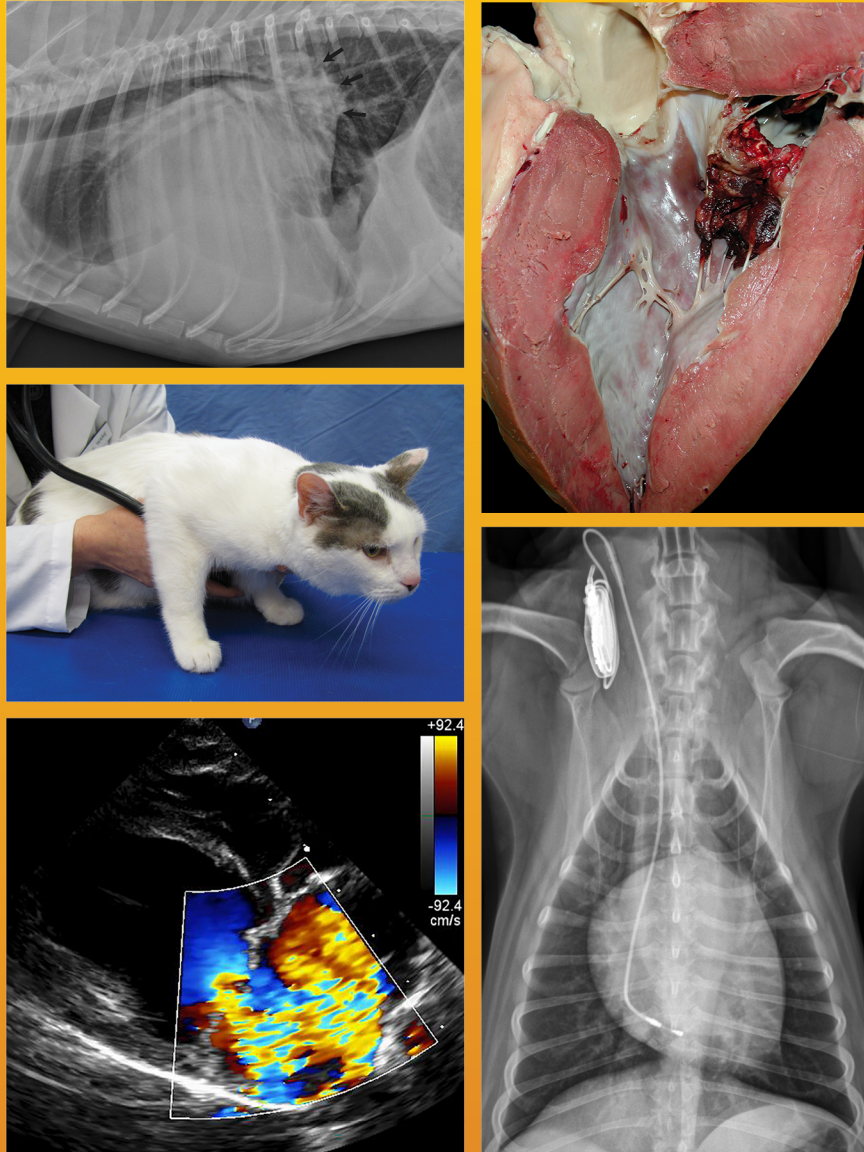


Cardiovascular Disease in Companion Animals Dog, Cat, and Horse

Second Edition



Wendy A. Ware
John D. Bonagura



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Taylor & Francis Group

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Wendy A. Ware, John D. Bonagura

with contributions by Brian A. Scansen



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ABBREVIATIONS

2D	two-dimensional	APC	atrial premature complex
3D	three-dimensional	A_R	(Doppler) atrial reversal (wave)
4D	four-dimensional	AR	aortic valve regurgitation
5-HT	5-hydroxytryptophan, serotonin	ARB	angiotensin receptor blocker
αSMA	alpha-smooth muscle actin	ARNI	angiotensin receptor blocker and neprilysin inhibitor
A	late diastolic (atrial kick) mitral or tricuspid inflow (motion or velocity)	ARVC	arrhythmogenic right ventricular cardiomyopathy
A-a	alveolar–arterial (O ₂ gradient)	AS	aortic stenosis
Ab	antibody	ASD	atrial septal defect
ABV	aortic balloon valvuloplasty (or BAV, balloon aortic valvuloplasty)	AST	aspartate aminotransferase
ACDO	Amplatz® Canine Duct Occluder	AT	(Doppler flow) acceleration time
ACE	angiotensin converting enzyme	ATE	arterial thromboembolism
Ach	acetylcholine	ATP	adenosine triphosphate
ACVIM	American College of Veterinary Internal Medicine	ATPase	adenosine triphosphatase
ADH	antidiuretic hormone	AV	atrioventricular
ADP	adenosine diphosphate	A-V	arteriovenous
ADPase	adenosine diphosphatase	AVP	arginine vasopressin
AF	atrial fibrillation	AVRT	atrioventricular reciprocating tachycardia
Ag	antigen	AVSD	atrioventricular septal defect
AHS	American Heartworm Society	BAL	bronchoalveolar lavage
ALD	aldosterone	BAPGM	Bartonella alpha Proteobacteria growth medium
ALS	advanced life support	BAV	balloon aortic valvuloplasty (or aortic balloon valvuloplasty, ABV)
ALT	alanine aminotransferase	BEG	“boutique,” exotic protein-based or grain-free (diets)
Ang	angiotensin	BENCH (study)	The effect of benazepril on survival times and clinical signs of dogs with congestive heart failure (BENCH study group, 1999; see Chapter 21 references)
Ang1R	angiotensin-1 receptor(s)	BLS	basic life support
Ang2R	angiotensin-2 receptor(s)		
ANP	atrial natriuretic peptide		
Ao	aorta/aortic		
AoSA	aorto-septal angle		
AoV	distance between the open aortic valve leaflets; maximal aortic orifice diameter		

