension is managed by administering either vasoconstrictors (phenylephrine) in cats with diastolic dysfunction (e.g., thickened ventricular walls), or positive inotropes (dobutamine or dopamine) in cats with myocardial failure or eccentric hypertrophy.
- Cardiac biomarkers (plasma NT-proBNP, serum cardiac troponins) are not known to help stratify anesthetic risk in cats and do not replace the minimum database for preanesthetic screening.

Feline Cardiology, First Edition. Etienne Côté, Kristin A. MacDonald, Kathryn M. Meurs, Meg M. Sleeper.
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INTRODUCTION

Risk associated with sedation or general anesthesia of cats with naturally occurring heart disease is understood via clinical reports and objective experience, but not blinded prospective studies. In general, studies of small animal morbidity and mortality show good correlation with the American Society of Anesthesiologists (ASA) physical status classification (Table 27.1) (Broadbelt et al. 2007, 2008; Dyson et al. 1998; Gaynor et al. 1999). As expected, this correlation suggests that increased severity of the disease increases anesthetic risk. Therefore, a cat with cardiac disease that is currently life-threatening (ASA class 4 or 5) is at higher risk of anesthetic complications than a cat with stable, yet even severe, cardiac disease (ASA class 3), and all efforts should be made to convert decompensated/symptomatic patients to stable/asymptomatic patients prior to anesthesia. In particular, nonurgent procedures on cats with congestive heart failure should be postponed until medical management is started and signs of heart failure have resolved or improved. Similarly, if medical management of cardiac disease without heart failure is indicated (e.g., beta blocker administration in an asymptomatic cat with hypertrophic cardiomyopathy), elective procedures should be postponed until the patient has been medicated for at least a few days, and reevaluated. Feline cardiovascular patients with the highest anesthetic risk are those with

- Active congestive heart failure
- Clinically significant bradyarrhythmias such as third-degree atrioventricular block or high-grade second-degree atrioventricular block
- Clinically significant tachycardias such as rapid (>280 beats/minute) ventricular tachycardia
- Intracardiac thrombi

Cats with severe atrial dilation may be more likely to be on the brink of developing congestive heart failure and/or thromboembolic disease, and may pose a higher risk than the cat with mild heart disease and minimal atrial dilation. This does not indicate that cats with severe atrial dilation cannot be anesthetized, but it reflects that their heart disease is usually more severe. The clinician must weigh the importance of the procedure with the risk of the anesthesia and recovery. For example, dental prophylaxis may carry an increased risk of anesthetic complications in a cat with cardiomyopathy and atrial enlargement, but if the periodontal disease is severe, and both the dental disorder and the cardiomyopathy are expected to worsen over time, general anesthesia and dental work may be optimal at that time. Cats with cardiac disease have a higher risk for malignant arrhythmias than normal cats. Anesthetic agents largely impact cardiovascular function in normal cats, and the effects are even more pronounced in cats with cardiac disease. Selection of the correct agents, support, and monitoring are all critical to a positive outcome. In particular, cats with active congestive heart failure, or a history of heart failure, require extremely careful management and intensive monitoring; anesthesia of these patients is best conducted by a specialist.

Cardiac disorders can be functionally classified into the following categories:

- Systolic myocardial failure (e.g., dilated cardiomyopathy)
- Diastolic dysfunction (increased ventricular wall stiffness secondary to restrictive cardiomyopathy (RCM), unclassified cardiomyopathy (UCM), concentric hypertrophy; ventricular thickening due to pressure overload, such as with systemic hypertension, or hypertrophic cardiomyopathy [HCM]); or pericardial disease)

Table 27.1. American Society of Anesthesiologists classification system

ASA Class	Definition	Example
I	A normal healthy patient	Young healthy cat undergoing a spay
II	A patient with mild systemic disease	Cat with mild mitral regurgitation without left atrial enlargement
III	A patient with severe systemic disease	Cat in congestive heart failure, stable with medical management
IV	A patient with severe systemic disease that is a constant threat to life	Cat with ventricular tachycardia
V	A moribund patient that is not expected to survive without the operation	Cat with major abdominal hemorrhage, in hypovolemic shock

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- Eccentric hypertrophy of the ventricle (e.g., ventricular septal defect)
- Ventricular underload/decreased preload (e.g., dehydration, hypovolemia of any cause) (Kittleson and Kienle 1998a).

A fifth category could be considered with signs of cardiac abnormalities but a structurally normal heart in a stable, euvolemic patient (e.g., physiologic murmur). Such murmurs are common in cats (Paige et al. 2009), and an echocardiogram definitively establishes the diagnosis by exclusion of structural heart disease. Each of the different types of cardiac disorders listed above requires specific, individual adjustments in anesthetic management.

Systolic myocardial failure (e.g., dilated cardiomyopathy) is characterized by a decrease in myocardial contractility. Anesthestic management relies on the use of positive inotropes if needed and avoidance of negative inotropes such as beta blockers unless required for the treatment of severe supraventricular tachycardia. Specifically, hypotensive crises in patients with systolic myocardial failure may benefit from intravenous infusion of dopamine or dobutamine, titrated to achieve acceptable arterial blood pressure. Cats with systolic myocardial failure who are already receiving beta blockers such as atenolol orally prior to anesthesia should continue to receive them pre- and postoperatively, barring bradycardia and/or active congestive heart failure

Diastolic dysfunction (e.g., RCM, UCM, or concentric hypertrophy/ventricular thickening such as seen with HCM) is characterized by decreased ventricular relaxation and compliance, and possibly dynamic left ventricular outflow tract obstruction (e.g., systolic anterior motion of the mitral valve) in cases of HCM. Patients with diastolic dysfunction usually benefit from a slow normal heart rate (to decrease myocardial oxygen consumption and maximize preload), avoidance of positive inotropes such as dopamine or dobutamine (which increase myocardial oxygen consumption and may increase outflow obstruction), and increased systemic vascular resistance (which increases coronary perfusion pressure and may decrease outflow obstruction). In practical terms, this translates to ***not*** skipping the dose of beta blocker or calcium-channel blocker on the morning of the anesthesia for cats receiving these medications, avoiding dopamine and dobutamine, and avoiding drugs that cause vasodilation (e.g., acepromazine) or stimulate the sympathetic nervous system (e.g., ketamine, Telazol®). Hypotension in cats with left ventricular thickening is addressed by decreasing inhalant anesthetic concentration if possible; careful volume expansion if hypovolemia is present; and if hypotension persists, administration of a vasoconstrictor such as phenylephrine, titrated to achieve acceptable arterial blood pressure (see "Treatment of Hypotension" below).

With eccentric hypertrophy (e.g., ventricular septal defect), circulating volume optimization, a normal heart rate, and normal to low systemic vascular resistance are beneficial. This means that volume underload (e.g., dehydration) warrants treatment with intravenous fluids, for example, whereas intravascular volume excess (e.g., congestive heart failure) requires fluid removal, such as with diuretics and/or centesis.

Cats with decreased preload/volume underload (e.g., dehydration, hypovolemia) benefit from intravascular volume optimization. Therefore, it is of critical importance to administer a fluid volume (IV crystalloid fluids, blood transfusion, or other, as dictated by clinical need) sufficient to restore normovolemia ***prior*** to anesthetic induction. Ideally, these measures should be performed prior to echocardiography, because chamber dimensions and wall thicknesses are altered by fluid balance (Campbell and Kittleson 2007).

The choice of drugs (Table 27.2) and support during anesthesia will be directed at achieving the goals mentioned above. Arrhythmias may be associated with other cardiac diseases, or they may be the primary disorder. Their short-term treatment during general anesthesia is discussed here (see Chapter 18 for in-depth discussion of arrhythmia management). An atropine challenge test (0.04 mg/kg SC or IV) should be done in all cats with sinus bradycardia, second-degree AV block, or third-degree AV block. Cats with high-grade second-degree atrioventricular block or third-degree atrioventricular block probably will not have any improvement in ventricular rate following atropine challenge, because antimuscarinic drugs (e.g., atropine, glycopyrrolate) are unlikely to increase the heart rate of these patients; these cats have a high anesthetic risk without a temporary pacemaker. Referral is therefore indicated for temporary cardiac pacing in such cases. Serum potassium levels should be measured in cats with significant bradycardia to evaluate for life-threatening hyperkalemia (see Chapter 18).

PREANESTHETIC PREPARATION

Prior to sedating and/or anesthetizing a cat with known or suspected cardiac disease, a current assessment of the severity of the disease should be obtained. Complete blood count and serum biochemical evaluation, thoracic radiographs, an electrocardiogram, and

Table 27.2. Drugs used in anesthesia for the feline cardiac patient

Drug	Dose	Route	Indication(s)	Notes
Atropine	0.01–0.04 mg/kg	SQ, IM, IV	Prevention or treatment of bradycardia	Use low dose if IV
Glycopyrrolate	0.005–0.01 mg/kg	SQ, IM, IV	Prevention or treatment of bradycardia	
Acepromazine	0.01–0.03 mg/kg	SQ, IM, IV	Sedation	Combine with opioid
Oxymorphone	0.02–0.1 mg/kg	SQ, IM, IV	Analgesia, premedication	
Hydromorphone	0.04–0.1 mg/kg	SQ, IM, IV	Analgesia, premedication	
Methadone	0.2–0.5 mg/kg	SQ, IM, IV	Analgesia, premedication	
Buprenorphine	0.01–0.03 mg/kg	SQ, IM, IV, buccal	Analgesia, premedication	
Butorphanol	0.1–0.4 mg/kg	SQ, IM, IV	Analgesia, premedication	
Midazolam	0.1–0.3 mg/kg	SQ, IM, IV	Sedation, muscle relaxation, reduction of dose of induction agent	May cause dysphoria
Diazepam	0.2–0.5 mg/kg	IV	Sedation, muscle relaxation, reduction of dose of induction agent	May cause dysphoria
Medetomidine	0.002–0.02 mg/kg	SQ, IM, IV	Sedation	0.02–0.04 mg/kg in fractious cats
Dexmedetomidine	0.001–0.01 mg/kg	SQ, IM, IV	Sedation	0.01–0.02 mg/kg in fractious cats
Ketamine	5–10 mg/kg	IM	Sedation	Use with other drugs
Telazol®	3 mg/kg	IM	Sedation	
Etomidate	0.5–1.5 mg/kg	IV	Induction	Use with benzodiazepine; titrate to effect
Propofol	4–8 mg/kg	IV	Induction	Titrate to effect
Ketamine	5 mg/kg	IV	Induction	Titrate to effect
Isoflurane	0–3%	Inhalation	Maintenance	
Sevoflurane	0–4%	Inhalation	Maintenance	
Fentanyl	0.005 mg/kg	IV	Loading dose, intraoperative analgesia/balanced anesthesia	
Fentanyl	0.006–0.024 mg/kg/h	IV	Constant rate infusion, intraoperative analgesia/ balanced anesthesia	
Nitrous oxide	50–70%	Inhalation	Intraoperative analgesia/ balanced anesthesia	Causes sympathetic stimulation
Dopamine	3–10 µg/kg/min	IV	Increase myocardial contractility	Titrate to effect on blood pressure
Dobutamine	3–10 µg/kg/min	IV	Increase myocardial contractility	Titrate to effect on blood pressure
Phenylephrine	0.2–1 µg/kg/min	IV	Increase systemic vascular resistance	Titrate to effect on blood pressure
Esmolol	0.1 mg/kg/min	IV	Treatment of tachyarrhythmias	
Edrophonium	0.5–1 mg/kg	IV	Treatment of supraventricular tachycardia	
Diltiazem	0.02–0.1 mg/kg	IV	Treatment of supraventricular tachycardia	
Lidocaine	0.5–1 mg/kg	IV	Treatment of ventricular arrhythmias	Do not exceed 4 mg/kg total dose

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cardiac ultrasound are recommended. Cardiac ultrasound should be performed in all cats with abnormal cardiac auscultation (murmur, gallop, or arrhythmia) prior to general anesthesia, since most cats with cardiac disease are asymptomatic (Paige et al. 2009; Gundler et al. 2008; Rush et al. 2002), and thoracic radiographs may be unremarkable if the disease has not resulted in moderate or severe cardiac enlargement and/or congestive heart failure. Normal auscultation does not exclude cardiac disease in cats, and clinical experience suggests that anesthetic death in apparently healthy cats is often associated with asymptomatic hypertrophic cardiomyopathy. Increased suspicion (e.g., breeds at risk; immediate relative has cardiomyopathy) should prompt a discussion with the owner of the potential for an increased risk despite normal auscultation, which further justifies the consideration of thoracic radiographs and/or echocardiography before anesthesia. Furthermore, in such patients, even if testing is not undertaken, anesthetic and monitoring protocols used in cats with heart disease may be preferred.

Anemia can be exacerbated by anesthesia (i.e., hemodilution or blood loss) and should be corrected if significant (e.g., hematocrit < 20%). Because some cardiac patients are sensitive to fluid overload, correction of anemia is best carried out prior to anesthesia, using slow administration of packed red blood cells and careful patient monitoring. Cats receiving loop diuretics may have electrolyte imbalances that should be corrected prior to anesthesia. Medications such as inotropes, diuretics, beta-adrenergic blockers and calcium-channel blockers should be administered the day of anesthesia. However, it may be preferable to withhold angiotensin converting enzyme inhibitors, since these drugs have been associated with severe, refractory hypotension in anesthetized humans. A study in cats showed that enalapril significantly worsens isoflurane-induced hypotension (Ishikawa et al. 2007).

ANESTHESIA

Diastolic Dysfunction

Hypertrophic cardiomyopathy is the most common cardiac disease in cats (Paige et al. 2009; Kittleson and Kienle 1998b). Other causes of diastolic dysfunction, including pressure overload due to systemic hypertension or aortic or pulmonic stenosis, RCM, UCM, HCM, and concentric ventricular hypertrophy due to hyperthyroidism, are managed similarly from an anesthetic standpoint, except that drugs known to raise arterial blood pressure (e.g., alpha-2 agonists such as medetomidine and dexmedetomidine) may be contraindicated in hypertensive patients. In addition, the primary cause should be treated when possible.

Cats with hypertrophic cardiomyopathy have decreased ventricular compliance, and maintenance of cardiac output requires a large ventricular volume and maintenance of (slow) sinus rhythm, which enhances diastolic filling. The atrial contribution to filling is important to cats with diastolic dysfunction. In cats with systolic anterior motion of the mitral valve, the determinant of the physical resistance to left ventricular outflow is not systemic vascular resistance but the severity of the left ventricular outflow tract obstruction.

In patients with moderate or severe left ventricular outflow tract obstruction (diagnosed by echocardiography), a decreased afterload, increased myocardial contractility, or decreased preload may worsen the severity of the obstruction. For example, in a cat with severe left ventricular outflow tract obstruction, avoidance of positive inotropes such as dobutamine, excessive vasodilation (e.g., excessively deep anesthetic plane), and excessively low preload (e.g., dehydration) are important to avoid increasing the obstruction. In contrast, factors such as bradycardia, mild myocardial depression, increased systemic vascular resistance, and avoidance of volume underload to the ventricle (e.g., ensuring normal hydration) typically improve systolic function and cardiac output in these cases. The degree of systolic anterior motion (SAM) of the mitral valve, and therefore obstruction to outflow from the left ventricle, is often thought to decrease with anesthesia based on the reduction of intensity of a heart murmur when some cats are under anesthesia. However, cats with physiologic murmurs (structurally normal hearts) also routinely experience a decrease in murmur intensity under anesthesia. A possible mechanism for both situations is a decrease in cardiac output associated with general anesthesia, resulting in less turbulence at the level of the dynamic obstruction. Therefore, reduction in intensity (or disappearance) of a murmur under anesthesia cannot be used for concluding that there is or is not structural heart disease in a given cat.