BNP	brain natriuretic peptide	DC	direct current
BP	blood pressure	DCM	dilated cardiomyopathy
BPV	balloon pulmonary valvuloplasty (or pulmonary balloon valvuloplasty, PBV)	DCRV	double-chambered right ventricle
		DDD	dual-paced, dual-sensed, dual-response (pacing mode)
BUN	blood urea nitrogen	DELAY (study)	Delay of appearance of symptoms of canine degenerative mitral valve disease treated with spironolactone and benazepril (Borgarelli, 2020; see Chapter 29 references)
Ca⁺⁺	calcium ion	DHA	docosahexaenoic acid
cAMP	cyclic adenosine monophosphate	DIC	disseminated intravascular coagulation
CATSCAN (study)	Cardiomyopathy prevalence in 780 apparently healthy cats in rehoming centers (Payne, 2015; see Chapter 33 references)	DISH	discrete interventricular septal hypertrophy
CaVC	caudal vena cava/caval	DMVD	degenerative mitral valve disease (also called chronic mitral valve disease, CVMD, and myxomatous mitral valve disease, MMVD)
CB	cutting balloon (catheter)	DNA	deoxyribonucleic acid
CBC	complete blood count	dP/dt	change in pressure/time (rate of LV pressure change)
CDI	color Doppler imaging (CF Doppler)	dP/dt_{max}	maximal rate of LV pressure rise during isovolumic contraction
CF	color flow (Doppler)	DSH	domestic shorthair (cat)
cGMP	cyclic guanosine monophosphate	DT	(Doppler flow) deceleration time
CK	creatine kinase	DUST	discrete upper septal thickening
CKCS	Cavalier King Charles Spaniels	DV	dorsoventral (position or view)
CK-MB	cardiac-specific isoenzyme of CK	E	early diastolic mitral or tricuspid inflow (motion or velocity)
CHD	congenital heart disease	E_a	early diastolic annular tissue velocity (sometimes expressed as E', e', or Em)
CHF	congestive heart failure	EADs	early afterdepolarizations
cm/s	centimeters/second	ECG	electrocardiogram/ electrocardiographic
CMVD	chronic mitral valve disease (also called degenerative mitral valve disease, DVMD, and myxomatous mitral valve disease, MMVD)	echo	echocardiographic/ echocardiography
CNP	C-type natriuretic peptide	ECM	extracellular matrix
CNS	central nervous system	ECVIM	European College of Veterinary Internal Medicine
CO	cardiac output	EDP	end-diastolic pressure (ventricular)
CO₂	carbon dioxide	EDTA	ethylene diamine tetraacetic acid
CPR	cardiopulmonary resuscitation	EDV	end-diastolic volume (ventricular)
CRI	constant/continuous rate infusion	EDVI	end-diastolic volume index
CRT	capillary refill time	EF	ejection fraction
CSA	cross-sectional area	EIPH	exercise-induced pulmonary hemorrhage
CT	computed tomography	ELISA	enzyme-linked immunosorbent assay
CTD	cor triatriatum dexter	eNOS	endothelial nitric oxide synthase
cTn	cardiac troponin (also, cTnI and cTnT)	EP	electrophysiologic
CURATIVE (guidelines)	Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care (Goggs, 2019; see Chapter 36 references)	EPA	eicosapentaenoic acid
CV	cardiovascular	Epi	epinephrine
CVP	central venous pressure		
CvRD	cardiovascular-renal axis disorder		
CW	continuous wave (Doppler)		
D5W	5% dextrose in water		
D	diastolic (wave or volume), depending on context		
DADs	delayed afterdepolarizations		

EPIC (study)	Effect of pimobendan in dogs with preclinical myxomatous mitral valve disease and cardiomegaly: the EPIC study (Boswood, 2016; see Chapter 29 references)	HRV	heart rate variability
EPSS	(mitral) E-point to septal separation	HSA	hemangiosarcoma
EROA	effective regurgitant orifice area	HT	(systemic) hypertension
Es, E_{max}	slope of the end-systolic pressure-volume relationship	HW	heartworm
ESVC	European Society for Veterinary Cardiology	HWD	heartworm disease
ESVI	end-systolic volume index	I_{Ca}	inward Ca ⁺⁺ current
ET	(Doppler flow) ejection time	I_f	funny current
ETN	endothelin	I_K	delayed rectifier K ⁺ current
f	fibrillation (waves)	I_{Kr}	rapid component of I _K
FA	fatty acid(s)	I_{Ks}	slow component of I _K
FAC	fractional area change	I_{K1}	inward rectifier K ⁺ current
FAST	focused assessment with sonography in trauma	I_{NCX}	sodium-calcium exchange current
FAT	focal atrial tachycardia	I_{to}	transient outward K ⁺ current
FATCAT (study)	Secondary prevention of cardiogenic arterial thromboembolism in the cat: the double-blind, randomized, positive-controlled feline arterial thromboembolism; Clopidogrel vs. Aspirin trial (Hogan, 2015; see Chapter 36 references)	ICS	intercostal space
FDA	(United States) Federal Drug Administration	IFA	immunofluorescent antibody
FDPs	fibrinogen/fibrin degradation products	IGF	insulin-like growth factor
FIV	feline immunodeficiency virus	IL	interleukin
Fr	French (diameter size, for catheterization equipment)	IM	intramuscular/intramuscularly
FS	fractional shortening	IMHA	immune-mediated hemolytic anemia
GAGs	glycosaminoglycans	iNOS	inducible nitric oxide synthase
GFR	glomerular filtration rate	INR	international normalization ratio
GI	gastrointestinal	IO	intraosseous
H₂O	water	IRIS	International Renal Interest Society
HARD	heartworm-associated respiratory disease	ISACHC	International Small Animal Cardiac Health Council
HCl	hydrochloride	ISFM	International Society of Feline Medicine
HCM	hypertrophic cardiomyopathy	ISI	international sensitivity index (for thromboplastin)
HFpEF	heart failure with preserved ejection fraction	IV	intravenous/intravenously
HFrEF	heart failure with reduced ejection fraction	IVRT	isovolumic (isovolumetric) relaxation time
Hg	mercury (as in mm Hg)	IVS	interventricular septum/septal
HOCM	hypertrophic obstructive cardiomyopathy	K⁺	potassium ion
HPB	high-pressure balloon	KCl	potassium chloride
HR	heart rate	kVp	kilovoltage peak
		L	cardiac long axis (VHS measurement), or liter, depending on context
		L1	first stage larvae
		L2	second stage larvae
		L3	third stage larvae
		L4	fourth stage larvae
		L5	immature adult heartworms, or fifth stage larvae
		L/R	left/right (echocardiograph inversion switch)
		L-to-R	left-to-right (shunt flow direction)
		LA	left atrium/atrial
		LAA	left atrial appendage
		LAFB	left anterior fascicular block
		LAO	left anterior oblique (position)
		LAu	left auricle (atrial appendage)
		LAx	long axis

LBBB	left bundle branch block	NT-proBNP	N-terminal probrain (B-type) natriuretic peptide
LD50	lethal dose causing death in 50% of cases	NYHA	New York Heart Association
LDH	lactate dehydrogenase	O₂	oxygen
LMWH	low molecular weight heparin	OTN	over-the-needle (catheter)
LPFB	left posterior fascicular block	P	pressure
LRS	lactated Ringer's solution	P wave	atrial muscle depolarization waveform
LV	left ventricle/ventricular	P-P	P wave to P wave interval
LVID	left ventricular internal dimension	ΔP	perfusion pressure
LVIDd	left ventricular internal diameter at end-diastole	PA	pulmonary artery/arterial
LVIDdN	LVIDd normalized to body weight	PAI-1	plasminogen activator inhibitor type 1
LVIDs	left ventricular internal diameter at end-systole	PBV	pulmonary balloon valvuloplasty (or BPV, balloon pulmonary valvuloplasty)
LVOT	left ventricular outflow tract	PCH	pulmonary capillary hemangiomatosis
MAP	mean arterial pressure	pCO₂	partial pressure of carbon dioxide
MAPSE	mitral annular plane systolic excursion	PCR	polymerase chain reaction
mAs	milliamperes x seconds	PCV	packed cell volume
MEA	mean electrical axis (on ECG)	PCWP	pulmonary capillary wedge pressure
MF	microfilariae	PDA	patent ductus arteriosus
MHS	manubrium heart score	PDE	phosphodiesterase
MHz	megahertz	PDE-3	phosphodiesterase-type 3 isoenzyme
miRNA	microRNA	PDE-5	phosphodiesterase-type 5 isoenzyme
mL	milliliter	PDK4	pyruvate dehydrogenase kinase isozyme 4
mm	millimeter	PEA	pulseless electrical activity
mm Hg	millimeters of mercury	PFO	patent foramen ovale
mm/s	millimeters/second	PG	pressure gradient
MMPs	matrix metalloproteinases	PH	pulmonary hypertension
MMVD	myxomatous mitral valve disease (also: chronic mitral valve disease, CMVD; degenerative mitral valve disease, DVMD)	PICALM	phosphatidylinositol-binding clathrin assembly protein
MR	mitral valve regurgitation (insufficiency)	PISA	proximal isovelocity surface area
MRI	magnetic resonance imaging	PLCVC	persistent left cranial vena cava
MS	mitral valve stenosis	PMI	point of maximal (murmur) intensity
m/s	meters/second	PNS	parasympathetic (cholinergic) nervous system
mV	millivolts	pO₂	partial pressure of oxygen
MVD	mitral valve dysplasia	PO	<i>per os</i> , oral/orally
MYBPC	myosin binding protein C	POC	point-of-care
Na⁺	sodium ion	PPDH	peritoneopericardial diaphragmatic hernia
NaCl	sodium chloride	PR	pulmonary valve regurgitation
NCX-1	sodium-calcium exchanger	PRAA	persistent right aortic arch
NE	norepinephrine	PREDICT (study)	Prediction of first onset of congestive heart failure in dogs with degenerative mitral valve disease (Reynolds, 2012; see Chapter 29 references)
NH	neurohormonal		
nNOS	neuronal nitric oxide synthase		
NO	nitric oxide		
NOS	nitric oxide synthase		
NPR	natriuretic peptide receptor		
NSAID	nonsteroidal anti-inflammatory drug		
NT-proANP	N-terminal proatrial (A-type) natriuretic peptide		

PRF	pulse-repetition frequency (of pulsed wave Doppler modalities)	RMP	resting membrane potential
PROTECT (study)	Efficacy of pimobendan in the prevention of congestive heart failure or sudden death in Doberman Pinschers with preclinical dilated cardiomyopathy (Summerfield, 2012; see Chapter 22 references)	RNA	ribonucleic acid
PS	pulmonary (pulmonic) stenosis	RPADI	right pulmonary artery distensibility index
PT	prothrombin time	rPDA	reversed patent ductus arteriosus
PTE	pulmonary thromboembolism	RRR	resting (sleeping) respiratory rate
PVC	premature ventricular complex	rt-PA	recombinant tissue plasminogen activator
PVOD	pulmonary veno-occlusive disease	RT-PCR	reverse transcriptase-polymerase chain reaction
PVR	pulmonary vascular resistance	RV	right ventricle/ventricular
PW	pulsed wave (Doppler)	RVIDd	right ventricular internal diameter in diastole
Q	flow	RVOT	right ventricular outflow tract
QRS	ventricular muscle depolarization waveform(s)	rVSD	reversed ventricular septal defect
QTc	heart rate-corrected QT interval	RyR2	cardiac ryanodine receptor
QUEST (study)	Effect of pimobendan or benazepril hydrochloride on survival times in dogs with congestive heart failure caused by naturally occurring myxomatous mitral valve disease (Häggström, 2008; see Chapter 21 references)	S	cardiac short axis (VHS measurement) or systolic (wave or volume), depending on context
R	resistance	S₁	first heart sound (“lub”)
R-R	R wave to R wave interval (also, QRS to QRS complex interval)	S₂	second heart sound (“dub”)
R-to-L	right-to-left (shunt flow direction)	S₃	third heart sound (ventricular gallop)
RA	right atrium/atrial	S₄	fourth heart sound (atrial gallop)
RAAS	renin-angiotensin-aldosterone system	SA	sinoatrial
RAO	right anterior oblique (position)	SAM	(mitral) systolic anterior motion
RAu	right auricle (atrial appendage)	SAS	subaortic stenosis
rASD	reversed atrial septal defect	SAX	short axis
RBBB	right bundle branch block	SC	subcutaneous/subcutaneously
RBC	red blood cell	SDMA	symmetric dimethylarginine assay
RCM	restrictive cardiomyopathy	SERCA	sarcoendoplasmic reticulum calcium ATPase
RDW	RBC distribution width	SI	sphericity index
RECOVER	Reassessment Campaign on Veterinary Resuscitation (see Chapter 25 reference citations)	SMOD	Simpson’s method of disks
REVEAL (study)	International collaborative study to assess cardiovascular risk and evaluate long-term health in cats with preclinical hypertrophic cardiomyopathy and apparently healthy cats (Fox, 2018; see Chapter 33 references)	SNS	sympathetic (adrenergic) nervous system
		SpO₂	oxygen saturation
		spp.	species
		SR	sarcoplasmic reticulum
		SSS	sick sinus syndrome
		SV	stroke volume
		SVEP (study)	Efficacy of enalapril for prevention of congestive heart failure in dogs with myxomatous valve disease and asymptomatic mitral regurgitation (Kvart, 2002; see Chapter 22 references)
		SVT	supraventricular tachycardia
		TFPI	tissue factor pathway inhibitor
		T of F	tetralogy of Fallot
		T wave	ventricular muscle repolarization waveform
		TAPSE	tricuspid annular plane systolic excursion

TDI	tissue Doppler imaging		
TdP	<i>torsades de pointes</i>		
TE	thromboembolism or thromboembolic		heart failure in dogs chronically treated with enalapril alone for compensated, naturally occurring mitral valve insufficiency. (Atkins, 2007; see Chapter 22 references)
TEE	transesophageal echocardiography/echocardiographic	VF	ventricular fibrillation
TFAST	thoracic focused assessment with sonography for trauma	VHD	valvular heart disease
TGF	transforming growth factor	VHS	vertebral heart size (score, scale, sum)
TICM	tachycardia-induced cardiomyopathy	VICs	valve interstitial cells
TIMPs	tissue inhibitors of MMPs	VLAS	vertebral left atrial size
TNF	tumor necrosis factor	Vmax	maximal (peak) velocity (spectral Doppler)
t-PA	tissue plasminogen activator	VO_{2 max}	maximal rate of O ₂ uptake
TR	tricuspid valve regurgitation	VPC	ventricular premature complex
TTE	transthoracic echocardiography	V/Q	(pulmonary) ventilation/perfusion
TVD	tricuspid valve dysplasia	VSD	ventricular septal defect
UCM	unclassified cardiomyopathy	VT	ventricular tachycardia
UFH	unfractionated heparin	VTI	velocity-time integral (Doppler echocardiography)
US	ultrasound	VVI	ventricular-paced, ventricular-sensed, inhibited (pacing mode)
v	vertebrae (as in VHS)	VVIR	ventricular-paced, ventricular-sensed, inhibited, rate modulation (pacing mode)
V	velocity	WBC	white blood cell
VD	ventrodorsal (position or view)	WPW	Wolff-Parkinson-White (preexcitation pattern or syndrome)
VDD	ventricular-paced, dual-sensed, dual-response (pacing mode)		
VECs	valve endothelial cells		
VETPROOF (study)	Results of the veterinary enalapril trial to prove reduction in onset of		

PREFACE TO *CARDIOVASCULAR DISEASE IN COMPANION ANIMALS*

(2nd edition to *Cardiovascular Disease in Small Animal Medicine*)

Our aim in writing this new and expanded edition was to create a comprehensive yet easily accessible clinical cardiology reference for practicing veterinarians, residents, interns, and veterinary students. Veterinary nurses and others with an interest in the subject might also find it useful. This book reflects the authors' extensive clinical and teaching experience in veterinary cardiology over the past four decades, as well as a review of wide-ranging literature. We have tried to present an overview of cardiovascular medicine in companion animal species that is relevant to veterinarians engaged in canine, feline, and equine clinical practices, and that is well-integrated across chapters, and richly illustrated. We hope this textbook will be helpful and easy to use in your study of cardiology, as well as your day-to-day practice. While the text is focused toward companion animal practitioners, we have included some advanced topics because we believe these provide a useful perspective regarding the current scope of veterinary cardiology.