Cats with hypertrophic cardiomyopathy are commonly premedicated with an opioid such as oxymorphone, hydromorphone, methadone, or buprenorphine. Butorphanol may be satisfactory for sedation prior to a nonpainful procedure, but its analgesic effect is likely weak, and μ-agonists (full or partial) are preferred for painful procedures. Midazolam (IM, SQ, IV) or diazepam (IV) may be added to improve sedation but may result in dysphoria in some cats. Glycopyrrolate may be added if the heart rate is excessively low (i.e., less than 90 bpm), but it is not routinely used in premedications because administering it pre-emptively may cause

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tachycardia. Glycopyrrolate is preferred to atropine because it tends to increase the heart rate less and may cause fewer arrhythmias (Mirakhur et al. 1978). The use of the alpha-2 adrenergic agonist medetomidine has been shown to reduce left ventricular outflow tract obstruction in cats with left ventricular hypertrophy (Lamont et al. 2002); however, the effect has not been studied in anesthetized cats, and it is unclear whether the hemodynamic effects of alpha-2 agonists would prove beneficial during anesthesia in cats with hypertrophic cardiomyopathy. Decreased heart rate and increased systemic vascular resistance (as produced by alpha-2 agonists) are usually beneficial, as is the sympatholytic effect; however, alpha-2 agonist administration does not provide good control of the intensity of these effects. Moreover, alpha-2 agonists may increase arterial blood pressure beyond desirable values, and hypertension increases myocardial oxygen consumption, which is undesirable with ventricular hypertrophy. In summary, available information is insufficient to support the use of alpha-2 agonists routinely for premedication in all cats with HCM. If necessary, reduction in heart rate can be achieved by titration of a short-acting beta blocker, such as esmolol, and increase in systemic vascular resistance by titration of a short-acting alpha-1 agonist such as phenylephrine. Acepromazine should be avoided because of its vasodilatory effect, and dissociative anesthetics (e.g., ketamine) are contraindicated because of the sympathetic stimulation they commonly produce.

Induction of anesthesia is best performed by careful titration of an injectable agent to effect, because induction with inhalation agents causes excitement and release of catecholamines. Etomidate (1–2 mg/kg IV) and a benzodiazepine (midazolam 0.25 mg/kg IV or diazepam 0.5 mg/kg IV) are preferred, particularly for severe cases or those with systolic dysfunction. However, this combination is not widely used or familiar in many clinical settings. For mild to moderate cases, propofol (4–8 mg/kg), either alone or, preferably, in combination with a benzodiazepine, is an acceptable induction combination. It does cause systemic vasodilation and decreased afterload. Thiopental and dissociative agents (ketamine, tiletamine) should be avoided, the former because of the tachycardia and ventricular arrhythmias it may induce, and the latter because of the sympathetic stimulation produced. Anesthesia is maintained with isoflurane or sevoflurane in oxygen. Sevoflurane may be slightly preferable, since data suggest that it reduces systemic vascular resistance to a lesser extent than isoflurane and that its vasodilatory effect may reach a ceiling at low to moderate concentrations (Pypendop and Ilkiw 2004). Both agents should be carefully titrated to effect, according to close monitoring of anesthetic depth. The minimum alveolar concentration of sevoflurane is approximately 1% higher than that of isoflurane, so higher requirements for sevoflurane should be expected.

Balanced anesthetic techniques, most commonly based on utilizing an opioid infusion (fentanyl) to reduce the amount of inhalant anesthetic and improve hemodynamics, have often been advocated in these patients. However, opioids decrease inhalant anesthetic requirements only moderately (Ferreira et al. 2009; Ilkiw et al. 1997, 2002) or not at all in cats (Brosnan et al. 2009). Additionally, at the doses reported to achieve reduced inhalant requirements, significant sympathetic stimulation has been reported (Pascoe et al. 1997), which would be detrimental to cats with most types of heart disease, notably hypertrophic cardiomyopathy. Low doses of opioids could be used, but benefits other than analgesia remain to be demonstrated. Epidural morphine can be used for providing analgesia, but conflicting results on its effect on anesthetic requirements have been published (Golder et al. 1998; Pypendop et al. 2006). Alternatives to opioids for balanced anesthesia that have been studied in cats include ketamine, nitrous oxide, and lidocaine. Ketamine and nitrous oxide produce sympathetic stimulation and may therefore not be good choices for cats with hypertrophic cardiomyopathy (Bovill 2006; Ebert and Kampine 1989); lidocaine produces significant cardiovascular depression in normal cats (Pypendop and Ilkiw 2005a) and is not an appropriate adjunct for balanced anesthesia in the cat. Alpha-2 adrenergic agonists (medetomidine, dexmedetomidine) at low doses may prove useful for balanced anesthesia in cats with hypertrophic cardiomyopathy. As in other species, in normal cats, dexmedetomidine dose-dependently decreases heart rate and inhalant requirements and increases systemic vascular resistance (Pypendop, unpublished data), which may be beneficial in cats with hypertrophic cardiomyopathy. In normal cats anesthetized with isoflurane and without any additional drug, optimal dosing of dexmedetomidine appears to be a loading dose of 0.5–1 μg/kg and a constant infusion rate of 0.5–1 μg/kg/h. Local or regional anesthesia should be used whenever possible, since it is expected to decrease anesthetic requirements, improve analgesia, and be safe if properly performed. For further information on such techniques, the reader is referred to review articles and veterinary anesthesia textbooks (Duke 2000; Lemke and Dawson 2000; Tranquilli et al. 2007).

Systolic Myocardial Failure and Volume Overload

Myocardial failure is caused by decreased myocardial contractility, and may be a primary cardiomyopathy (i.e., dilated cardiomyopathy) or more commonly sec-

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ondary to other cardiac diseases that cause significant ventricular volume overload (e.g., patent ductus arteriosus, congenital or degenerative mitral or tricuspid valve disease). Primary myocardial failure is rare in cats. However, systolic myocardial failure secondary to other cardiac diseases (shunts, valvular insufficiencies, severe end stage hypertrophic cardiomyopathy, etc.) is more commonly seen. The main feature in ventricular volume overload is eccentric hypertrophy, which is defined as an increased end-diastolic ventricular volume and normal wall thickness. Maintenance of normal cardiac output requires normal to high-normal heart rate (i.e., 140–180 bpm), and low to normal systemic vascular resistance. Although maintenance of adequate preload is necessary (implying adequate administration of intravenous fluids and correction of dehydration or hypovolemia prior to anesthesia), avoidance of fluid overload is also important (see Chapter 24).

Cats with myocardial failure or volume overload usually should receive an opioid such as oxymorphone, hydromorphone, methadone, or buprenorphine, and an anticholinergic such as atropine (0.02 mg/kg SQ, IM) or glycopyrrolate (0.01 mg/kg SQ, IM), unless tachycardia (HR > 200 bpm) is present, for anesthetic premedication. A target for physiologically appropriate heart rates ranges from 140–180 bpm during anesthesia, with avoidance of heart rates under 120 and over 200 bpm. Alpha-2 agonists should be avoided because of their vasoconstrictive effect. Benzodiazepines, low doses of acepromazine, or dissociative anesthetics (ketamine, Telazol®) could be added if additional sedation is necessary, but in the author's experience, it is rarely the case. While an argument could be made for the potential benefit of acepromazine-induced vasodilation, the effect is poorly controlled, and excessive vasodilation results in hypotension, which may not be easily managed in these patients. Benzodiazepines may produce dysphoria rather than sedation in some feline patients (Ikiw et al. 1996). Induction of anesthesia is preferably achieved using etomidate and a benzodiazepine, particularly if systolic dysfunction is present. Dissociative anesthetics such as ketamine or Telazol® may be used, but the cardiovascular stimulation associated with their administration requires a normally functioning sympathetic nervous system, which may not be present in some of these patients. If sympathetic stimulation does not occur, dissociative anesthetics decrease myocardial contractility, which is detrimental in these patients. In the absence of systolic dysfunction, propofol may be used with careful dose titration to the lowest effective dose allowing intubation. Anesthesia is maintained with isoflurane or sevoflurane. Both agents decrease myocardial contractility and cause vasodilation. Although mild to moderate vasodilation may be beneficial by reducing afterload, the decrease in myocardial contractility is undesirable, particularly in cases with systolic dysfunction. Therefore, the lowest possible inhalant anesthetic concentration should be used, and maintenance of cardiac output may require the use of positive inotropes such as dopamine or dobutamine (see "Treatment of Hypotension," below). Techniques allowing a reduction of inhalant dose may be beneficial; for example, local and regional anesthetic techniques are recommended as adjuncts to general anesthesia whenever feasible (Duke 2000; Lemke and Dawson 2000; Tranquilli et al. 2007).

As mentioned above, the use of balanced anesthesia with opioids is often useful, but while it produces analgesia, it may have limited effects on anesthetic requirements in cats. However, sympathetic stimulation seen with high doses of opioids would not necessarily be detrimental in cats with eccentric hypertrophy (ventricular volume overload), contrary to cats with diastolic dysfunction. Systemic lidocaine (Pypendop and Ilkiw 2005a), and alpha-2 agonists (Pypendop, unpublished data) should be avoided in patients with myocardial failure, because both dose-dependently increase systemic vascular resistance. Nitrous oxide and ketamine produce mild sympathetic stimulation and may be beneficial. However, no data on the cardiovascular effects of ketamine in inhalant-anesthetized cats are available, and nitrous oxide appears to increase systemic vascular resistance in normal cats anesthetized with isoflurane compared to isoflurane alone (Pypendop et al. 2003).

Decreased Preload

In these diseases (e.g., significant pericardial effusion and cardiac tamponade, severe dehydration, mitral or tricuspid stenosis), reduction of ventricular filling leads to decreased ventricular volume and cardiac output. The goal is therefore to maximize preload. Although rarely clinically seen in cats, severe pericardial effusion should be drained prior to induction of anesthesia or immediately thereafter in patients intolerant of the procedure under sedation. Optimization of preload relies on judicious fluid administration, and low normal (i.e., 90–120 bpm) heart rate to maximize diastolic filling time. Opioids are typically used for premedication, and anticholinergics are avoided, except if moderate to severe bradycardia (HR < 80 bpm) is present. Etomidate and a benzodiazepine, or propofol are used for induction of anesthesia. Dissociative anesthetics and thiopental should be avoided because they increase heart rate. Anesthesia is maintained with isoflurane or sevoflurane in oxygen. High doses of opioids, nitrous oxide, and ketamine should be avoided during maintenance of anesthesia because they increase heart rate.

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Nonpathologic Murmurs

A common cause of heart murmurs in cats is dynamic right ventricular outflow tract obstruction. This is not considered a pathologic finding. An echocardiogram is needed to differentiate an innocent murmur caused by dynamic right ventricular outflow tract obstruction from other pathologic murmurs caused by structural or functional cardiac disease. Similarly to other causes of nonpathologic murmurs, anesthesia can be conducted as in any other cat without cardiac disease.

ANESTHETIZING THE FRACTIOUS CAT

Fractious cats with suspected or known cardiac disease are particularly challenging to anesthetize, because the information available is often limited, a thorough physical examination is often not possible, and heavy sedation may be required for placement of an intravenous catheter. This increases the risk of sedation/anesthesia in these patients and should be discussed with the owner. Three basic options are available: box induction with an inhalant anesthetic, intramuscular administration of a dissociative (Telazol® or ketamine), or intramuscular administration of an alpha-2 agonist. An opioid/benzodiazepine combination can be tried, but will often not provide adequate sedation in these patients.

Because hypertrophic cardiomyopathy is the most common cardiac disease in cats, and it may not be possible to assess the severity of the disease without sedation or anesthesia, sympathetic stimulation should be avoided as much as possible. Box induction with an inhalant anesthetic and dissociative agents cause sympathetic stimulation, the former because of the stress associated with the technique, and the latter due to a drug effect. Therefore, alpha-2 agonists are preferred in this situation. Medetomidine or dexmedetomidine are the agents of choice, since xylazine has been reported to be arrhythmogenic. Higher doses (medetomidine 20–40 µg/kg; dexmedetomidine 10–20 µg/kg) than in nonfractious patients may be required. If an injection cannot be performed, box induction with an inhalant is the only option, but the risk associated with the technique should be understood and approved by the owner.

SUPPORT AND MONITORING

A lead II ECG, temperature, and blood pressure should be monitored during anesthesia. The ECG should ideally be assessed during induction of anesthesia as well. Blood pressure is routinely measured using noninvasive techniques, preferably with Doppler (see Chapter 21). Oscillometric methods can be used but may have lower accuracy. The gold standard for blood pressure measurement during invasive or long-duration procedures is direct measurement, if resources are available. Once the cat is anesthetized, a 24-gauge catheter is inserted in the dorsal pedal or femoral artery and connected to a pressure transducer and monitor. Arterial catheterization is challenging in cats and should be attempted only by experienced personnel. Advantages of direct blood pressure measurement include better accuracy, and continuous measurement, which is particularly useful if hemodynamic instability is expected. Disadvantages, in addition to the technical difficulty, include risks for clotting, hemorrhage, poor perfusion of the area distal to the catheter, and infection. Using a continuous flushing device, catheterizing the dorsal pedal rather than the femoral artery, limiting arterial catheterization to 6 hours or less, and using an aseptic technique limit these risks.

Ventilation can be spontaneous, unless marked hypoventilation occurs or in cases in which the intraoperative onset of pulmonary edema interferes with oxygenation. In these cases, intermittent positive pressure ventilation with or without positive end-expiratory pressure is usually indicated. Oxygenation should be assessed by blood gas analysis, or by the use of a pulse oximeter.

Fluid administration and replacement of blood loss must be judicious to optimize preload without causing pulmonary edema. Typically, crystalloids are administered at a slower rate than in the normal cat; however, hypovolemia should be adequately corrected, and large volumes of fluid should be administered if necessary. A typical fluid protocol for a cat with substantial heart disease (structural abnormalities demonstrated on echocardiography or moderate cardiomegaly on thoracic radiographs) is administration of lactated Ringer's solution at a rate of 3–5 ml/kg/h. Colloids should be used with extreme caution because they expand the circulating volume for a longer period of time and may result in plasma volume expansion greater than the volume administered. This leads to an increased risk of iatrogenic congestive heart failure with these fluids. The author typically avoids the use of colloids in cardiac patients, except for the treatment of anemia with blood products. Monitoring of central venous pressure may provide limited but sometimes useful guidance for fluid administration, but does not reflect filling pressures on the left side of the heart or reliably predict development of pulmonary edema in cats with left heart disease. Central venous pressure monitoring may be useful in following trends of overall fluid balance and is extremely useful for monitoring cats with right heart disease (see Chapter 24).

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TREATMENT

Treatment of Hypotension

Universal techniques for treatment of hypotension in all types of heart disease include reducing inhalant dose (i.e., decreasing anesthetic depth with or without using anesthetic adjuncts) and correction of hypovolemia if present, using fluids. Treatment of hypovolemia should be done cautiously, since most patients with cardiac disease tolerate fluid loading poorly. With the exception of massive fluid loss (e.g., major hemorrhage), small fluid boluses (e.g., 5 ml/kg) should be given in increments until hypovolemia is corrected, or signs of fluid overload are observed. In anesthetized patients, fluid overload is usually detected as a decrease in oxygenation (based on blood gas analysis or pulse oximetry), due to development of pulmonary edema. Arterial blood gas analysis will provide an earlier warning than pulse oximetry but requires catheterization or direct puncture of an artery. Fluid overload should be treated immediately with diuretics and/or vasodilators.