The extensive use of visual images is a core feature of this book, as it was for the previous edition. Many new images are included, while others have been brought forward from the first edition. The vast majority of clinical images were collected during the course of the authors' practices. We are indebted also to a number of colleagues, who generously allowed us to include their images in various chapters. In addition, some figures originally published elsewhere have been included, with permission, to help illustrate key concepts. We are especially pleased that Dr. Brian A. Scansen agreed to write a new chapter on *Cardiac Catheterization and Angiocardiology* (Chapter 6) for this edition because of his extensive expertise and current developments in this area. Brian also contributed importantly to the chapters on *Other Cardiovascular Malformations* (Chapter 28) and *Thromboembolic Disease* (Chapter 36).

We have organized this text into five main sections. The first, *Fundamentals of Clinical Cardiology* (Chapters 1–6), presents clinically relevant overviews of cardiovascular structure and function; aspects of the cardiovascular examination; and the diagnostic modalities of cardiac radiography, echocardiography, electrocardiography, and cardiac catheterization and angiocardiology. The second section (Chapters 7–19) offers a problem-based approach to various *Clinical Manifestations of Cardiovascular Disease*. Section three (Chapters 20–22) focuses on the clinical syndrome of *Heart Failure*, from its pathophysiology and clinical signs to management strategies. Section four of the book (Chapters 23–25) deals with *Heart Rhythm Disturbances*, including underlying mechanisms and consequences, antiarrhythmic drugs and other therapeutic options, and the management of various arrhythmias. The final and largest section (Chapters 26–40) contains chapters on important congenital and acquired *Cardiovascular Diseases* of dogs, cats, and horses. We have cited some specific references within the text but have not attempted to reference every statement

in the book. Many of the original sources we reviewed during our writing are included in the *Suggested Additional Readings and References* list at the end of each chapter. More extensive bibliographies and a collection of supplemental media, are available online for the interested reader. The videos and additional images are especially useful for learning about modalities such as echocardiography.

We have striven for consistency in our use of abbreviations throughout the book. For ease of reference, a list of abbreviations is included. One pitfall inherent to a volume covering such a broad and intertwined subject as cardiovascular disease is the risk of discussing certain concepts repeatedly in different chapters. In an effort to avoid unplanned redundancy and control the overall size of the text, we have chosen to include many cross-references within. We recognize that this can be an annoyance to the reader, but hope that by referencing specific page numbers as much as possible, any inconvenience will be minimized.

This project has been an “adventure” of greater proportions than we originally anticipated. Yet, despite the many challenges along the way, stubborn perseverance as well as a sense of humor allowed us to bring it to conclusion... and remain friends. We want to thank Michael Manson and Jill Northcott of Manson Publishing, for requesting the writing of this second edition and for coordinating its transition while in-process to CRC Press, Taylor and Francis Group. We also are most grateful to Alice Oven, Senior Editor for Veterinary Medicine at CRC Press, Taylor and Francis Group, for her steadfast patience and encouragement throughout the lengthy writing process. In addition, we thank Linda Leggio, Production Editor at Taylor and Francis, and Elizabeth King, Project Manager at KnowledgeWorks Global, for their mighty efforts in shepherding this project into its final form. There are many others who, in various ways, have contributed to our ability to write this book. We want to acknowledge our many colleagues, mentors, patients and their owners, as well as the house officers and thousands of students we have taught over the years. We have learned a huge amount from you all, and hope that what we have written will in turn benefit others. Finally, our sincere thanks and appreciation to our family members and friends who, willingly or not, have supported us through this process. You now can stop asking us if the book is finally finished.

Wendy A. Ware and John D. Bonagura

ABOUT THE AUTHORS

Wendy Ware is *Professor Emerita* of the Departments of Veterinary Clinical Sciences and Biomedical Sciences at the Iowa State University College of Veterinary Medicine. She served as Cardiologist in the ISU Lloyd Veterinary Medical Center for many years and was the first faculty member to hold the Phyllis M. Clark Professorship in Cardiology. Wendy is a Diplomate of the American College of Veterinary Internal Medicine (specialty of Cardiology) and former President of the ACVIM Board of Regents. She also has served as Associate Editor for Cardiology for the Journal of Veterinary Internal Medicine. Dr. Ware authored the textbook *Cardiovascular Disease in Small Animal Medicine*, and subsequently, co-wrote and edited *Self-Assessment Color Review of Small Animal Cardiopulmonary Medicine*, both produced by Manson Publishing. She has authored the “Disorders of the Cardiovascular System” section in Nelson & Couto’s *Small Animal Internal Medicine* since its inaugural edition. Her other contributions include numerous journal articles and individual book chapters, as well as many hours of continuing education presentations to veterinarians.

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Section I

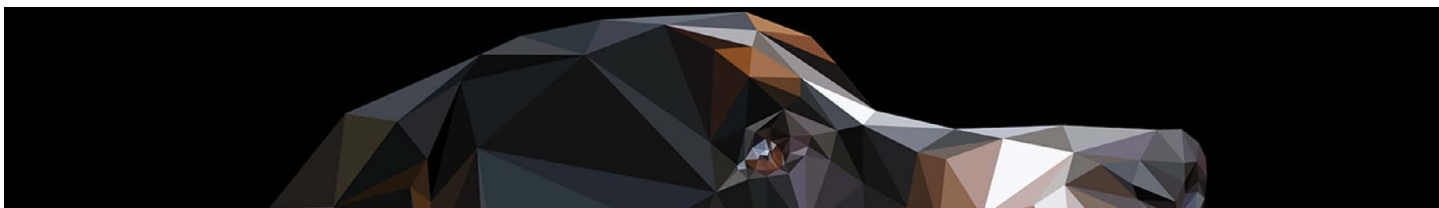
Fundamentals of Clinical Cardiology



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1



THE NORMAL CARDIOVASCULAR SYSTEM

Knowledge of cardiac anatomy and physiology is essential for understanding, diagnosing, and treating diseases of the heart and blood vessels. This chapter offers an overview of normal cardiovascular (CV) structure and function, with some important clinical correlations that illustrate their relevance to clinical practice.

General Considerations

The CV system delivers nutrients and removes metabolic by-products throughout the body. It also supports flow-dependent organ functions such as ventilation and urine formation. The two major component circulations (pulmonary and systemic) are linked in series; therefore, a functional abnormality involving either circulation could negatively affect the other. The coronary circulation originates from the aortic root and returns myocardial venous blood to the heart. The systemic circulation supplies the various organs of the body through a set of parallel circulations. The smaller pulmonary circulation provides oxygen (O_2) and carbon dioxide (CO_2) exchange and contributes to acid-base regulation. **Figure 1.1** schematically illustrates the normal path of blood flow and approximate normal pressures for small animals. Right-sided pressures tend to be higher in large animals, related in part to posture and head position.

Three complementary diagnostic perspectives help provide a conceptual framework for understanding CV system abnormalities: anatomic localization, (patho)physiologic or functional abnormality, and etiologic diagnosis. Each yields insight into a patient's underlying disease process and can inform clinical management decisions. The anatomic localization of disease might involve the cardiac valves (and endocardium), myocardium, pericardium, cardiac impulse formation and conduction system, the respiratory system (with its secondary effects on the heart), or the systemic vasculature. Functional abnormalities could relate to a leaky or

stenotic cardiac valve, poor myocardial contractility (systolic dysfunction), impaired cardiac filling (diastolic dysfunction), arrhythmias and their effect on cardiac output (CO), abnormal systemic-pulmonary communications (shunts), congestive heart failure, pulmonary hypertension, systemic hypertension, or cardiogenic shock. In most cases, a combination of physiologic abnormalities is involved. Third, the patient's etiologic diagnosis is important to consider. Specific etiologies might involve degenerative disease, congenital malformation (anomaly), metabolic or endocrine disease, a neoplastic or nutritional disorder, inflammatory disease (infective or parasitic, immune-mediated, idiopathic), ischemia, and iatrogenic injury, toxicity, or trauma. The reader is referred to the chapters on specific diseases and clinical problems in this text as well as the section "Suggested Additional Reading and References" and online bibliography for further details.

The Heart

External Features

The heart is comprised of four chambers, four cardiac valves, two great vessels, and a number of systemic and pulmonary venous attachments. Superficially the chambers are divided by different grooves or sulci. The atria are dorsal to the coronary or atrioventricular (AV) groove that surrounds the heart circumferentially. The paraconal sulcus (groove) on the left cranio-lateral surface of the heart separates the left ventricle (LV) from the outflow portion of the right ventricle (RV). The subsinuosal sulcus (groove) is located caudally and separates the caudal portions of the RV and the LV. Because the ventricular septum is angled, these grooves only approximate the demarcation of these chambers. As animals age, fat is gradually deposited within these cardiac sulci; this is especially dramatic in horses. In animals with cachexia, the normally white epicardial fat and connective tissue undergo serous atrophy,

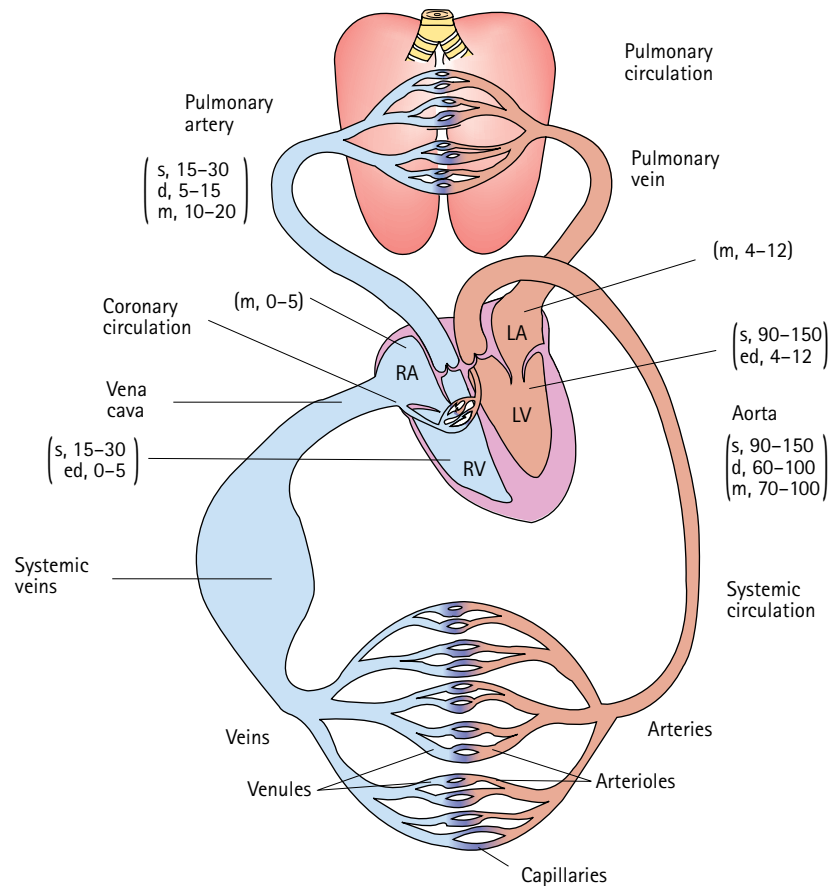


Figure 1.1 Schematic diagram of the cardiovascular system. Examples of normal pressures (mm Hg) in different regions noted in parentheses. d, diastolic; ed, end-diastolic; LA, left atrium; LV, left ventricle; m, mean; RA, right atrium; RV, right ventricle; s, systolic.

taking on a gelatinous appearance at necropsy. Epicardial fat must be distinguished from superficial cardiac lymphatics that appear as white streaks over the cardiac surface. These are seen most prominently in horses.

The pericardium is a double-layered sac that surrounds the heart. It consists of a thin visceral (epicardial) layer of mesothelial cells that is closely adhered to the heart. This lining reflects at the heart base to form the serous lining of the fibrous, parietal pericardium. The latter is contiguous with the mediastinal pleura. A small amount of serous fluid acts as a lubricant between the visceral and parietal pericardial layers. The pericardial space is a common site of disease, which often involves abnormal fluid accumulation and cardiac tumors. See [Chapter 35](#) for more information about pericardial structure and clinical disorders.

The left and right coronary arteries arise from the sinuses of Valsalva, behind the left and right coronary cusps (leaflets) of the aortic valve, respectively. These arteries course over the external surface of the heart before their branches penetrate into the myocardium (**Figure 1.2**). The left coronary artery divides into a circumflex branch that traverses the AV (coronary) groove and a paraconal branch, which descends along the craniolateral sulcus separating the two ventricles.

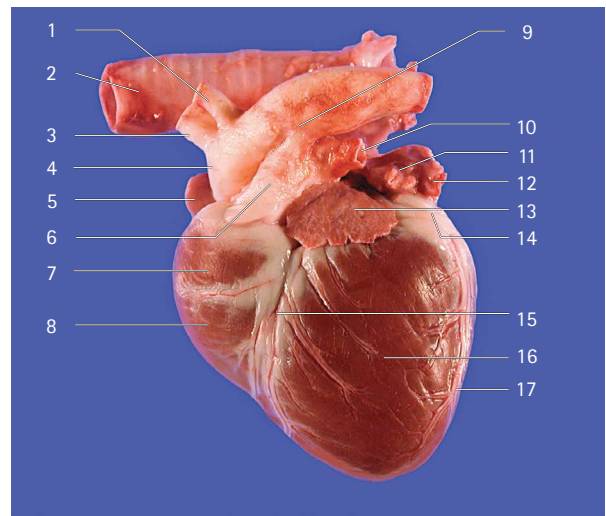


Figure 1.2 Canine heart: External view from the left. 1. L subclavian a., 2. Trachea, 3. Brachiocephalic trunk, 4. Aorta, 5. R auricle, 6. Main pulmonary a. (pulmonary trunk), 7. Conus arteriosus, 8. R ventricle, 9. Ligamentum arteriosum, 10. L pulmonary a., 11. Pulmonary v., 12. L atrium, 13. L auricle, 14. Coronary groove (with circumflex branch of L coronary a.), 15. Cranial (paraconal) interventricular branch of L coronary a., 16. L ventricle, 17. Caudal (subsinoasal) interventricular branch of L coronary a. a., artery; L, left; R, right; v., vein.