Appropriate treatment of hypotension when it is not related to hypovolemia and after the inhalant dose has been reduced as much as possible is determined by the type of cardiac disease. In cases of concentric hypertrophy, the administration of vasoconstrictors (phenylephrine, norepinephrine) is indicated, and the administration of positive inotropes (dobutamine, dopamine) is contraindicated; the opposite is true for eccentric hypertrophy or myocardial failure. In cases of decreased preload, if optimizing preload is difficult or impossible (e.g., mitral or tricuspid valve stenosis), vasoconstrictors are likely to be more effective than positive inotropes. If a vasoconstrictor is used, phenylephrine may be preferable to norepinephrine, because of the former's lack of effect on beta-1 adrenergic receptors, although a study in healthy cats suggested an increase in stroke volume at high dose, which may reflect a positive inotropic effect (Pascoe et al. 2006). Once euvolemia is achieved, the author typically titrates phenylephrine to obtain adequate blood pressure, starting with an infusion of 0.5 µg/kg/min. Dopamine and dobutamine are commonly used for their positive inotropic effect. Both can be titrated to produce adequate blood pressure, starting with an infusion of 5 µg/kg/min. Higher doses (i.e., >10 µg/kg/min) of dopamine may cause vasoconstriction and should be avoided in cases of eccentric hypertrophy, particularly if systolic dysfunction is present. Dobutamine appears to cause mild vasodilation, which may mask its positive inotropic effect as indirectly assessed by blood pressure measurement, despite an overall increased cardiac output (Pascoe et al. 2006). The positive inotropic effect of both drugs is similar. In animals that would tolerate mild vasoconstriction (e.g., cats with diastolic dysfunction such as HCM patients), dopamine is preferred because it increases blood pressure more consistently than dobutamine, allowing easier titration to effect. However, in patients with congestive heart failure and severe systolic dysfunction, increases in afterload are poorly tolerated, and because dopamine administration carries the risk of arterial constriction via stimulating alpha-1 adrenergic receptors, dobutamine is preferred. Both dopamine and dobutamine increase heart rate, but this effect usually is seen at doses higher than those needed to increase cardiac output and/or blood pressure.

Treatment of Arrhythmias

Treatment of bradycardia (see Chapter 18) and first- and second-degree atrioventricular blocks in anesthetized cats usually relies on the use of anticholinergics (e.g., atropine, glycopyrrolate). If anticholinergics are ineffective, or in cases of third-degree atrioventricular block, a beta-1 adrenergic agonist such as dopamine can be used. The dose required to produce a positive chronotropic effect (increased heart rate) is usually higher than that producing a positive inotropic effect (increased ventricular contractility). The author titrates dopamine to effect, starting with an infusion of 10 µg/kg/min. Alternatively, isoproterenol has been used. However, isoproterenol is more arrhythmogenic than dopamine, and while it increases heart rate more consistently than dopamine, it is a nonselective beta-agonist. The effect on beta-2 adrenergic receptors produces vasodilation and potentially severe hypotension. It is therefore usually avoided in anesthetized cats. In some cats with third-degree AV block, neither drug effectively increases heart rate. The most effective approach to bradycardia associated with third-degree atrioventricular block is the placement of a temporary pacemaker, and patients should be referred prior to anesthesia if this procedure is unavailable.

The need for treatment of supraventricular tachycardia in normovolemic anesthetized cats is dictated by the arrhythmia's hemodynamic effects and the underlying condition. If the underlying cause cannot be identified or treated, beta-adrenergic antagonists are usually recommended. Esmolol (0.1 mg/kg/min IV) is commonly used in anesthetized patients because of its short duration of action. Alternatively, drugs that increase vagal tone can be used and will not affect myocardial contractility. The author uses edrophonium, an acetylcholinesterase inhibitor, at the dose of 0.5–1 mg/kg IV. Management of marked, persistent tachycardia (i.e., heart rate >180 bpm) in patients with concentric hypertrophy during anesthesia relies on the use of beta blockers such as esmolol or propranolol. The former is usually preferred because of its short duration of action. Calcium

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channel blockers such as diltiazem (0.02–0.1 mg/kg; begin low and repeat as needed) can also be administered intravenously.

The treatment of ventricular arrhythmias is considered necessary during anesthesia if they cause hypotension, are multifocal, or are malignant (e.g., R on T phenomenon). Lidocaine at a low dose (0.5–1 mg/kg bolus, repeated if necessary up to 4 mg/kg) can be used in cats with normal cardiac function, but should be used very cautiously in cats with cardiac disease, particularly during anesthesia, since it may result in a severe decrease in cardiac output, presumably due to an effect on myocardial contractility. A study in normal cats anesthetized with isoflurane showed that lidocaine dose-dependently reduced cardiac output, despite also reducing requirements for isoflurane (Pypendop and Ilkiw 2005a,b). Alternatively, short-acting beta blockers like esmolol can also be used.

Anesthetic Management of Cats with Shunting Defects

Left-to-right cardiovascular shunts including ventricular septal defects or patent ductus arteriosus may lead to volume overload of the left ventricle and possibly left heart failure. During anesthesia, shunting may be reduced by increasing pulmonary vascular resistance, decreasing systemic vascular resistance, or both. Carbon dioxide has been reported to cause systemic vasodilation and pulmonary vasoconstriction (Barer et al. 1967; Price 1960), so mild-moderate permissive hypercapnia (e.g., $PaCO_2$ 50–60 mm Hg) may be beneficial.

Right-to-left shunting through ventricular septal defects or patent ductus arteriosus may be reduced by increasing systemic vascular resistance, and can be worsened with systemic hypotension. Baseline arterial blood gas analysis or pulse oximetry often reveals significant hypoxemia prior to anesthesia. Titration of vasoconstrictors such as phenylephrine may result in improved oxygenation. Shunting through a patent foramen ovale (often in conjunction with pulmonic stenosis) are usually unresponsive to modulation of arterial resistance or other interventions.

POSTOPERATIVE MONITORING AND RECOVERY

Oxygen should be administered until extubation. If iatrogenic fluid overload is suspected, thoracic radiographs should be taken prior to recovery, and treatment should be instituted if indicated. After extubation, pulse rate, respiratory rate and pattern, and body temperature should be monitored at least every 15 minutes until the cat is totally recovered and deemed normal. The chest should be ausculted bilaterally on a regular basis, particularly if an abnormal respiratory pattern or tachypnea is present. Pulse oximetry can sometimes be obtained by placing the probe on the ear, or on a toe web. Some cats require oxygen supplementation for a few hours after anesthesia based on persistently low arterial oxygen content on blood gas, persistent desaturation on pulse oximetry, or cyanosis. Continuous oxygen supplementation can be achieved by placing the patient in an oxygen cage, or, if such a cage is not available, in an induction box with a high oxygen flow.

PLANNING ANESTHESIA IN THE CARDIAC PATIENT WITHOUT AN ECHOCARDIOGRAM

Although an echocardiogram is an invaluable tool to diagnose the presence and specific type and extent of cardiac disease, sometimes clients are unable to pursue a thorough diagnostic workup prior to anesthesia. Murmurs in cats are not definitive for presence of structural heart disease; 69% of asymptomatic cats with murmurs in one study had no evidence of cardiomyopathy or cardiac disease (Paige et al. 2009). On the converse, absence of a murmur does not exclude presence of heart disease; only 31% of asymptomatic cats with cardiomyopathy had murmurs in one study (Paige et al. 2009). As a precaution, an abnormal cardiac auscultation including a murmur or gallop heart sound should raise suspicion of possible heart disease, and thoracic radiographs should be taken if further diagnostic workup with an echocardiogram is not possible. Radiographic evidence of significant cardiomegaly and pulmonary edema or pleural effusion demand treatment and further justify diagnostic workup with echocardiography, blood pressure, and a minimum data base, and postponing or canceling (if elective) the anesthetic procedure.

If an echocardiogram is not possible but anesthesia is deemed indispensable, the practitioner is forced to predict the form of heart disease present in the cat, which is very difficult or impossible. Because cardiomyopathies, and hypertrophic cardiomyopathy in particular, are the most common heart diseases in cats, the practitioner may want to assume that this disease is present. A generic "cardiac" anesthetic protocol can be used in cats without significant arrhythmia or heart failure if unspecified cardiac disease is suspected. This anesthetic protocol is particularly adapted to moderate hypertrophic cardiomyopathy, but it is unlikely to result in severe complications if another form of mild cardiac disease is present. Premedication includes an opioid and avoidance of acepromazine and anticholinergics. Induction may include propofol (4 mg/kg) and diazepam (0.3 mg/kg), or etomidate (1–2 mg/kg) and diaze-

pam (0.5 mg/kg) IV. Ketamine or thiopental should be avoided. Lower fluid rates of 3–5 ml/kg/hr are recommended to avoid fluid overload and potentiation of congestive heart failure. Anticholinergics such as glycopyrrolate or atropine should not be administered routinely, but given at low dose if bradycardia (HR <120 bpm) develops. Treatment of hypotension is more problematic since the appropriate approach heavily depends on the type of cardiac disease. If a drug is necessary, a vasoconstrictor such as phenylephrine is usually selected because of the higher prevalence of hypertrophic cardiomyopathy compared to other types of diseases, but it would be contraindicated in cases of systolic dysfunction. Lack of definitive information obtained from an echocardiogram prevents the clinician from making educated decisions, and the increased risk associated with this should clearly be discussed with, and approved by, the owner.

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SECTION P

Cardiac Screening Programs

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Cardiac Screening Programs

Key Points

- Effective screening programs have the ability to identify disease, or the risk of a familial disease, and can provide recommendations on how to use the information provided.
- Hypertrophic cardiomyopathy is the most commonly requested disease for screening, and screening strategies may include both annual echocardiography and mutation screening, depending on the breed.

INTRODUCTION

Effective use of, and institution of, screening programs is dependent on two important elements. The first is accurate diagnosis of the affected state. The second is that guidelines are present to make specific recommendations once the affected status of the breeding animal has been determined.

Modes of Inheritance

Cardiac disease (e.g., hypertrophic cardiomyopathy) in the cat is most often inherited in an autosomal dominant fashion, but other modes of inheritance including autosomal and X-linked recessive are possible.

An autosomal dominant trait is one in which the disease is carried on an autosomal chromosome and typically causes clinically evident changes even with only one gene copy of the mutation. Evaluation of pedigrees of an affected animal should demonstrate that males and females are equally affected and that every affected cat has at least one affected parent. Animals that show the phenotype (clinical presentation) can be either heterozygous (one copy of the mutation) or homozygous (two copies of the mutation).

Autosomal recessive traits are those carried on an autosomal chromosome as well but since they are recessive the cat will not demonstrate the clinical presentation unless both copies of the individual's gene have the mutation. Evaluation of pedigrees of affected cats should show that the disease appears to "skip" a generation (parents do not show the trait) and males and females should equally show the phenotype. Mating two cats that appear normal will produce approximately 25% of offspring with the affected trait and 75% that do not demonstrate the trait. This suggests that the two parents are silent carriers of a recessive trait. If both parents show the trait, all offspring should show the trait.

X-linked traits are caused by a mutation in a gene carried on the X chromosome (i.e., not autosomal). They are most commonly recessive. Therefore, males will almost always show the affected trait because they only have one X chromosome. Because females have two X chromosomes, they may be silent carriers if they have the mutant copy of the gene on only one of their X chromosomes. They will show the phenotype if both X chromosomes have the mutant copy of the gene. Evaluation of pedigrees of affected animals should show more affected males than females and an affected male crossed with a normal female should produce silent carrier (normal phenotype, no clinical evidence of disease) females.

Genetic diseases are also impacted by a phenomenon referred to as *genetic penetrance*. Genetic penetrance determines how much of a trait is demonstrated in the individual. If a trait has incomplete or varied penetrance (feline hypertrophic cardiomyopathy, for example), not

Feline Cardiology, First Edition. Etienne Côté, Kristin A. MacDonald, Kathryn M. Meurs, Meg M. Sleeper.
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all of the individuals with a causative mutation will actually show the trait and they will not all show the same disease severity. For example, some Maine coon cats with the Maine coon hypertrophic cardiomyopathy mutation may have severe ventricular hypertrophy and develop congestive heart failure; littermates with the same mutation may not ever show the disease. The mechanisms for the phenomenon of variable disease penetrance are poorly understood even in human genetics. It is possible that environmental or genetic factors may have an impact on a particular mutation. Importantly, not all individuals that carry a genetic mutation or are the offspring of affected parents will show the disease, or will show it with the same severity.

CONGENITAL DEFECTS

Overall, the incidence of congenital heart defects in the cat is much less common than the incidence of acquired heart diseases like cardiomyopathies (see Section D). Although many congenital defects have been demonstrated to be inherited in the dog, this has not yet been shown in the cat and the majority of congenital heart defects do not appear to be overrepresented in a particular breed.

Diagnosis

Congenital defects in cats are most commonly characterized by a significant structural change in the heart that results in turbulent blood flow, so the presence of a heart murmur should be the first indication of the underlying defect. However, presence of an arrhythmia is also abnormal in kittens, and may also suggest a congenital heart defect. Careful echocardiographic evaluation, ideally by a veterinary cardiologist, should be performed to accurately diagnose the type of defect. This is important for planning of a breeding program, since not all defects will be inherited in the same way and knowledge of the defect will help in making accurate recommendations. However, a specific mode of genetic transmission for any feline congenital defect is not known.

Recommendations

Very little is known about the inheritance of congenital defects in the cat and very few breed predispositions have been observed (see Chapter 10). The lack of information about the heritability of specific defects means that strong recommendations usually cannot be provided. It should also be remembered that not all defects are heritable; some are simply spontaneously occurring. The infrequent identification of a congenital heart defect in a breeder's line should not result in significant concern about an inheritable trait.

Use of an animal with a congenital defect for breeding should be strongly discouraged. Although an animal with a defect does not necessarily suggest a heritable trait, there is a risk of passing on even a spontaneously occurring trait to the progeny. Additionally, queens with congenital heart disease may be personally put at risk with the fluid shifts and stress of pregnancy.

Repeated use of an unaffected animal that has produced a single or even litters of affected kittens is not necessarily wrong since the defect may or may not be heritable. However, since it is possible that an unaffected animal could carry a recessive heritable trait, it should not be bred to the same mate again since it is possible that they both carry a recessive trait. The breeder can be advised to breed again with a different mate. Additionally, they should not breed to a related mate (also called *line breeding*), because this could emphasize a recessive trait as well. If additional affected offspring are produced, the individual cat should no longer be used for breeding.

Adult Onset Disease

Hypertrophic cardiomyopathy is the most common heart disease for which cardiac screening is requested because it is the most common adult onset cardiac disease in the cat and a familial etiology has been demonstrated in at least some breeds (Kittleson et al. 1999; Meurs et al. 2005, 2007). Although there is some evidence that there is a familial component to development of DCM with taurine deficiency, it is not typically screened for since taurine supplementation can cause resolution of the disease (Pion et al. 1987; Lawler et al. 1993).

HYPERTROPHIC CARDIOMYOPATHY

Signalment

Hypertrophic cardiomyopathy has been demonstrated to be inherited in the Maine coon and Ragdoll breeds (Kittleson et al. 1999; Meurs et al. 2005, 2007). It has been suggested that it may be inherited in other breeds as well including Sphynx, British shorthair, Norwegian Forest cat and Siberian among others, but complete studies have not been done. In the Maine coon, hypertrophic cardiomyopathy has been demonstrated to be inherited as an autosomal dominant trait (Meurs et al. 2005). Hypertrophic cardiomyopathy is likely to be inherited in the same mode in the Ragdoll as well, but definitive proof is lacking at present.

Diagnosis

The antemortem diagnosis of hypertrophic cardiomyopathy is based on echocardiography (see Chapter 7). Screening programs classify cats as clear, indeterminate,

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or affected. This is an adult onset disease and the age of onset may vary significantly from cat to cat, even within the same breed. Therefore, a single screening really represents only the status of the cat's heart at that point in time, and the most accurate screening programs require annual screening with echocardiography until at least 10 years of age.