The left coronary system is dominant in most dogs, which means the circumflex branch supplies the subsinuosal artery that is distributed to the caudal aspect of the heart. Most cats and horses have a right dominant system, where the subsinuosal artery is derived from the right coronary artery. Coronary artery malformations and myocardial infarctions caused by extramural coronary artery disease occur sporadically in companion animals, however atherosclerotic coronary disease, so common in humans, is rare.

Venous return from the systemic circulation enters the right atrium (RA) through the cranial vena cava, caudal vena cava, and potentially from the azygous vein, which often connects to the cranial vena cava (**Figure 1.3**). Pulmonary venous return enters the dorsal left atrium (LA). There are seven pulmonary veins in most species, although three major pulmonary venous confluences are typically visualized by echocardiography in dogs and cats. Venous anomalies are under-recognized, as suggested by computerized tomography studies in dogs. Some venous admixture occurs normally when systemic bronchial veins, which serve the visceral pleura of the lungs, join the pulmonary veins and mix desaturated with well-oxygenated blood. These venous connections can become clinically relevant in the settings of congestive heart failure, pulmonary hypertension, and cyanotic congenital heart disease. Venous return from the heart muscle is via small coronary veins that eventually drain into the great coronary (cardiac) vein. This vein empties into the coronary sinus, an opening into the RA just ventral to that of the caudal vena cava.

The LV forms the caudoventral aspect of the heart; its point, termed the cardiac apex, normally is located to the left of the midline in dogs, cats, and horses (**Figure 1.2**). The apex is especially prominent and pointed in horses (**Figure 1.4**).

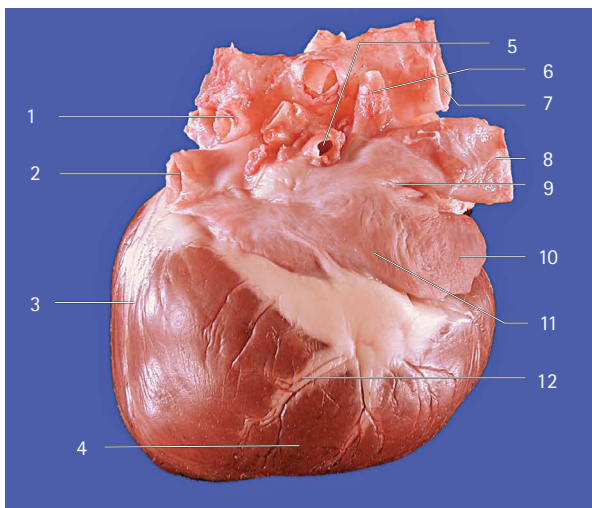


Figure 1.3 Canine heart: External view from the right. 1. Pulmonary v. ostium, 2. Caudal vena cava, 3. Caudal (subsinoosal) interventricular sulcus, 4. R ventricle, 5. R pulmonary a., 6. Azygous v., 7. Trachea, 8. Cranial vena cava, 9. Region of sinoatrial node, 10. R auricle, 11. R atrium, 12. Branches of R coronary a. a., artery; L, left; R, right; v, vein.

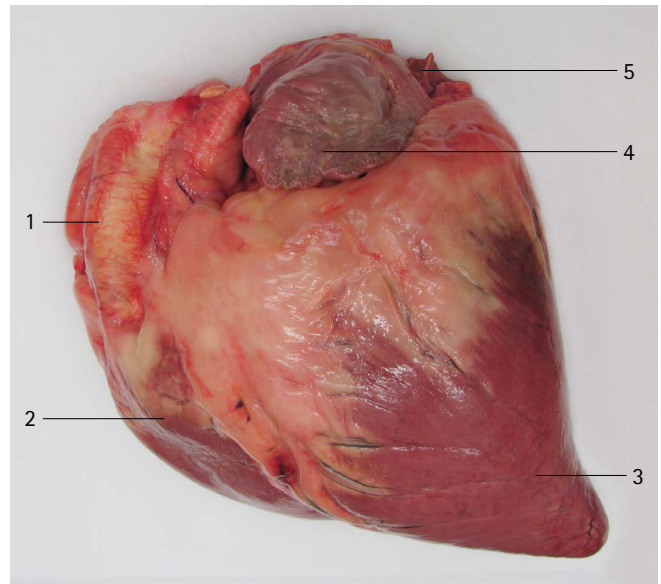


Figure 1.4 Equine heart: External view from the left. 1. Main pulmonary a. (pulmonary trunk), 2. R ventricle (outflow region), 3. L ventricle (note pointed apex), 4. L auricle, 5. L atrium. a., artery; L, left; R, right.

Palpation of the apical (precordial) impulse during physical examination is useful because it provides an important landmark for valve region and murmur localization during cardiac auscultation. The LV is cone-shaped and surrounded on its right, cranial, and left craniodorsal aspects by the RV. The LA straddles the midline dorsocaudal to the LV; its appendage or left auricle (LAu) projects cranio-laterally with the blind end (tip) directed toward the pulmonary artery (PA). The LAu can become especially prominent in cats with cardiomyopathy and is the major source of arterial thromboembolism in this species (see **Chapters 33** and **36**).

The aorta arises from the center of the heart base, cranial to the LA and to the right of the PA. The bulbous sinuses of Valsalva, from which the two coronary arteries originate, join the ascending aorta at the sinotubular junction. The ascending aorta projects cranially and rightward, then smoothly arches dorsally and to the left to join the descending aorta. Because the ascending aorta angles to the right of midline, cardiac murmurs that originate from the LV outflow region (as with sub-aortic stenosis) often radiate well to the cranial right thorax, as turbulent flow enters the ascending aorta. The definitive aortic arch normally is derived from the left fourth fetal arch. Persistence of the right arch, instead of the left, is the most common cause of a vascular ring anomaly that entraps the esophagus and prevents normal swallowing of solid food in neonates (p. 516). Beyond the aortic arch, the fetal ductus arteriosus extends ventrally and cranially from the descending aorta to connect with the PA, at the origin of its left principal branch. This duct normally closes shortly after birth, leaving just a remnant (*ligamentum arteriosum*). However, persistent patency of this structure is common in dogs and also occurs in cats and in horses (rarely). Because this vascular connection is

extracardiac, the murmur of patent ductus arteriosus is heard best over the PA at the left, craniodorsal heart base (p. 441).

The RA occupies the dorsal right aspect of the heart, above the RV inflow tract; however it expands cranially and caudally to join the two vena cavae. The right atrial appendage or auricle (RAu) is broader-based than the LAu; its tip points cranially and to the left. Additionally, pectinate muscles are not confined to the RAu. The inlet of the RV is to the right of the midline. Heart murmurs caused by tricuspid valve disease are heard best on the right side of the chest. However, the RV traverses the midline cranial to the LV. The RV outflow tract and PA form the left craniodorsal aspect of the heart. Accordingly, while the pulmonary valve is part of the “right heart” it is anatomically located on the left side of the thorax. Murmurs caused by pulmonary valve disease are loudest at the left cranial heart border. When viewed from a left thoracotomy or by echocardiography, the PA lies superficial to (left of) the aorta and immediately cranial to the LAu. It divides into two main branches, the left and the right PAs. The left branch typically extends dorsal to the tracheal carina, and might be evident on lateral thoracic radiographs.

Internal Features

The inner lining of the heart is known as the endocardium (**Figure 1.5**). It consists of three layers. A continuous sheet of endothelial cells covers the internal cardiac surface and is contiguous with the intimal layer of attached arteries and

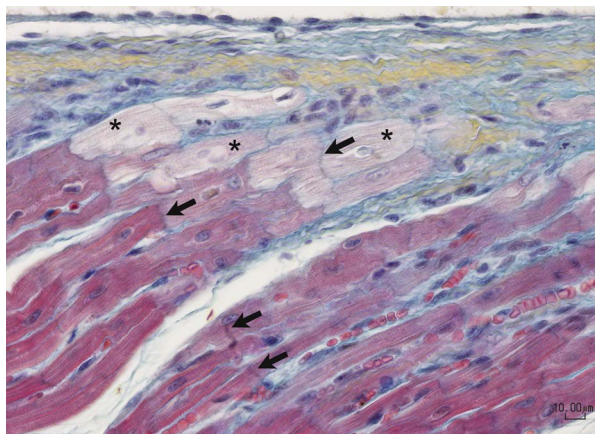


Figure 1.5 Photomicrograph showing endocardial and part of inner myocardial layers from the left ventricle of a dog. The endocardium consists of an endothelial layer (top of image), some subendothelial connective tissue, and a deeper subendothelial layer containing pale-staining Purkinje cells (black asterisks). Purkinje cells (fibers) are modified myocytes with rapid-conduction properties and fewer contractile elements than regular myocytes. Below these conduction fibers is the deeper red myocardium itself (bottom half of image). Purple-staining intercalated disks (black arrows) join the ends of adjacent regular myocytes and Purkinje cells; the centrally located nuclei of these cells also are visible. There is a dense capillary network within the myocardium. Rows of red blood cells within capillaries lie between the myocytes in the lower right portion of this image. Crossman's trichrome stain; 40× magnification. (Image courtesy of Dr. E Uemura.)

veins. Just below the endothelium lies a thin subendothelial layer of collagen and elastic fibers, with a few smooth muscle cells. The deeper portion of the endocardium (subendocardial layer) consists of connective tissue that often contains specialized cardiomyocytes capable of rapid cardiac conduction (Purkinje cells). The myocardium, with its working contractile cells, lies between the endocardium and pericardium; it forms the bulk of the cardiac wall. In general, the wall thickness of each cardiac chamber reflects the degree of systolic pressure generated within.

The four cardiac valves are thin, flexible fibrous flaps covered with endothelium. Each valve is anchored to a valve annulus, characterized by varying degrees of fibrous ring or tissue organization. These valvular rings, along with connective tissue at the center of the heart (membranous septum and fibrous trigone), form the “fibrous skeleton” of the heart.

Left Heart The LA includes a smooth-chambered venous cavern (body) that collects venous return and a muscular appendage (LAu), which is of different embryologic origin. Interlacing pectinate muscles produce a raised and irregular internal surface within the auricle. Venous return from the multiple pulmonary veins enters the dorsal LA. Three venous inflows (or ostia) usually are evident in dogs on color Doppler echocardiography and computed tomography (CT). These represent a confluence of pulmonary veins from the right cranial and middle lobes (seen closest to the atrial septum), the left and right caudal and accessory lung lobes, and the two segments of the left cranial lobe (entering craniolateral to the caudal confluence). The left AV (mitral) valve separates the LA from the LV. The atrial septum separates the LA from the RA and includes the flap of the fetal *foramen ovale*, which is a common location for atrial septal defects.

There is a short segment of cardiac septum, between the atrial and ventricular septa, that interconnects all four cardiac chambers; this is termed the AV septum. The septal mitral leaflet inserts more dorsally than the septal tricuspid leaflet into the AV septum and because of this ventrodorsal offset, the left side of the AV septum functions as ventricular septum while the right side is indistinguishable from the atrial septum. Defects in the AV septum are associated with both (primum) atrial and (inlet) ventricular septal defects, as well as malformations of the AV valves (p. 466).

The conical LV connects to the LA at the mitral valve and to the aorta at the aortic valve (**Figures 1.6** and **1.7**). The LV endocardial surface is fairly smooth, with only shallow indentations (*trabeculae carneae*). Thin false tendons (variously called “LV moderator bands” or “LV trabecula”) span the distance between the subaortic ventricular septum and papillary muscles, and represent ramifications of the specialized conduction tissues of the left bundle branch. The ventricular mass is formed mostly by a continuum of myocardial fibers arrayed in layers of varying orientation from endocardium to epicardium and base to apex. Between the cardiomyocytes (histologically) are supporting elements that include normal

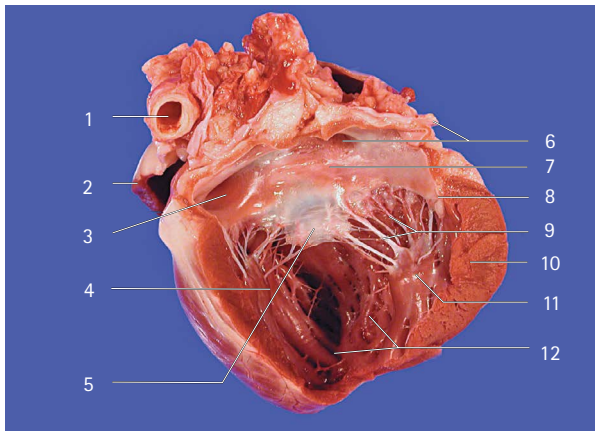


Figure 1.6 Canine heart: Left ventricular inflow tract. 1. Descending aorta, 2. R ventricular wall (cut), 3. L auricle, 4. Ventral (subauricular; anterior) papillary m., 5. Septal (anterior) mitral cusp, 6. Pulmonary v., 7. Interventricular septum, 8. Parietal (posterior) mitral cusp (cut), 9. Chordae tendineae, 10. L ventricular free wall, 11. Dorsal (subatrial; posterior) papillary m., 12. Trabeculae carneae. L, left; m., muscle; R, right; v, vein.

collagen as well as intramural coronary vessels and capillaries (Figure 1.5). Disease of the heart muscle is referred to generally as “cardiomyopathy”; several forms are clinically important in companion animals (see Chapters 32–34).

The LV has an inflow region (inlet) and outflow tract (outlet). The ventricle fills during diastole and ejects blood during systole. Myocardial contraction causes longitudinal, radial, and circumferential shortening; this increases intraventricular pressure and functionally narrows the LV, which pushes blood toward the outflow tract and aorta. Rotational movements in opposite directions at the apex and base also cause the LV to twist and untwist during systole and diastole, respectively. These movements are captured by 2D echocardiography and more advanced analysis methods that track

myocardial deformation (strain). Both ventricles share and are separated by the interventricular septum (IVS), which extends from the aortic root to the ventricular apex. The subaortic region of the IVS is thinner and contains more fibrous elements than the rest of the (muscular) IVS. The IVS forms an arc along the right-cranial aspect of the circular LV when viewed in cross-section by echocardiography, CT, or magnetic resonance imaging (MRI). The thicknesses of the LV wall and IVS depend on the size of the animal, the systolic pressure load, and LV diastolic volume. LV wall and IVS thicknesses are similar; however, the septum does include both LV and RV components and often is slightly thicker in diastole than the LV free wall when measured by 2D echocardiography. This is especially obvious dorsally in some feline breeds such as Maine Coon cats and Bengals, as well as in normal horses.