Recommendations

Clear

Cats that have no auscultable murmur, gallop, or arrhythmia and have a normal echocardiographic exam are considered to be clear of hypertrophic cardiomyopathy at that time, but as mentioned above, should be evaluated annually.

Indeterminate

It is not uncommon for adult cats to have some indication of cardiac abnormalities, including the presence of an auscultable murmur in the face of a normal echocardiogram or the presence of some echocardiographic abnormality that does not truly meet the criteria of an affected cat. Some of these cats may progress to develop hypertrophic cardiomyopathy; others will never advance at all. Therefore, cats that are classified as having an indeterminate status should ideally be at least temporarily withheld from the breeding program until their disease status is more certain, which is assessed by repeat echocardiography. A recheck in 6–12 months with an echocardiogram could be considered.

Affected

Given the heritability of the disease in at least some breeds of cats, breeding of affected cats cannot be recommended. Additionally, once an affected cat has been identified, the siblings and parents of the affected cat should be screened by echocardiography and all offspring carefully followed echocardiographically on an annual basis in order to identify affected animals as soon as possible.

GENETIC SCREENING

A causative DNA mutation has now been identified in two breeds of cats, the Maine coon and the Ragdoll (Meurs et al. 2005, 2007).

In the Maine coon, a genetic mutation has been identified in the myosin binding protein C (MYBPC3) gene, a cardiac sarcomeric protein involved in cardiac contraction (Meurs et al. 2005). It is also a commonly mutated gene responsible for familial hypertrophic cardiomyopathy in humans (Keren et al. 2008). The mutation in the Maine coon results in a single base pair change from a guanine to a cytosine in the 31st codon of the gene. This mutation changes the highly conserved amino acid alanine to proline, a large amino acid with a ring. Cats that are homozygous for the mutation (both chromosomes in a pair contain the mutated gene) often appear to develop a more severe form of hypertrophic cardiomyopathy and may show clinical signs before 4 years of age. Cats that are heterozygous (only one of two chromosomes in a pair has the mutated gene) may develop the disease at a later age and have milder signs (Meurs et al. 2005). Additionally, for reasons not well understood, a small percentage of cats with the mutation may not ever show clinical signs of the disease, and this is referred to as *decreased penetrance of disease*. Genetic modifiers that affect the expression and penetrance of the disease are likely but have yet to be determined. Some Maine coon cats develop familial hypertrophic cardiomyopathy in the absence of the mutation of myosin binding protein C, and likely possess a different mutation that is yet to be identified.

A substitution mutation has also been identified in the myosin binding protein C gene in the Ragdoll cat (Meurs et al. 2007). However, the Ragdoll mutation is different from the Maine coon mutation and is a cytosine to thymine substitution in the 820th codon, which changes the amino acid produced from arginine to tryptophan. It is extremely unlikely that the Maine coon and Ragdoll mutations were inherited from a common ancestor since the mutations are different and are located in such different regions of the gene. It is more likely that these are two novel mutations that developed independently. In the Ragdoll, homozygous cats appear to be very severely affected with development of heart failure and thromboembolic episodes often before 2 years of age. Heterozygous cats appear to have a much more mild form of the disease that may include only mild papillary muscle hypertrophy.

In both cases, the mutations appear to be quite breed-specific. The Maine coon mutation is specific for the Maine coon and the Ragdoll mutation is specific for the Ragdoll. Affected Sphynx, British shorthair, Siberian, Bengal, and Norwegian Forest cat have been screened for, but do not have, the mutation (Meurs et al. 2009).

Mutation Screening

Genetic testing is now available to test a cat for either the Maine coon or Ragdoll mutation by submitting a DNA sample to a reputable screening laboratory. High-quality DNA samples can be obtained either from a blood sample submitted in an EDTA tube or by brushing the buccal mucosa of the cat with a special buccal swab, although many labs will even accept samples submitted on a cotton swab. Buccal swabbing is particularly

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helpful for testing young kittens in which it may be difficult to obtain a blood sample. Additionally, an owner can perform the buccal swabbing at home without stressing the cat and mail the swabs directly to the screening laboratory.

Once the sample is provided to the laboratory it can be analyzed in a number of ways. The gold standard for testing is to perform DNA sequencing for actual visualization of the mutation. Less reliable but faster assays are available but often have not been fully validated.

The test results should verify that the cat is negative, heterozygous, or homozygous for the mutation. Cats that test negative do not have the mutation. This does not mean that they will not develop hypertrophic cardiomyopathy; it simply means that they will not develop the form of the disease caused by the specific genetic mutation. Although these mutations have been shown to be the cause of hypertrophic cardiomyopathy in many Maine coons and Ragdoll cats, there are some cats that are echocardiogram-positive for hypertrophic cardiomyopathy that do not have the specific mutations.

Recommendations

Over a 2-year period of time, 35% of the Maine coon submissions for genetic screening at Washington State University were found to be positive for the mutation (only 9% of all samples were homozygous-positive) (Fries et al. 2008). Likewise, 28% of the Ragdoll submissions were positive (8% homozygous). Due to this apparently high prevalence of the mutation in both breeds, it would seem to be unwise to recommend that all cats with these mutations be removed from a breeding program since this could result in dramatically altering the genetic makeup of these breeds. Additionally, it should be emphasized that, because of the reduced and varied penetrance observed with this disease, not all cats that have the mutation, particularly if they are heterozygous, will develop a clinical form of the disease.

Homozygous cats

These cats are at a very high risk of developing a severe form of the disease (particularly Ragdolls), and will certainly pass on the mutation to offspring since both copies of their MYBPC3 gene contain the mutation. Homozygous cats should not be used for breeding and should be further evaluated with an echocardiogram.

Heterozygous cats

The heterozygous cat should be carefully evaluated. Cats that have many strong positive breed attributes and are disease-negative (normal phenotype, i.e., clear echocardiogram) at time of breeding could be bred to a mutation-negative cat. Their lack of clinical disease may suggest that they have a very mild form of the disease or that they just do not show evidence of this adult onset clinical disease yet. Therefore these cats should be used only if they are exceptional for the breed and they should be clinically evaluated for the disease by annual echocardiograms. If they develop the clinical disease, they should be eliminated from the breeding program. The offspring from the mating of a positive heterozygous and a negative cat should be screened for the mutation, and if possible, a mutation-negative kitten with desirable traits should be selected to replace the mutation-positive parent in the breeding colony. Over a few generations this will decrease the prevalence of the disease mutation in the population, and the aim is to do so without altering the genetic makeup of the breed significantly. Finally, disease-negative but mutation-positive cats should be evaluated annually for presence of disease via echocardiography because they may develop phenotypic expression of the disease (i.e., left ventricular hypertrophy) over time.

OTHER FORMS OF CARDIOMYOPATHY

Due to the lower prevalence of both restrictive and dilated cardiomyopathy and the lack of information about a familial basis of these diseases in cats, screening programs have not yet been developed. In human beings, both dilated and restrictive cardiomyopathies have been well documented as inherited diseases (Kimura 2008; Sen-Chowdhry et al. 2010). Therefore, although there is no known familial component of these diseases in the cat, if they are observed with frequency in a particular family or particular breed, a familial etiology should be strongly suspected and echocardiographic screening should be considered.

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SECTION Q

Which Drug for Which Disease?

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Which Drug for Which Disease?

INTRODUCTION

In a field with as few objective, evidence-based guidelines as feline cardiology, this is no doubt the most difficult chapter to write. Seemingly any conclusion on cardiovascular therapeutics in the cat can be criticized or dismantled if one tries hard enough. Yet as clinicians, we know that every patient represents the point at which concrete decisions must be made: treatment or no treatment? If treatment, what is best, and for how long? Our clinical grounding makes it impossible for us to be satisfied with criticizing a lack of evidence while streams of cats with heart disease pass through our hands. We have written these treatment approaches as a work-in-progress, fully aware—and hopeful—that, as we write these words, the data that prove us right or wrong are in the making.

We are indebted to Dr. Lionel Opie and his seminal book, *Drugs for the Heart*, for providing the title and concept for this chapter.

HYPERTROPHIC CARDIOMYOPATHY—COMPENSATED ("ASYMPTOMATIC")

The cause of HCM in cats is proven to be one or more genetic mutation(s) in some cats, and this pattern appears heritable. Therefore, in the absence of gene therapy, treatment consists of selective breeding and, for individual cats, drugs that slow or delay the cardiomyopathic process. There is either an absence of clinical studies of some commonly used cardiac drugs in the asymptomatic state, or a lack of evidence of benefit in some small-scale clinical reports. Therefore, two important considerations of treatment of compensated HCM in the absence of proof of efficacy are safety and convenience. Contraindications to any of the following treatments include intolerance (patient's resistance to medication administration, adverse effect, exacerbation of other disease states such as asthma with beta blockade, or others) and financial, temporal, or other client limitations that ultimately lead the client to elect for premature discontinuation of monitoring, or even euthanasia, after misconstruing the importance of the heart disease or its treatment:

- Beta blocker (atenolol 6.25–12.5 mg/*cat* PO q 12–24h). Beta blockers appear to be the most useful drug to reduce the severity of left ventricular outflow tract in cats with systolic anterior motion of the mitral valve, and cats with moderate or severe obstructions may receive symptomatic benefit as well as reduced concentric hypertrophy associated with lessening the pressure overload to the left ventricle. Additional benefits of beta blockade in cats with HCM may include decreased myocardial oxygen demand via prevention of tachycardia; increased diastolic filling time augmenting coronary blood flow; and reduction of direct toxic effects of catecholamines on myocardium, which may lessen concentric hypertrophy or development of arrhythmias. Atenolol appears to reduce myocardial damage short-term as evidenced by lower serum cardiac troponin-I concentrations in treated cats (Côté 2007). No studies have evaluated potential long-term benefit, however.
- Calcium-channel blocker, regular formulation (diltiazem hydrochloride 7.5 mg/*cat* PO q 8h). In one clinical trial, there was reduced hypertrophy and improved diastolic relaxation in a small but significant number of cats with HCM and congestive heart failure (Bright et al. 1991). Based on preliminary findings in a small number of asymptomatic cats, diltiazem had no measurable benefit in structural or functional parameters (Schober et al. 2007). Currently, this drug is disfavored because of frequency of dosage administration (compliance) or adverse effects of the sustained release formulations including sporadic changes in serum levels and high potential for side effects. The

Feline Cardiology, First Edition. Etienne Côté, Kristin A. MacDonald, Kathryn M. Meurs, Meg M. Sleeper.
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regular formulation (administered q 8 hours) may be considered in asthmatic cats who are intolerant to atenolol due to exacerbation of bronchoconstriction and have marked hypertrophy and/or moderate to severe systolic anterior motion of the mitral valve.
- Calcium-channel blocker, sustained release (diltiazem: Cardizem-CD or Dilacor-XL). Not recommended due to adverse effects and variable absorption of this human formulation in the cat.
- ACE inhibitor (benazepril 0.25 mg/kg PO q 24h, enalapril 0.25–0.5 mg/kg PO q 24h, ramipril 0.25–0.5 mg/kg PO q24 h). Disparate results of two studies, showing either no improvement in hypertrophy or mild antihypertrophic effect in the compensated state (Taillefer and Di Fruscia 2006 et al.; MacDonald et al. 2006); long-term benefit unproven.

Clinical States (Patient Status Based on History and Physical Examination)

Early, compensated HCM (mild LV hypertrophy, no left atrial enlargement)

- Acceptable treatments: atenolol, or diltiazem HCl (q 8h), or no treatment.

Systolic anterior motion of the mitral valve (documented echocardiographically)

- If congestive heart failure is absent: atenolol, or no treatment.
- If congestive heart failure is present: furosemide and an ACE inhibitor (enalapril or benazepril); atenolol if clinical signs of congestive heart failure are well-controlled and patient is overtly normal (controversial; some use a lower dosage of atenolol, if any).

Left atrial enlargement (moderate or severe)

- Acceptable treatments (none has been shown to be superior to any other, nor superior to no, treatment):
  - Aspirin, regular dose (81 mg/*cat* PO q 3d); or
  - Aspirin, low-dose (5 or 20 mg/*cat* PO q 3d); or
  - Warfarin (0.25–0.6 mg/*cat* PO q 24h, adjusted to maintain prothrombin time between 1.5 and 2.5 times highest normal value); or
  - Low molecular weight heparin (dalteparin: 150 IU/kg SC q 4h; enoxaparin 1.5 mg/kg SC q 6–8 h); pharmacokinetics in the cat require short dosage intervals, which may be impractical for many owners as well as very expensive; or
  - Clopidogrel (18.75 mg/*cat* PO q 24h with food).

Severe LV hypertrophy

- Acceptable treatments: atenolol, ACE inhibitor, both, or none. No proven benefit to treatment even with massive LV hypertrophy, but beta blockade and/or ACE inhibition likely beneficial if easily administered.

Congestive heart failure: see below
Aortic thromboembolism: see below
Syncope: see "Arrhythmias," below

DILATED CARDIOMYOPATHY (DCM)

Early, compensated disease, where impostors (chamber dilation from alpha-antagonist sedatives, pathologic bradycardias), valvular regurgitation, and left-to-right shunting have been ruled out:

- Taurine (250 mg PO q 8–12h). Taurine status (whole blood +/- plasma) must be assessed in all cats with echocardiographic findings consistent with DCM, since supplementation can be curative for taurine-deficiency–induced myocardial failure (Pion et al. 1987). Despite safety and low cost of taurine, long-term empiric supplementation should be preceded by confirmation of low blood levels because the tablet is large and the act of pill administration may be significantly onerous to patient or owner (and not of benefit when blood/plasma levels are within normal limits). No known benefit to supplementation when taurine levels are within normal limits.
- Digoxin (0.01875–0.03125 mg/*cat* PO q 48h). No conclusive benefit shown in feline DCM from digoxin alone. Nevertheless, digoxin is justifiably part of most treatment protocols when DCM has progressed to cause CHF, not before. Monitor for clinical signs of toxicosis (vomiting, diarrhea, lethargy, inappetence). May assess serum levels, though no known correlation to benefit or outcome in the cat (used mainly to rule in/out toxicosis).
- Pimobendan (1.25 mg/*cat* PO q 12h). Dosage extrapolated from canine studies (4–10 times higher than human dosage). Informally described in 11 cases of feline RCM (Sturgess et al. 2007). Risks associated with long-term treatment are unknown in the cat, but early clinical experience is encouraging. Off-label, and considered investigational use.
- ACE inhibitor: no known benefit prior to congestive heart failure, but coupled with furosemide it is part of the standard of care for treatment of heart failure.
- Beta blocker: contraindicated, due to decreased inotropic function and heart rate (risk of inadequate cardiac output) induced by beta blockade at recommended dosages. Microdose (e.g., <2 mg/*cat* PO q

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12h) could be beneficial in compensated state based on asymptomatic human DCM, but unproven (and dosage accuracy may be difficult).
- Calcium-channel blocker: as for beta blocker; may be indicated if a severe supraventricular tachyarrhythmia coexists with DCM.

Congestive heart failure: see below
Aortic thromboembolism: see below
Syncope: see "Arrhythmias," below

RESTRICTIVE/UNCLASSIFIED CARDIOMYOPATHY

Early (compensated) state is rarely identified, likely because the lesion of RCM/UCM is almost always silent (no murmur) and because its gradual progression elicits adaptive mechanism that maintain a compensated state until severe signs of congestive heart failure, aortic thromboembolism, or both, are evident. No specific treatment is recommended prior to the onset of clinical signs. Anticoagulant therapy is indicated in cats with evidence of spontaneous echocardiographic contrast (i.e., smoke and red blood cell aggregation), an intracardiac thrombus, or may be considered in cats with moderate or severe atrial dilation. When congestive heart failure is present:

- Digoxin (0.01875–0.03125 mg/*cat* PO q 48h). Controversial. No conclusive benefit shown in feline RCM/UCM from digoxin. Mainly used for neurohormonal, autonomic, and other benefits, since its benefits for systolic function are not relevant in RCM/UCM (disorder of diastolic dysfunction). May be useful as a negative chronotropic agent via increased vagal tone in cats with atrial fibrillation or other supraventricular tachyarrhythmias. Monitor for clinical signs of toxicosis (vomiting, diarrhea, lethargy, inappetence). May assess serum levels, though no known correlation to benefit or outcome in the cat (used mainly to rule in/out toxicosis).
- Pimobendan (1.25 mg/*cat* PO q 12h). Controversial. Dosage extrapolated from canine studies (4–10 times higher than human dosage). Informally described in 11 cases of feline RCM (Sturgess et al. 2007). Risks associated with long-term treatment are unknown in the cat, as are benefits. Benefits in heart failure patients may be due to the balanced vasodilation (arterial and venodilator) and positive lusitropy, as well as the positive inotropic effects. Off-label, and considered investigational use.

Congestive heart failure: see below
Aortic thromboembolism: see below
Syncope: see "Arrhythmias," below

CONGESTIVE HEART FAILURE

Diuretic level 1: mainstay of treatment, adequate in most cases. Furosemide (acute crisis inpatient: 2–6 mg/mg IV as needed to produce improvement in respiratory signs, then rapidly tapered as dictated by response; chronic home treatment: 0.5–4 mg/kg PO q 8–24h, adjusted based on sodium intake, tractability/ease of pilling, and resolution of signs and stability, aiming for lowest effective dose).

Diuretic level 2 (progressive heart failure): with chronic furosemide treatment, diuretic resistance may develop (e.g., increasing dosage but persistent edema/effusion, and evidence of lack of systemic diuretic effect [normal/disproportionately nonelevated BUN or serum creatinine, or urine specific gravity >1.025]). In these instances, furosemide may be replaced with torsemide (0.3 mg/kg PO q 24h, or divided q 12h) or hydrochlorothiazide.

Diuretic level 3 (refractory heart failure): instead of, or in addition to, torsemide addition to furosemide, a second diuretic may be added to treatment if chronic furosemide is insufficient (patient experiences recurrent CHF). First, review possible sources of excess sodium intake, mineralocorticoid sources, and unnecessary stress/tachycardia, all of which should be controlled or abolished in conjunction with diuretic therapy. Some cats do well with intermittent (2–3x/weekly) SQ injections of supplemental furosemide given by the owner at home.

- Spironolactone (1–2 mg/kg PO q 12h). May be contraindicated in cats due to severe ulcerative facial dermatitis in some cats; or
- Hydrochlorothiazide (1–2 mg/kg PO q 12h), reduce by half when patient is stable and sodium intake is low.

Centesis: thoracentesis if pleural effusion shown to be sufficiently voluminous to be causing dyspnea.
ACE inhibitor: indicated concurrently with diuretics treatment for all disorders causing heart failure. With HCM, improvement in echocardiographic parameters and some clinical indicators (Amberger et al. 1999) but mild or insignificant in many cats (Fox 2003, 2004).
Beta blocker: generally not initiated for the first time after the onset of congestive heart failure due to risk of excessive heart rate suppression. Exception: ectopic tachycardias (rapid/frequent atrial or ventricular tachycardia). Beta blockade is maintained during CHF if patient was already receiving it prior to decompensation, except if heart rate is conspicuously low

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(e.g., <160 beats/minute despite being in congestive heart failure) or cat is hypotensive, in which case beta blocker may be contributing and discontinuation is recommended.

Calcium-channel blocker: May have less negative inotropic effect compared to beta blockers, so an ideal choice for treatment of supraventricular tachyarrhythmias in patients with heart failure and myocardial failure, but it will be ineffective for ventricular arrhythmias.

Nitrates: nitroglycerin topical ointment acceptable irrespective of cause of CHF (venodilator); nitroprusside is a potent balanced arterial and venous dilator and is contraindicated in cases of hypertrophic obstructive cardiomyopathy, because arteriodilation may increase left ventricular outflow tract obstruction (LVOTO), or in hypotensive patients.

Oxygen supplementation: (40–50% FiO2; or high oxygen flow rate in a modified oxygen cage). Acceptable provided it can be given without compromising monitoring or causing hyperthermia or hypercarbia, as has occurred in closed oxygen cages.

AORTIC THROMBOEMBOLISM

Acute treatment consists of parenteral administration of drugs to delay (anticoagulants) or actively lyse (thrombolytics) blood clots, analgesics, plus supportive care. Both approaches have their proponents, with favor generally falling to a more conservative (anticoagulant) approach due to the lower incidence of catastrophic adverse effects and high cost of thrombolytic therapy coupled with the same short-term survival rate.

Chronic treatment consists of anticoagulation to reduce the risk or rethrombosis/reembolization and specific therapy for the underlying heart disease/heart failure if present.

Thrombolysis: requires 24-hour intensive care monitoring for emergency treatment of life-threatening reperfusion syndrome or hemorrhage

- Streptokinase (90,000 IU IV, then 45,000 IU IV CRI). Incidence of bleeding and reperfusion injury matches or exceeds benefits in cats. Not recommended in cats.
- Tissue plasminogen activator (5 mg/*cat* IV CRI over 1.5–5h). Similar effects and results as streptokinase. Not recommended in cats.

Anticoagulation:

- Acceptable treatments (none has been shown to be superior to any other, nor superior to no treatment):
  - Aspirin, regular dose (81 mg/*cat* PO q 3d); or
  - Aspirin, low-dose (5 or 20 mg/*cat* PO q 3d); or
  - Warfarin (0.25–0.6 mg/*cat* PO q 24h, adjusted to maintain prothrombin time between 1.5 and 2.5 times highest normal value); or
  - Low molecular weight heparin (dalteparin: 150 IU/kg SC q 4h; enoxaparin 1.5 mg/kg SC q 6–8 h); pharmacokinetics in the cat require short dosage intervals, which may be impractical for many owners; or
  - Clopidogrel (18.75 mg/*cat* PO q 24h with food) (Hogan and Ward 2004; Hogan et al. 2004)

SYSTEMIC HYPERTENSION

As defined by objective guidelines (Brown et al. 2007), systemic hypertension warranting treatment in cats consists of systolic blood pressure, accurately measured and with the least possible level of patient anxiety, that exceeds 180 mm Hg. A gray zone exists between 160 and 180 mm Hg, where treatment is warranted if target organ damage is observed or considered to be imminent:

- Amlodipine 0.625–1.25 mg/cat PO q 24h. Safe and efficacious. Goal is reduction of arterial blood pressure by 10–20% (ideally to high-normal levels), and improvement in target organ damage, if any has occurred (Henik et al. 1997; Elliott et al. 2001).
- Benazepril, enalapril. No demonstrable efficacy as antihypertensives in cats, but may be considered as an additional medication in cats not adequately responding to high dose amlodipine. May be used in hypertensive cats that have proteinuria secondary to protein losing nephropathy, and can be used in conjunction with amlodipine while carefully monitoring blood pressure.
- Atenolol. No demonstrable efficacy as an antihypertensive in cats, but may be useful in markedly tachycardic cats with inadequate blood pressure reduction on high-dose amlodipine, added to the amlodipine (not as a substitute).

CONGENITAL HEART DISEASE

Because congenital heart malformations may be identified early through auscultation of a heart murmur in an asymptomatic cat/kitten, the first goal of treatment should be to cure the patient with surgical repair of the lesion.

Surgical correction of congenital cardiovascular defects can realistically be accomplished with the following:

- Patent ductus arteriosus (coil embolization or thoracotomy and ligation)
- Vascular ring anomaly (thoracotomy for ligation and division of ligamentum arteriosum)

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- Arteriovenous fistula (coil embolization or identification and ligation)
- Ventricular septal defect (typically large) causing left-sided congestive heart failure (pulmonary artery banding procedure)

The small size of the feline heart makes it a poor candidate for both open-heart procedures and catheter-based interventions. Partial or complete palliation may be achieved for valvular pulmonic stenosis through thoracotomy and instrument dilation.

For the other congenital malformations, including ventricular and atrial septal defects, mitral and tricuspid dysplasias, and others, medical treatment generally is indicated only after clinical signs of decompensation have occurred (an exception could be beta blockade, such as atenolol 6.25–12.5 mg PO q 12h in cats with disorders causing marked pressure overload, notably severe pulmonic, pulmonary artery, or aortic stenosis):

- Congestive heart failure: see above
- Aortic thromboembolism: see above
- Syncope: see "Arrhythmias," below
- Severe polycythemia (HCT >60% in the cat); in patients with right to left shunts)
  - Phlebotomy (withdraw 10 ml/kg body weight, may repeat later the same day) as needed q 3–8 weeks or more based on clinical response; target HCT is 60–68%.
  - Anticoagulation is not recommended, due to bleeding disorders paradoxically associated with congenital heart disease–induced polycythemia in children.

ARRHYTHMIAS

Broadly, feline arrhythmias can be divided into the following 3 clinical categories:

1. Those occurring in patients with compatible overt clinical signs such as syncope/collapse
2. Those in which clinical signs are present but they may or may not be caused by the arrhythmia
3. Those discovered as an incidental finding in an otherwise well cat

The first step is diagnosis of the specific arrhythmia, which may require extended ECG monitoring/telemetry if the arrhythmia is only intermittent. Treatment is dictated by the type and clinical severity of the arrhythmia.

Premature Atrial Complexes/Atrial Tachycardia (AT)/Atrial Fibrillation (AF)

- After underlying causes have been identified and optimally controlled, including resolution of congestive heart failure, consider atenolol (6.25 mg/*cat* PO q 12–24h) if clinical signs are present (clinical arrhythmia categories 1 and 2) with AT or AF. Consider the same treatment in any of the 3 categories if AT or AF persists at a rate of >260 beats/minute for several consecutive minutes or more.
- Target is to obtain a perfusing rhythm, i.e., an adequate cardiac output, typically requiring a heart rate of <260 beats/minute. If initial dose of atenolol is insufficient and the cat is not decompensated with active heart failure, the atenolol dose can be increased to 12.5 mg/*cat* PO q 12h. Other treatment options are to consider switching to sotalol (2 mg/kg PO q 12h) or adding digoxin (0.01875–0.03125 mg/cat PO q 48h) unless HCM is present.

Premature Ventricular Complexes/Ventricular Tachycardia

- After underlying causes have been identified and optimally controlled, including resolution of congestive heart failure, consider lidocaine (0.25–1 mg/kg IV) or esmolol (50–200 mcg/kg/min IV CRI) if patient is in clinical category 1 or 2 and showing signs of hemodynamic compromise (e.g., poor/absent pulse, depressed mentation) at the time of examination. If such signs abate, or are not present (category 3), verify that underlying causes such as hypokalemia, hyperthyroidism, and hypoxemia, are optimally managed and if so, consider atenolol (6.25 mg/*cat* PO q 12–24h) if ventricular rate is consistently >260 beats/minute for several consecutive minutes or more.

The target is a perfusing rhythm, i.e., an adequate circulation, typically requiring a heart rate of <260 beats/minute. If atenolol is insufficient at starting dose, may increase the dose to 12.5 mg/cat q 12h or consider switching to sotalol (2 mg/kg PO q 12h), or mexiletine (e.g., 3 mg/kg PO q 12h) may be added but pharmacokinetic/pharmacodynamic studies in the cat are lacking to support safety of such treatment.

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SECTION R

Drug Formulary

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Drug Formulary

The following compilation of cardiovascular medications has been obtained from published reports in original journal articles, conference proceedings, and textbooks. Wherever possible, itemized reference citations are given for rapid identification of source material by readers wanting information in greater detail. This index does not reflect original scientific research, and its compilers make no claims regarding efficacy, safety, or any other properties of drugs as listed here. Information concerning efficacy, safety, and other properties of these drugs is the domain of the original authors, reviewers, editors, or a combination of these, who investigated and reported the data in the primary publications from which this information is drawn, together with the responsibility of the prescribing veterinarian for ensuring that all reasonable resources are consulted prior to recommending, administering, or withholding a medication.

It also is worth noting that no drug has ever been approved by the U.S. Food and Drug Administration for use in feline heart disease. Therefore, this listing necessarily involves extralabel use, for which the prescribing veterinarian must assume responsibility concerning treatment application/implementation, adverse effects of administering or withholding treatment, owner-informed consent, and all other related issues.

Abbreviations used in the index are as follows: Cap = capsule; Ch = chewable tablet; CRI = constant rate infusion; ER = extended release; H = human brand name; HM = human formulation; Inj = injectable; IM = intramuscular; IV = intravenous; Liq = oral liquid; OTC = over-the-counter (nonprescription); PRN = as needed; SQ = subcutaneous; SR = sustained release; Tab = tablet; V = veterinary brand name; VM = veterinary formulation.

Feline Cardiology, First Edition. Etienne Côté, Kristin A. MacDonald, Kathryn M. Meurs, Meg M. Sleeper.
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Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Acepromazine *(PromAce [V], AtraVet [V])*	Phenothiazine tranquilizer	0.005–0.02 mg/kg IV, or 0.01–0.1 mg/kg IM, SQ	• Causes variable degrees of arteriodilation and reflex tachycardia, which can be detrimental (myocardial oxygen deficit, worsening of outflow tract obstruction, etc.). • One of the most controversial drugs in feline cardiovascular anesthesia, with some cardiologists routinely advocating and using low-dose protocols, and others considering this drug contraindicated in all cats with cardiovascular disease. • Higher doses generally reserved for cats without cardiovascular disease. • Precautions if using this drug include: low dosage (combined with other drugs such as an opioid for adequate sedation), assessment of perfusion during sedation, and avoidance in elderly, dehydrated, or overtly ill patients. • Historically advocated for arteriodilation in aortic thromboembolism, but no longer because of lack of convincing benefit and risk of adverse effects.	10 mg/ml Inj VM
Activase—see Tissue plasminogen activator				
Adrenaline—see Epinephrine				
Aldactone—see Spironolactone				
Altace—see Ramipril				
Alteplase—see Tissue plasminogen activator				
Amlodipine *(Norvasc [H])*	Dihydropyridine-type (predominantly arterial smooth muscle-specific) calcium channel blocker for systemic hypertension	0.625–1.25 mg/cat PO q 24 h, may increase to q 12 h for refractory cases	Drug of choice for treatment of hypertensive cats when treatment of the underlying cause is insufficient. Hypotension rare at standard dosages. Transdermal formulation not recommended due to unpredictable serum amlodipine levels in hypertensive cats (16–58% of equivalent serum levels compared to PO dosing in same cats).	2.5, 5, 10 mg Tab HM
Antisedan—see Atipamezole				

Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Apresoline—see Hydralazine				
Aspirin, ASA	Nonsteroidal anti-inflammatory used for prophylactic anticoagulation	Standard dosage: 81 mg/cat PO q 48–72 h Minidose: 5 or 20 mg/cat PO q 72 h	Questionable efficacy as anticoagulant, but generally very safe. No proven clinically relevant anticoagulant effect at any dose in cats.	81, 300, 600 mg Tab HM OTC
Atenolol *(Tenormin [H])*	Beta-1 selective blocker for hypertrophic cardiomyopathy, tachyarrhythmias	0.25–1 mg/kg PO q 12–24 h	• Used in absence of congestive heart failure (e.g., occult hypertrophic cardiomyopathy) or controlled heart failure (e.g., pulmonary edema/effusions are resolved with diuretics and/or centesis), but not during fulminant congestive heart failure. • Indicated for supraventricular or ventricular tachyarrhythmia but not sinus tachycardia (control underlying cause instead). • With such precautions, beta-blocker–induced congestive heart failure, hypotension, anorexia remain possible but are very rare in cats. • Transdermal formulation not reliable. • Poor efficacy as sole treatment for systemic hypertension in cats. • Used in hyperthyroidism to minimize cardiac effects.	25, 50, 100 mg Tab HM
Atipamezole *(Antisedan [V])*	Reversal agent for alpha-agonist sedatives	50–200 mcg/kg IM, IV, or divided into both routes	Exact dosage is same volume as volume of medetomidine or dexmedetomidine administered. IV use for immediate reversal; may give half IV, half IM for both immediate and sustained reversal.	5 mg/ml Inj VM
Atravet—see Acepromazine				
Atropine	Anticholinergic/ Parasympatholytic	0.01–0.044 mg/kg SQ, IM, IV	Useful for treatment of transient, vagally mediated bradycardia (e.g., general anesthesia, cardiac arrest). Avoid preemptive use in cardiac patients preoperatively (unnecessary tachycardia) unless bradycardia is documented prior to induction. Use as needed (IV boluses 0.01–0.02 mg/kg) when bradycardia is documented. Do not use in congestive heart failure unless bradycardia is present.	0.54 mg/ml Inj VM

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Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
B Vitamin complex	Vitamin supplement		Unsubstantiated use for reduction of risk of thromboembolic disease based on identification of lower serum vitamin B12 levels in cats with aortic thromboembolism.	
Benazepril *(Fortekor [V], Lotensin [H])*	Angiotensin-converting enzyme (ACE) inhibitor	0.25–0.5 mg/kg PO q 24 h	Adjunctive treatment with diuretics in congestive heart failure. Benefits of mixed renal-hepatic elimination likely of minimal clinical importance. Safe drug—anorexia, sedation, hyperkalemia rare. Veterinary formulation not available in United States. Theoretical additional benefits (e.g., reduction of myocardial fibrosis and hypertrophy), and efficacy may be diminished over time (ACE inhibitor tolerance) based on extrapolations from other species. Possible reduction in left ventricular thickening with chronic treatment during compensated ("asymptomatic") state but unclear impact on long-term prognosis. Minimal efficacy (if any) as single agent for treating systemic hypertension. No significant risk of worsening severity of left ventricular outflow tract obstruction in HOCM due to arteriodilation in cats.	5, 20 mg Tab VM 5, 10, 20, 40 mg Tab HM
Betapace—see Sotalol				
Brethine—see Terbutaline				
Brevipace—see Esmolol				
Buprenorphine *(Buprenex [H])*	Opiate agonist	0.005–0.01 mg/kg IV,IM; may be given per os in fractious cats	Sedation for echocardiography or other noninvasive procedures; used for pain management of acute arterial thromboembolism. Fewer respiratory center effects than hydromorphone. Management of concurrent disorders (e.g., pulmonary edema, pleural effusion) should always precede sedation for lower risk. Higher dosage reserved for severe pain or sedating difficult but otherwise healthy, young cats suspected of having mild heart disease.	0.324 mg/ml Inj HM
Butorphanol *(Torbugesic [V])*	Mixed opiate agonist-antagonist	0.05–0.2 mg/kg IV, IM, SQ	Sedation for echocardiography or other noninvasive procedures. Low dose for aged, unstable, or otherwise compromised cats; management of concurrent disorders orders (e.g., pulmonary edema, pleural effusion) should precede sedation for lower risk. Higher dosage reserved for difficult but otherwise healthy, young or middle-aged cats suspected of having mild heart disease. May be combined with dexmedetomidine or low-dose acepromazine for heavy sedation. Rarely exceed total dose 1.5 mg/cat.	2, 10 mg/ml Inj VM

Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Calan—see Verapamil				
Calcium gluconate	Mineral	50–200 mg/kg slow IV with ECG monitoring (90 mg [=4.5 mEq] elemental calcium per 1000 mg of calcium gluconate)	Treatment for critical hyperkalemia. Cardioprotective: does not lower serum potassium level but helps normalize ionic gradient in myocytes by raising threshold for depolarization. Especially useful for urethral obstruction-associated hyperkalemia (75% of cats are concurrently hypocalcemic). Infuse slowly (5–15 minutes) and monitor ECG during infusion for signs warranting immediate discontinuation including: sudden decrease in heart rate; PVCs; QT interval shortening.	10% (100 mg/ml) or 23% (230 mg/ml) in solution = most common. Inj. HM, VM
Cardizem—see Diltiazem				
Clopidogrel *(Plavix [H])*	Thienopyridine antiplatelet anticoagulant	18.75 mg/cat PO q 24 h	Indicated for prevention of thromboembolic disease or to stop enlargement of existing thrombus/embolus. Not thrombolytic (will not reduce existing clot). Efficacy in feline aortic thromboembolism remains under investigation, may be superior to aspirin. Generally very safe, low risk of hemorrage. Mechanism: irreversible inhibition of ADP binding to its platelet receptor, preventing platelet activation and conversion of platelet IIb/IIIa receptor to its active form. Many reports of ptyalism, distaste by cats; consider wrapping carefully in treat or placing in gelatin capsule; give with food to minimize GI effects that occur in ≈10% of cats. Low risk of hemorrhagic complication.	75 mg Tab HM
Corlopam—see Fenoldopam				
Coumadin, Coumarin—see Warfarin				
Dalteparin—see Heparin, low molecular weight				
Demadex—see Torsemide				

Continued

Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Dexmedetomidine *(Dexdomitor [V])*	Alpha-2 agonist sedative and analgesic	40 mcg/kg IM	General sedation, notably in cats with hypertrophic cardiomyopathy. Onset of sedation 5–15 minutes after injection; peak at 30 minutes; sedation dissipated by 3 hours after injection. Reflex bradycardia is a response to vasoconstriction and need not be treated, even with heart rates <70 beats/minute (18% of cats); if concern, blood pressure can be measured and normal to elevated levels are expected. Indication in HCM is based on arterial vasoconstriction, decreasing heart rate, which improves diastolic filling and reduces myocardial oxygen consumption. Contraindicated in systemic hypertension. Rare cases of postadministration pulmonary edema; monitor respiratory character and rate. Greater potency than medetomidine equates to a lower dosage for similar sedation. Vomiting may occur within minutes after administration; cats should be fasted prior to dosing. Reversal agent: atipamezole (Antisedan) in equal volumes to dexmedetomidine dose.	0.5 mg/ml (= 500 mcg/ml) Inj VM
Diazepam *(Valium [H])*	Benzodiazepine sedative	0.1–0.5 mg/kg IV	Almost always used in conjunction with other agents, notably butorphanol (for moderate sedation) or either dexmedetomidine or ketamine (for heavy sedation). Safe; very minimal cardiovascular effect. Provides mild additional sedation, no practical effect if given as sole drug. Main disadvantage over midazolam is no IM route.	1, 10 mg/ml Inj HM
Digoxin *(Lanoxin [H])*	Cardiac glycoside	0.01875–0.03125 mg/cat PO q 48h (= 1/8–1/4 of 0.125 mg tablet)	Indicated for dilated cardiomyopathy causing congestive heart failure. Possible indications in restrictive/unclassified cardiomyopathy, dilated cardiomyopathy prior to congestive heart failure. Contraindicated in hypertrophic cardiomyopathy. Home monitoring for signs of digoxin toxicosis (warranting immediate discontinuation) is essential: vomiting, inappetence, lethargy, and/or diarrhea. Target serum levels (now 0.5–1 ng/ml; previously 1–2 ng/ml) not correlated to any benefit in cats, merely extrapolated from human medicine; effects on increasing vagal tone seen at lower doses. Lower dosage warranted when concurrent treatment with furosemide, aspirin, and low sodium diet. IV form not recommended (greater risk of toxicosis, and benefits of digoxin are chronic rather than acute). Adjunctive therapy as mild negative chronotrope for supraventricular tachyarrhythmias.	0.125mg T HM Caution: 0.25 mg tabs also available (avoid due to risk of double-dosing) Elixir (0.05 mg/ml) usually disliked by cats

Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Dilacor—see				
Diltiazem sustained release (*Cardizem CD*, *Dilacor XL [both H]*)	Calcium-channel blocker, non-dihydropyridine type	10 mg/kg PO PO q 24h (Dilacor, compounded); or 30 mg/cat PO q 24h (Cardizem CD)	Hypertrophic cardiomyopathy. Convenience of once- daily dosage now appears outweighed by erratic bioavailability in the cat and reversible but severe adverse effects including anorexia, vomiting, lethargy, weight loss, and evidence of hepatopathy in a substantial proportion of treated cats in 2 independent studies, and lack of demonstrable efficacy.	60, 90, 120,180, 240, 360, 420 mg ER Cap HM
Diltiazem HCl *(Cardizem [H])*	Calcium-channel blocker, non-dihydropyridine type	1.75–2.4 mg/kg PO q 8h	Hypertrophic cardiomyopathy. Shown to improve clinical signs in the original feline HCM study (ref. Bright); appropriate for HCM if antitachycardia effects (which are less pronounced with calcium channel blockers) are not necessary and three-times daily medication administration is acceptable. May be less effective than atenolol for reducing severity of left ventricular outflow tract obstruction in cats with HOCM. Often replaced by atenolol (q 12–24h dosing).	30,60, 90,120 mg Tab HM
Diltiazem IV *(Cardizem [H])*	Calcium-channel blocker, non-dihydropyridine type	0.125–0.35 mg/kg slow IV bolus (1–2 minutes); PRN	Severe (HR > 300/min), persistent atrial tachycardias. Risk of acute bradycardia and hypotension warrants judicious uptitration: administer low dose and monitor for effect, then repeat if needed. Adjunct measures (e.g., reduction of anxiety and other sources of sympathetic stimulation) are essential. Contraindicated in sinus tachycardia (find and manage underlying cause) and all bradycardias.	5 mg/ml Inj HM
Disal—see Furosemide				

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Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Dobutamine *(Dobutrex [H])*	Beta-1 selective adrenergic agonist	1–10 mcg/kg/min IV CRI, adjust rate PRN	Critical systolic dysfunction (severe dilated cardiomyopathy causing refractory congestive heart failure; or life-threatening low output heart failure, end-stage restrictive/unclassified cardiomyopathy). Contraindicated in hypertrophic cardiomyopathy, with possible exception of near-terminal states with poor systolic function demonstrated echocardiographically. Long-term benefit is unknown and dubious for any form of heart disease in the cat. Used for medical bridging to surgical cure in human cardiology; rarely applies to feline patients. Do not confuse with dopamine. Sample formulation for 5 mcg/kg/min: 2 ml (25 mg) in 100 ml 5% dextrose = 250 mcg/ml. Administration at half maintenance rate = 30 ml/kg/d = 1.25 ml/kg/h = 0.02 ml/kg/min = 5 mcg/kg/min. Begin at lower end of dosage range and adjust according to response. Reports of causing seizures in some cats.	12.5 mg/ml (250 mg vial) Inj HM
Domitor—see Medetomidine				
Dopamine *(Intropin [H])*	Alpha- and beta-adrenergic agonist	0.5–10 mcg/kg/min IV CRI, adjust rate PRN	Critical hypotension; cardiogenic shock. Must be titrated based on response, which requires monitoring arterial blood pressure, mentation, and mucous membrane color at a minimum. Efficacy for treating acute renal failure questionable. Contraindicated in congestive heart failure unless the patient is both hypotensive and normovolemic/ hypervolemic. Sample formulation for 4 mcg/kg/min: 0.5 ml of 40 mg/ml (20 mg) in 100 ml 5% dextrose = 200 mcg/ml. Administration at half maintenance rate = 30 ml/kg/d = 1.25 ml/kg/h = 0.02 ml/kg/min = 4 mcg/kg/min. Begin at lower end of dosage range and adjust according to response.	40, 80, 160 mg/ml Inj HM
Doxapram *(Dopram [V])*	Direct central nervous system respiratory stimulant	1.1 mg/kg (for gas anesthesia) or 5.5–11 mg/kg (for barbiturate anesthesia) IV	Treatment for apnea that is unresponsive to standard corrective measures (e.g., decrease concentration/reverse anesthetic). Rarely indicated in feline cardiology.	20 mg/ml Inj VM

Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Enalapril *(Enacard [V], Vasotec [H])*	Angiotensin-converting enzyme (ACE) inhibitor	0.25–0.5 mg/kg PO q 12–24 h	Adjunctive treatment with diuretics in congestive heart failure. Safe drug—anorexia, sedation, hyperkalemia are rare. Theoretical additional benefits (e.g., reduction of myocardial fibrosis) and loss of efficacy over time (ACE inhibitor tolerance) unproven in clinical feline cardiology at present. Therefore, no proven benefit to treatment prior to congestive heart failure. Minimal efficacy (if any) as single agent for treating systemic hypertension.	1, 2.5, 5, 10, 20 mg Tab VM
Enoxaparin—see Heparin, low molecular weight				
Epinephrine (adrenaline)	Catecholamine	0.01–0.05 mg/kg IV	Treatment for asystolic or bradycardic cardiac arrest. Administer low dosages and repeat as needed (q 30–60 seconds if necessary) to reduce likelihood of severe tachycardic response (causing myocardial oxygen depletion and rearrest). Triple dosage if administering intratracheally.	1 : 1000 (1 mg/ml) or 1 : 10 000 (0.1 mg/ml) Inj VM,HM
Esmolol *(Brevipace [H])*	Ultrashort acting beta blocker	25–200 mcg/kg/min IV CRI	Used for terminating SVT or for slowing heart rate for diagnostic purposes: • in HCM, to identify whether chronic, oral beta blocker administration is likely to reduce left ventricular outflow obstruction. • in supraventricular tachycardia, to better identify presence or absence of P waves and make an ECG diagnosis. May bolus 200–500 mcg/kg slow IV (1 minute) initially, or begin at low dose and titrate upward to desired effect. Contraindicated in congestive heart failure, hypotension, or bradycardia.	10, 20, 250 mg/ml Inj HM
Fenoldopam *(Corlopam [H])*	Dopamine D-1 agonist antihypertensive	0.1–0.6 mcg/kg/min IV CRI	Treatment of systemic hypertensive crises. Maintains or increases glomerular pressure while lowering systemic arterial pressure in humans. Rapid onset and offset of action. Only anecdotal reports in feline medicine. Very costly.	10 mg/ml Inj HM
Fortekor—see Benazepril				
Fragmin—see Heparin, low molecular weight				

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Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Furosemide *(Lasix [H], Salix [V], Disal [V]; frusemide)*	Loop-type diuretic	0.5–4 mg/kg PO q 12–48h (chronic CHF); up to 3–4 mg/kg PO q 8h for chronic refractory CHF; 2–6 mg/kg IV once, then PRN (acute CHF)	Indicated for congestive heart failure (esp. cardiogenic pulmonary edema; adjunct to delay recurrence of pleural effusion, ascites, and other cardiogenic fluid retention). Onset of action ≤1 h after IV use, peak at 2–3 h. Typically used in conjunction with an ACE inhibitor and low-sodium diet (to minimize diuretic dose, but only if palatable to cat). Promotes excretion of Na^+, K^+, Cl^-, H^+, Ca^{2+} via blockage of Na/K/2Cl cotransporter in thick segment of ascending loop of Henle in renal tubule. Effect occurs intraluminally, after drug has been excreted into tubule. Larger volume of urine (and less K^+ wasting) than equivalent natriuresis-inducing doses of thiazide diuretics. Higher dosages usually in acute congestive heart failure (hours/days of use), lower doses and addition of other drugs (ACE inhibitor, Na restriction, others) with chronic (weeks–years) treatment. Cats usually dislike oral syrup formulation. Drug is plastic- and light-sensitive; do not store or dispense in syringes for more than several hours. For CRI, calculate total dosage for 24h and administer in small volume (e.g., 50 ml) 5% dextrose in water, protecting administration set from light.	50 mg/ml Inj VM 10 mg/ml Inj HM 12.5,50 mg Tab VM 20,40,80 mg Tab HM 10 mg/ml Liq VM
Heparin-low molecular weight *(Enoxaparin [Lovenox]; Dalteparin [Fragmin] [H])*	Anticoagulant	Dalteparin: 150 IU/kg SC q 4h Enoxaparin: 1.5 mg/kg SC q 6–8 h	Low molecular weight heparins (LMWH) produce a more consistent, longer-lasting, and more effective level of anticoagulation in humans and possibly in cats compared to unfractionated heparin. Considered safer than warfarin (lower incidence of excessive bleeding). May be administered without monitoring coagulation parameters, although optimal anticoagulation may be achieved in the cat with serum antifactor Xa activity = 0.5–1 IU/ml.	Dalteparin: 2500 IU/0.2 ml, 5000 IU/0.2 ml, 7500 IU/0.3 ml, 10 000 IU/1 ml, 25 000 IU/3.8 ml Inj HM Enoxaparin: 100, 150 mg/ml Inj HM
Heparin-unfractionated ("regular")	Anticoagulant	200–300 IU/kg IN q 6h	Aortic thromboembolism (acute management). Mechanism of action is antithrombin (AT) potentiation; therefore, contraindicated (ineffective) in AT-deficient states, e.g., protein-losing nephropathy (suspicion if proteinuria) or enteropathy. Not thrombolytic; reduces rate of formation of thrombus but no active lysis of existing thrombus. Unproven (variable) efficacy in cats; may be monitored via aPTT measurements (should be 1.5–2.5× baseline) but such values may occur despite subtherapeutic serum heparin levels; antifactor Xa activity (levels of 0.35–0.7 U.ml) has been recommended as a target for heparin anticoagulation in dogs.	1000, 2000, 2500, 5000, 10 000, 20 000, 40 000 IU/ml Inj HM

Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Hydralazine *(Apresoline [H])*	Direct arterio-dilator	2.5 mg/cat PO q 12–24h	Second- or third-line treatment for systemic hypertension. Almost completely replaced by amlodipine due to amlodipine's superior efficacy and fewer adverse effects in cats.	10,25,50, 100 mg Tab 20 mg/ml Liq HM
Hydrochloro-thiazide *(HydroDiuril [H])*	Thiazide diuretic	1–2 mg/kg PO q 12h; usually decrease to 0.5–1 mg/kg PO q 12h when stable	Second diuretic, generally added when long-term furosemide treatment is no longer adequate (relapse of congestive heart failure despite high-dose furosemide). Begun when inpatient is stable and preparing to be discharged, or when relapse of CHF produces minimal clinical signs (cat is still comfortable). Monitor renal function and electrolytes as for other diuretics (e.g., 1–2 weeks after starting treatment, then q4–12 weeks depending on stability, patient comfort/tractability, etc.)	25,50,100mg Tab HM
Imidapril *(Prilium [V])*	Angiotensin-converting enzyme (ACE) inhibitor	0.5 mg/kg PO q 24h	Adjunctive treatment of congestive heart failure (with concurrent diuretic treatment). Veterinary formulation is lyophilized powder reconstituted into oral solution (increased dosage accuracy) and stored refrigerated. Theoretical additional benefits of ACE inhibition (e.g., reduction of myocardial fibrosis) and loss of efficacy over time (ACE inhibitor tolerance) unproven in clinical feline cardiology at present. Therefore, no proven benefit to treatment prior to congestive heart failure. Available in Europe and Canada (for dogs; as for many drugs, feline use is off-label).	5,10 mg/ml Liq VM
Inderal—see Propranolol				
Intropin—see Dopamine				
Isoproterenol *(Isuprel [H])*	Beta adrenergic agonist	0.04–0.08 mcg/kg/min IV CRI, adjusted PRN	Indicated for severe/critical bradycardia, notably sinus bradycardia that fails to respond to atropine, or third-degree AV block during stabilization for pacemaker implantation. Begin at low infusion rate and increase gradually to desired effect; sudden high dose may cause excess effect (extreme tachycardia). Sample formulation for 0.04 mcg/kg/min: place 1 ml (0.2 mg) in 100 ml 5% dextrose = 2 mcg/ml. Administration at half maintenance rate = 30 ml/kg/d = 1.25 ml/kg/h = 0.02 ml/kg/min = 0.04 mcg/kg/min.	0.2 mg/ml Inj HM
Isoptan—see Verapamil				

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Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Kabikinase—see Streptokinase				
Ketamine *(Ketaset [V], Vetalar [V])*	Dissociative anesthetic	1–4 mg/kg IV	Sedative, often combined with acepromazine or diazepam. Increases heart rate and may trigger decompensation (e.g., congestive heart failure) in cats with compensated "asymptomatic" cardiomyopathy. This risk, and prolonged duration of effect (up to several hours) discourage higher dosages (10 mg/kg). Alters echocardiographic measurements significantly. Effective immobilization beyond the degree obtained with standard dosages of opiates; useful for very fractious or uncooperative patients when benefit of procedure outweighs risk of sedation. Mild analgesic properties via NMDA receptor antagonism. Higher dosages such as IM dosage (33 mg/kg) not recommended in cardiac patients.	100 mg/ml Inj VM
Lactated Ringer's Solution (LRS)	Parenteral replacement-type crystalloid fluid	50–90 ml/kg per 24h IV CRI + deficits + ongoing losses	Shown to be safe at 70–90 ml/kg IV bolus in anesthetized healthy cats; however, a smaller circulating blood volume exists in cats compared to dogs, and substantial interindividual variability, mean that ongoing monitoring for iatrogenic congestive heart failure is essential in any cat, especially if underlying heart disease is suspected or documented.	100,250 500, 1000 ml IV HM
Lanoxin—see Digoxin				
Lasix—see Furosemide				
Levophed—see Norepinephrine				

Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Lidocaine *(Xylocaine [H], lignocaine*)	Amide Na-channel blocking (class Ib) local anesthetic	0.25–1 mg/kg IV slowly	Main indication is ventricular arrhythmias: PVCs, ventricular tachycardia. Recommend starting at bolus of 0.25–1 mg/kg, to be repeated up to 2 mg/kg total dose. If this effectively breaks the ventricular tachycardia, a CRI should be continued, since half-life is very short. IV bolus required to achieve therapeutic levels quickly, as there would be a delay of several hours for therapeutic effect if just using a CRI. Ensure that serum [K^+] is normal; hypokalemia both triggers PVCs/VT and makes them refractory to lidocaine. Cats reported to be sensitive to CNS adverse effects of lidocaine; monitor mentation when administering. Goal of treatment is hemodynamically adequate rhythm (i.e., acceptable pulse quality, alertness, reduction in syncopal episodes), which does not necessarily equate to a normal ECG. Mechanism:binds to sodium channels following depolarization, prolonging repolarization. Result is more homogeneous electrical activity, i.e., antiarrhythmic effect. Adverse effects in cats may be neurologic (acute depression, ataxia, seizures) or cardiovascular (hypotension, collapse). Constant rate infusion may be administered at 10–15 mcg/kg/min. Sample formulation for 10 mcg/kg/min: 2.5 ml (50 mg) in 100 ml 5% dextrose = 500 mcg/ml. Administration at half maintenance rate = 30 ml/kg/d = 1.25 ml/kg/h = 0.02 ml/kg/min = 10 mcg/kg/min. Begin at lower end of dosage range and adjust according to response. May be preceded by IV propranolol administration in VT, in the absence of CHF, hypotension, or severe myocardial failure. Analgesic use (e.g., as part of morphine-lidocaine-ketamine infusion) not recommended in cats due both to risk of toxicity and demonstrated lack of analgesia when administered IV.	20 mg/ml (2% soln) VM,HM
Lisinopril *(Prinivil [H], Zestril [H])*	Angiotensin-converting enzyme [ACE] inhibitor	0.25–0.5 mg/kg PO q 24h	Adjunctive treatment (with diuretic) of congestive heart failure. Historical interest in large dogs due to lower cost; availability of other ACE inhibitors with feline-specific information or equally low cost now makes this drug of little use in cats.	2.5, 5, 10, 20, 30, 40 mg Tab HM
Lopressor—see Metoprolol				
Lotensin—see Benazepril				

Continued

Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Lovenox—see Heparin, low molecular weight				
Magnesium chloride	Mineral	75–100 mg/kg/24h IV (100 mg = 1 mEq Mg^{2+})	Ventricular antiarrhythmic. 50% of dose can be given in 2–4 hours if necessary (e.g., documented hypomagnesemia and rapid/symptomatic ventricular tachycardia). Do not exceed 200 mg/kg daily. Unsubstantiated in the cat; rarely used (preference for magnesium sulfate).	200 mg/ml (=1.97 mEq/ml) Inj
Magnesium hydroxide	Mineral	1–2 mEq/kg/d PO (29 mg magnesium hydroxide = 1 mEq Mg^{2+})	Supplementation for chronic hypomagnesemia (e.g., induced by diuretics). Excess dose may be laxative; monitor for diarrhea and adjust dosage accordingly. Common formulation of magnesium hydroxide is Milk of Magnesia, which contains 2.4–2.9 mEq (70–84 mg) mg^{2+} per gram, or approximately 13.66 mEq (396 mg) Mg^{2+} per 5 ml teaspoon.	Many HM OTC
Magnesium sulfate	Mineral	30 mg/kg slow IV (125 mg = 1 mEq Mg^{2+})	Ventricular antiarrhythmic.* Treatment of choice when ventricular tachycardia coexists with hypomagnesemia. Option for treatment of any refractory symptomatic ventricular arrhythmia. Hypomagnesemia may occur concurrently with hypokalemia (either spontaneously or due to drug effects, e.g., diuretics) but cats with HCM do not have lower serum Mg levels than control cats. *Considered 3rd line treatment for cardiac arrest, after epinephrine/electrical defibrillation, lidocaine/vasopressin.	100, 125, 500 mg/ml (0.8, 1, 4 mEq/l, respectively) Inj HM
Medetomidine *(Domitor [V])*	Alpha-2 agonist sedative and analgesic	40–80 mcg/kg IM; dosage of 10–40 mcg/kg is often adequate for echo (10–20 minutes), especially if IV and/or with other sedatives in combination (acepromazine, butorphanol, ketamine, other)	General sedation, notably used in cats with hypertrophic cardiomyopathy. Onset of sedation 5–15 min. after injection; peak at 30 minutes; sedation dissipated by 3 hours postinjection. Reflex bradycardia is a response to vasoconstriction and need not be treated; if concern, blood pressure can be measured and normal to elevated levels are expected. Indication in HCM is based on arterial vasoconstriction, decreasing heart rate, which improves diastolic filling and reduces myocardial oxygen consumption. Contraindicated in systemic hypertension. Rare cases of post- administration pulmonary edema; monitor respiratory character and rate. Vomiting may occur within minutes after administration; cats should be fasted prior to dosing. Raises ventricular diameter in dogs (alters echo results) and same is anecdotally observed in cats, reducing appearance of LV thickening and possibly conveying appearance of systolic dysfunction. Largely replaced by dexmedetomidine.	1 mg/ml (= 1000 mcg/ml) Inj VM

Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Metoprolol *(Lopressor [H])*	Beta-1 specific adrenergic blocker	2–15 mg/cat PO q 8h	Poorly studied in cats, likely because of inconvenience of tablet splitting (smallest tablet size is 25 mg). As with all beta blockers, start at low dose and uptitrate to desired effect. Same general characteristics as atenolol (which generally supersedes metoprolol in the cat). Metoprolol tartrate is regular formulation; metoprolol succinate is sustained release (but pharmacokinetics of release/ absorption/metabolism are unknown in the cat).	25, 50 mg Tab 25, 50, 100 mg SR Tab All HM
Mexiletine *(Mexitil [H])*	Class Ib anti-arrhythmic	3 mg/kg PO q 8–12 h	A safe dosage has not been established for the cat; similar drug class as lidocaine; therefore indication is PVCs/VT, and risks of adverse effects (ataxia, seizures; or bradycardia, collapse) are more likely in this species than in the dog at the standard canine dosage of 4–8 mg/kg PO q 8–12h. May be considered in cats that have severe myocardial failure that cannot tolerate a beta blocker for treatment of severe ventricular arrhythmias, or in combination with a beta blocker or sotalol in refractory ventricular arrhythmias. Increasingly difficult to obtain due to decreased demand in human cardiology.	150, 200, 250 mg Cap, Tab HM
Midazolam *(Versed [H])*	Benzodiazepine sedative	0.1–0.5 mg/kg IM or IV	Almost always used in conjunction with other agents, notably an opioid (for moderate sedation) or either medetomidine or ketamine (for heavy sedation). Safe; very minimal cardiovascular effect. Provides mild additional sedation, no practical effect if given as sole drug. Previously expensive, now inexpensive as generic. Main advantage over diazepam is equal efficacy as IM or IV injection.	1, 10 mg/ml Inj HM
Minipress—see Prazocin				

Continued

Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Nitroglycerin	Nitrate vasodilator	Apply 1/8"–1/4" (2–5 mm) strip to hairless skin q 6–8 h × 24–48 h (pinna or medial thigh); or 12 h on, 12 h off alternating for 3 days	Vasodilator (preferentially venodilator in topical ointment formulation) with variable (mild if any) effect. Main indication is acute congestive heart failure, where venodilation increases venous "reservoir" capacity, reducing intravascular hydrostatic pressure and reducing further immediate edema formation. Wear gloves when handling/applying, to avoid human transdermal absorption (vasodilation causes headaches, hypotension). Nitrate tolerance signifies loss of efficacy after approximately 48 h of continuous treatment. Prevent patient from licking site of application. No studies have evaluated it in cats; anecdotally appears unlikely to be harmful. An intravenous formula used as a CRI is available for balanced arterial and venous dilation, but has not been studied in cats, and nitroprusside is typically chosen for the purpose of potent balanced vasodilation in the acute setting.	2% ointment for topical use HM
Nitroprusside *(Nitropress [H])*	Nitrate vasodilator	0.5–5 mcg/kg/min IV CRI, adjusted PRN	Acute potent balanced (arterial and venous) vasodilation, typically as part of management of critical congestive heart failure, as an afterload and preload reducer. In the cat, the high prevalence of hypertrophic cardiomyopathy (where any excess vasodilation is detrimental via eliciting reflex sinus tachycardia [causing less diastolic filling time, more myocardial oxygen consumption, etc.]) means this drug is used infrequently. Constant (q 5–10 minutes) blood pressure monitoring via Doppler or direct arterial line is necessary for confirming normotension during treatment. Loss of efficacy after 48 h (nitrate tolerance), so used intermittently if at all. Cyanide poisoning is possible if high doses used over 1–2 days.	25 mg/ml Inj HM
Norepinephrine *(Levophed [H], noradrenaline)*	Catecholamine	0.05–2 mcg/kg/min IV CRI, adjusted PRN	Main indication is critical hypotension (principal drug action is alpha-agonism). Requires constant blood pressure monitoring during infusion, and dose titration to desired effect.	1 mg/ml Inj HM
Norvasc—see Amlodipine				

Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Omega-3 fatty acid supplement	Antioxidant nutritional supplement	Optimal dosage unknown	Antioxidant effects of documented benefit in human coronary artery disease, where the pathophysiologic mechanism contains an important inflammatory component; no such component demonstrated in feline heart disease, and thus, no indication for this product in feline cardiology to date. High doses (40 mg/kg EPA, 25 mg/kg DHA) may lessen cardiac cachexia in dogs with heart failure; effect in cats is unknown. May lessen production of catabolic inflammatory cytokines TNF and IL-1, which may be a component of cardiac cachexia.	
Phenylephrine	Vasopressor; postsynaptic alpha-adrenergic agonist	1–3 mcg/kg/min IV CRI, adjusted PRN	Indicated for acute hypotension or anesthesia-related hypotension unresponsive to other initial anesthetic modifications in the euvolemic cat, especially when underlying cause is diastolic heart disease (e.g., HCM, RCM/UCM) where vasoconstriction is generally better tolerated than in systolic heart disease (e.g., DCM). Begin infusion at low end of dosage range and increase to desired effect (usually low-normal arterial blood pressure) while monitoring blood pressure continuously.	10 mg/ml Inj HM
Pimobendan *(Vetmedin [V])*	Inodilator (positive inotrope and arterial dilator)	0.625–1.25 mg PO/cat q 12h	Anecdotal reports of use in congestive heart failure caused by either dilated cardiomyopathy or restrictive/unclassified cardiomyopathy in cats; phosphodiesterase III inhibitor causes vasodilation of arteries and veins, which reduces afterload and preload. Calcium sensitizing agent increases affinity of troponin C to calcium, which increases contractility, without the expense of increased myocardial O2 consumption (unlike dobutamine). Theoretical concern over whether it may potentiate ventricular arrhythmias. No prospective studies have been done in cats at this time, so its use is based on extrapolations from canine studies or anecdotal clinical experience. Contraindicated in hypertrophic cardiomyopathy. No support for use in any compensated ("asymptomatic") heart disease. Contraindicated when nature of cardiac lesion is unknown.	1.25, 2.5, 5 mg Ch (USA) Cap (Canada, Europe, Australasia) VM
Pitressin—see Vasopressin				
Plavix—see Clopidogrel				

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Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Potassium chloride IV supplement	Electrolyte	Always less than than 0.5 mEq/kg/h	Supplement to treat hypokalemia (or prevent hypokalemia during fluid therapy). Typically add KCl to IV fluid bag to total 20 mEq/l, and administer at maintenance rate. May add total of 40 mEq/l to fluid bag if serum [K^+] <3.5 mEq/l, or 60 mEq/l if serum [K^+] <3 mEq/l, or 80 mEq/l if serum [K^+] <2.5 mEq/l. Never administer more than 0.5 mEq/l/hr (i.e., never bolus IV fluid supplemented with KCl).	2 mEq/l Inj VM,HM
Potassium salts oral supplement *(Tumil K [V], No Salt [H])*	Electrolyte	0.5 mEq/kg/day PO, adjusted based on serum [K^+]	Chronic supplementation to offset documented excessive loss (common with diuretics) or concurrent K^+-sensitive disorder (e.g., PVCs, VT). Serum [K^+] should be measured on blood drawn in green-top (heparin) tubes, not red-top, to minimize in vitro K^+ release from activated platelets, masking hypoK^+. KCl: 1 mEq = 75 mg. K gluconate: 1 mEq = 234 mg. K citrate: 1 mEq = 108 mg. $KHCO_3$: 1 mEq = 100 mg. Tumil K: 2 mEq (468 mg) K gluconate per tablet, ¼ tsp powder, or ½ tsp gel.	Many VM, HM
Prazocin *(Minipress [H])*	Alpha-1 adrenergic blocker	0.25–0.5 mg/cat PO q 24h	Treatment for systemic hypertension. Less well studied and seemingly less effective and safe than amlodipine, which is preferred. Use for feline urethral obstruction may decrease arterial blood pressure and could trigger congestive heart failure in a previously compensated cat with heart disease via reflex sinus tachycardia; not recommended in cats with preexisting HCM.	1,2,5 mg Cap HM
Prilium—see Imidapril				
Prinivil—see Lisinopril				
ProBanthine—see Propantheline				

Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Procainamide *(Pronestyl, Procan [H])*	Class Ia anti-arrhythmic	3–8 mg/kg PO q 6–8h 1–2 mg/kg slow IV; may follow with 10–20 mcg/kg/min IV CRI	Third-choice orally active ventricular antiarrhythmic (if sotalol, atenolol ineffective). Efficacy poorly studied in cats. Regular formulation preferred over sustained-release, despite increased dosing frequency. Sustained-release formulations can be given less often (q 8–12 h) in other species, but also unpredictably absorbed, including undigested tablet passed intact in feces. Many interactions with other drugs. Increasingly difficult to obtain due to decreased demand in human cardiology. IV use for ventricular tachycardia not responsive to lidocaine, start at low dose and monitor for significant hypotension as a common side effect.	250,375, 500 mg Tab 250,500, 750, 1000 mg SR Tab 500 mg/ml Inj HM
PromAce—see Acepromazine				
Pronestyl—see procainamide				
Propantheline *(ProBanthine [H])*	Orally active vagolytic	0.8–1.6 mg/kg PO q 8h	Medical treatment for pathologic bradycardias (i.e., third-degree or high-grade Mobitz type II second-degree AV block; sinus node dysfunction/sick sinus syndrome; sinus bradycardia) when underlying cause is optimally controlled. This medication usually is ineffective in cats with these bradyarrhythmias but it may be administered as an attempt to noninvasively treat the arrhythmias. Signs of parasympathetic excess (notably constipation) are dose-limiting. Pacemaker implantation becomes necessary if severe clinical signs caused by bradycardia are apparent.	7.5, 15 mg Tab HM

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Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Propranolol *(Inderal [H])*	Nonspecific beta blocker	0.05 mg/cat IV bolus, repeat as needed q 1–2 minutes to maximum dosage 0.3 mg q 15–20 minutes.	Generally replaced by atenolol for oral use, because atenolol is beta-1 specific (whereas propranolol's beta-2 blocking effects may cause bronchoconstriction in addition to its cardiac/beta-1 blocking effects), because propranolol requires q 8h dosing in the cat, and because transient gastrointestinal and hepatobiliary adverse effects are reported more commonly with oral propranolol than atenolol in cats. For IV use, propranolol remains useful when treating rapid supraventricular tachycardias or ventricular tachycardia; low-dose administration is repeated as needed q 1–5 minutes to avoid acute bradycardia/hypotension. Underlying hypovolemia/dehydration, anxiety, pain, and other sources of sympathetic stimulation must always be controlled first before IV beta-blocker administration. Constant ECG monitoring during and for 10–30 minutes after IV administration to assess heart rate (neither excessively suppressed nor inadequately reduced) and rhythm (ideally, conversion to sinus rhythm/sinus tachycardia). Goal = perfusing rhythm (e.g., heart rate <260 beats/minute), not perfect ECG.	1 mg/ml Inj HM
Ramipril *(Altace [H], Vasotop [V])*	Angiotensin-converting enzyme (ACE) inhibitor	0.5 mg/kg PO q 24h	Long-acting (half-life in the cat >20 h) ACE inhibitor. Trough ACE inhibition = 81% at 24h in the cat, warranting q 24h dosing. As monotherapy, does not alter cardiac mass or diastolic function in cats with hypertrophic cardiomyopathy. No consistent blood pressure lowering effect	0.625, 1.25, 2.5, 5 mg Tab VM 1.25, 2.5, 5,10 mg Tab HM
Salix—see Furosemide				
Sotalol *(Betapace [H])*	Beta-adrenergic and potassium channel blocker	2 mg/kg PO q 12h or 20 mg/cat q 12 h	Broad-spectrum antiarrhythmic (supraventricular or ventricular tachyarrhythmias) indicated mainly for rapid and/or symptomatic ventricular tachycardia where correction of the underlying cause is not possible or was unsuccessful. Lower dosages mainly produce beta-blocking (class II) effects; higher dosages for class III (K^+-channel/repolarization-prolonging) effects, but beta-blocking effects may be more significant than K^+-blocking effects in controlling feline ventricular arrhythmias. As with any beta blocker, the drug should not be started when the patient is in fulminant congestive heart failure. Minimal feline-specific information available. Large tablet concentration makes compounding essential. Multiple drug interactions, mainly regarding class III effects and QT interval prolongation (theoretically increased risk of R on T phenomenon, acute ventricular fibrillation)	80,120,160 240 mg Tab HM

Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Spironolactone *(Aldactone [H])*	Aldosterone antagonist diuretic	1–2 mg/kg PO q 12h	Associated with prolonged survival in human heart failure patients, both via diuretic effects and tissue anti-aldosterone effects (e.g., reduction of formation of fibrous tissue in myocardium). Also K-sparing and synergistic diuretic effects with long-term furosemide therapy, improving hypokalemia and lessening effects of diuretic tolerance by using sequential nephron blockade, respectively. No such benefits shown in cats. Cats with asymptomatic HCM given spironolactone 2 mg/kg PO q 12h × 4 months showed no improvement in hypertrophy compared to placebo and 31% of cats (all Maine coon) developed severe facial ulcerative dermatitis requiring termination of treatment.	25, 50, 100 mg Tab HM
Streptokinase *(Kabikinase, Streptase [both H])*	Thrombolytic	90,000 IU IV, then 45,000 IU IV CRI	Aortic thromboembolism of recent onset (<8 h); emboli that have been present for >8 h are less likely to be lysed, increasing risk of adverse effects compared to beneficial effects. Absolute contraindications include intracardiac thrombus (risk of detachment and embolization), unconfirmed embolic disease (if a reasonable possibility exists that clinical signs are due to trauma, neoplasia, or other nonembolic disorder), and existing or expected bleeding tendency. As with other thrombolytics, the proportion of cats that benefit from greater return of pulses (superior to anticoagulation alone, e.g., heparin) is negated or outweighed by the number of severe adverse reactions, including hyperkalemia and hemorrhage (manifesting as overt blood loss—hematuria, epistaxis, ecchymoses—or internal bleeding—neurologic dysfunction, dyspnea due to pulmonary hemorrhage, weakness and pallor due to GI bleeding). Requires intensive 24-hour critical care and monitoring. Overall survival to discharge = 33%.	250,000 IU, 750,000 IU, 1,500,000 IU Inj HM
Taurine	Essential amino acid	125–250 mg PO q 12h	Supplementation for chronic treatment of taurine-deficient systolic dysfunction/dilated cardiomyopathy. Indicated when whole blood and/or plasma taurine levels are low, which may occur with a nutritionally balanced or unbalanced diet. Reversal of cardiomyopathy occurs in many cats, with improvement in clinical signs during the first 2 weeks of taurine supplementation and radiographic/echocardiographic improvement in the next 2–4 weeks.	250 mg Tab OTC
Tenormin—see Atenolol				

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Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Terbutaline *(Brethine [H])*	Beta-2 adrenergic agonist	0.625–1.25 mg PO per cat q 12h	Mainly indicated for bronchoconstrictive airway disease (allergic/asthmatic respiratory disorders) but some crossover to cardiac beta-1 receptors justifies trial use in cats with pathologic bradycardia (high-grade Mobitz type II second-degree AV block; third-degree AV block; sick sinus syndrome) or bradycardia secondary to high vagal tone that persists despite treating underlying cause or if a cause cannot be identified. Adverse/excessive effects = tachycardia, mydriasis. Few cases of symptomatic bradycardia in the cat respond to this (or any) medication, and pacemaker implantation becomes necessary.	2.5,5 mg Tab 1 mg/ml Inj HM
Ticlopidine *(Ticlid [H])*	Anticoagulant	(none)	Not recommended in cats because early studies identified dose-limiting anorexia at dosages required for antiplatelet effects.	250 mg Tab HM
Tissue plasminogen activator (t-PA; *Alteplase [H], Activase [H])*	Thrombolytic	5 mg/cat IV CRI over 1.5–5 h	Aortic thromboembolism of recent onset (<8 h); emboli that have been present for >8 h are less likely to be lysed, increasing risk of adverse effects compared to beneficial effects. Absolute contraindications include intracardiac thrombus (risk of detachment and embolization), unconfirmed embolic disease (if a reasonable possibility exists that clinical signs are due to trauma, neoplasia, or other nonembolic disorder), and existing or expected bleeding tendency. As with other thrombolytics, the proportion of cats that benefit from greater return of pulses (superior to anticoagulation alone, e.g., heparin) is negated or outweighed by the number of severe adverse reactions, including pigmenturia (36%), scleral hemorrhage (18%), rectal bleeding (9%), central nervous system dys- function (40%), and hyperkalemia (36%), for an overall rate of survival to discharge of only 27%. Requires intensive 24-hour critical care and monitoring. Alteplase: 1 mg = 580 000 IU. Other forms (different potency): Reteplase/Retavase/Rapilysin, Tenecteplase/ TNKase.	50,100 mg Inj HM (Alteplase)
Torbugesic—see Butorphanol				

Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Torsemide *(Demadex [H], torasemide)*	Loop diuretic	0.1–0.3 mg/kg PO q 24h (or divided into q 12h)	Similar effect to furosemide but more potent; produces diuretic effect similar to 1–3 mg/kg furosemide, but may be less prone to "braking effect" (diuretic resistance over time). May be considered when diuretic response to high-dose furosemide is diminished, in refractory heart failure. Some consider decreasing the furosemide dose 50% when adding on, can always uptitrate. May cause severe dehydration, so careful monitoring of renal values, serum electrolytes, clinical status, as for other loop diuretics.	5, 10 20 mg Tab 100 mg Cap 10 mg/ml Inj HM
Valium—see Diazepam				
Vasopressin *(Pitressin [H])*	Noncatecholamine vasoconstrictor peptide	0.2–0.8 U/kg IV	Newer application in cardiac arrest-associated hypotension: may be similar to epinephrine for treatment of hypotension in this setting. Administer low dose and repeat as necessary based on presence of pulse, blood pressure monitoring (can repeat q 3–5 min, and can alternate with epinephrine).	20 U/ml Inj HM
Vasotec—see Enalapril				
Vasotop—see Ramipril				
Verapamil *(Calan, Isoptan, Verelan [all H])*	Calcium-channel blocker	0.05 mg/kg slow IV; may repeat twice, 5–30 minutes between doses	Indicated for severe, uncontrolled supraventricular tachycardias after correctable systemic causes have been addressed. Avoid (or reduce dosage) if structural heart disease is present; risk of triggering congestive heart failure (or aggravating it, if already present) if heart rate suppression is excessive; verapamil is also a negative inotrope (contraindicated in DCM and any other situation where ventricular contractility is compromised). The use of diltiazem IV has surpassed verapamil, due to fewer negative inotropic effects with diltiazem. Previous use as oral drug for feline HCM has not persisted, likely due to absence of demonstrated efficacy (like other drugs for this disease) and greater ease of q 12–24 h pilling with atenolol.	2.5 mg/ml Inj HM
Versed—see Midazolam				
Vetalar—see Ketamine				
Vetmedin—see Pimobendan				

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Generic Name (Brand Name)	Indications/Drug Type	Dosage and Possible Routes of Admin.	Comments	Available sizes
Warfarin *(Coumadin [H])*	Vitamin K antagonizing anticoagulant	0.25–0.6 mg/cat PO q 24h	Powerful orally active anticoagulant indicated for prevention of recurrent thromboembolism. Variable efficacy, including either inadequate or excessive anticoagulation; anticoagulant effect is optimized via weekly plasma prothrombin time measurement, targeting 1.5–2.5 times upper limit of normal. Subjectively the most effective anticoagulant in feline medicine but also the most prone to adverse effects. Brief period of inhibition of proteins C and S (natural anticoagulants) at onset of treatment suggests transient hypercoagulability and warrants overlap between injectable (heparin) treatment during acute phase of thromboembolism treatment (2–4 days) and start of chronic oral warfarin treatment. Treatment if signs of excessive anticoagulation: stop warfarin; if needed, vitamin K (2.5– 3 mg/kg IM or SQ), plus plasma transfusion if bleeding. Anticoagulant function helps prevent formation of new thrombi but does not actively degrade existing thrombi.	1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg T HM
Xylocaine—see Lidocaine				
Zestril—see Lisinopril				

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