The mitral valve, similar to the right AV (tricuspid) valve, is part of an “apparatus” comprised of several different support structures including the chordae tendineae, papillary muscles, valve annulus, and atrial wall (Figure 1.6). Disease of any component or geometric changes in the atria or ventricles can lead to valvular dysfunction (usually insufficient closure). Degenerative mitral valve disease is the most important cause of heart disease in the dog (Chapter 29). Abnormal mitral valve function also occurs commonly with cardiomyopathies, congenital malformations, and infection (endocarditis).

The two mitral leaflets are identified by an inconsistent nomenclature. The cranioventral leaflet also is called the anterior, cranial, or septal leaflet. The leaflet closer to the LV free wall, and positioned more caudodorsally, is called the posterior, caudal, parietal, or mural leaflet. Regardless of veterinary nomenclature, clinicians (especially echocardiographers) most often use the human terminology of “anterior” and “posterior” for these mitral components. The anterior mitral leaflet is cranial, contiguous with the caudal aspect of the aortic root, and extends more fully into the lumen of the LV chamber when compared to the posterior leaflet. This mitral-aortic fibrous continuity is an important anatomic feature of cardiac anatomy and is especially useful during echocardiography. The anterior leaflet functionally separates the LV inflow and outflow tracts (Figure 1.7), with the former confined by the mitral valve orifice and the latter formed by the anterior leaflet, ventricular septum, aortic valve orifice, and proximal aorta. The posterior mitral leaflet has a wider mural circumference and includes some incomplete scallops, which are especially prominent in horses. The mitral valve is open in diastole and closed during systole to facilitate the one-way movement of blood.

The mitral valve is supported by stout chordae tendineae of varying thicknesses that attach each leaflet to the two large papillary muscles (also identified by human echocardiographic nomenclature). The anterior and posterior papillary muscles arise near the left cranial (septal) and right caudal (mural) aspects of the LV, respectively. Variation in the arrangement of papillary muscles is not uncommon (as is the case in humans) and a smaller “third” papillary muscle often is observed by echocardiography cranial to

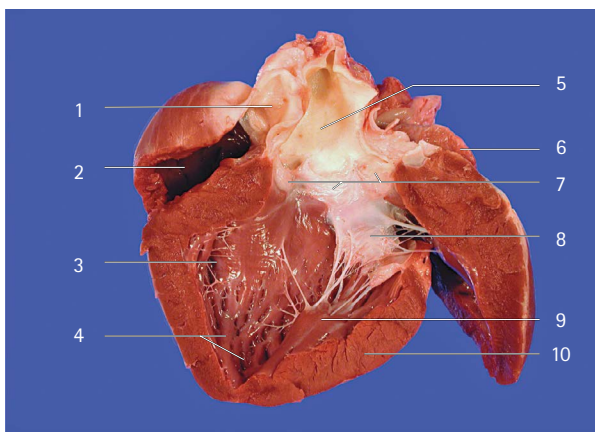


Figure 1.7 Canine heart: Left ventricular outflow tract. 1. Pulmonary trunk, 2. R ventricular outflow region (conus), 3. Interventricular septum, 4. Trabeculae carneae, 5. Ascending aorta, 6. L auricle, 7. Aortic valve cusps, 8. Septal (anterior) mitral cusp, 9. Dorsal (subatrial; posterior) papillary m., 10. L ventricle. L, left; m., muscle; R, right.

the anterior papillary muscle. This structure—perhaps similar to the anterolateral muscle bundle of Moutaert in human hearts—often is misdiagnosed as an anomaly, and it becomes more prominent when there is LV hypertrophy.

Chordae tendineae from both papillary muscles attach to each mitral leaflet. The chordae typically divide into several branches before inserting either at the free edge or onto the ventricular surface of the leaflet. Chordae that support the leaflet's free edge are known as commissural chordae tendineae. Chordae that insert into the leaflet's ventricular surface (sometimes called “mitral valve leaflet chordae”) provide major support for the leaflet during systole; they usually are thicker than the commissural chordae. Other classification schemes also have been used for chordae tendineae, including designation of primary chords (attaching to the leaflet edge) and secondary chords (attaching to the ventricular surface of the valve). If one of these collagenous strands ruptures, the severity of valvular regurgitation (insufficiency) that results relates in part to the chord's insertion site and structure. Chapter 29 provides additional details about the normal mitral valve.

The aortic valve has three semilunar leaflets (cusps) and is located centrally within the fibrous cardiac skeleton (Figure 1.8). The right and noncoronary cusps of the aortic valve are located dorsally, above the subaortic IVS. The valve normally opens fully during systole. During diastole, the higher aortic pressure holds the leaflets closed to prevent backflow into the LV. Obstruction to LV outflow, most often at the subvalvular level (subaortic stenosis), is a relatively common congenital malformation in dogs. Aortic valve regurgitation (insufficiency) occurs sporadically in dogs, especially with infective endocarditis of this valve. Aortic valve degeneration and insufficiency is quite common in older horses.

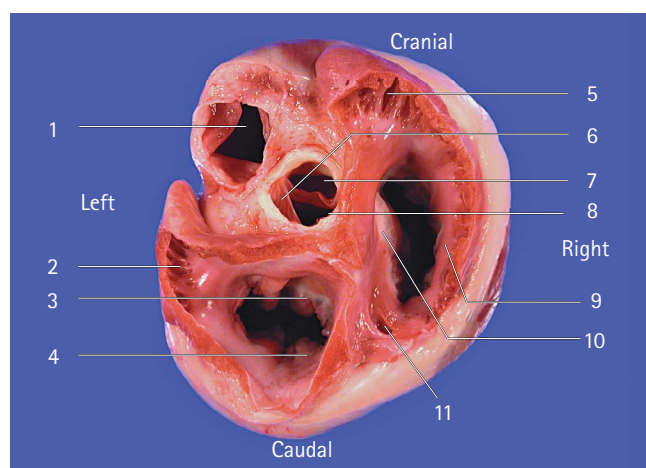


Figure 1.8 Canine heart: Dorsal view showing orientation of cardiac valves. 1. Pulmonary valve, 2. Pectinate mm. in L auricle, 3. Mitral valve: Septal (anterior) leaflet, 4. Mitral valve: Parietal (posterior) leaflet, 5. Pectinate mm. in R auricle, 6. Aortic valve: L cusp, 7. Aortic valve: R cusp, 8. Aortic valve: Noncoronary (septal) cusp, 9. Tricuspid valve: Parietal leaflet, 10. Tricuspid valve: Septal leaflet, 11. Coronary sinus. L, left; mm., muscles; R, right.

Right Heart The RA is relatively large, with a venous cavern that ends blindly in a somewhat more muscular RAu. The auricle has a broad base and the pectinate muscles project from this appendage into the RA proper. The sinoatrial (SA) node is located subepicardially in the cranial RA, near the junction of the cranial vena cava and RAu and opposite the crista terminalis. The SA node artery, which arises from the right coronary artery, supplies blood to the SA node. The AV node is located subendocardially in the ventral right aspect of the interatrial septum, near the septal tricuspid leaflet. Both of these nodes, although microscopic, are critically important to normal impulse formation and cardiac conduction. They are highly influenced by the autonomic nervous system; each node receives extensive sympathetic and parasympathetic innervation. The RA contains three to four venous openings: the cranial and caudal vena cavae; the coronary sinus; and the azygous vein, although this is variable in some animals. The right side of the atrial septum includes the *fossa ovale*, the remnant of the fetal *foramen ovale*; this is the most common location for an atrial septal defect.

The RV lies ventral to the RA. The normal RV free-wall thickness is about 30–40% of the LV free-wall thickness. This reflects the much lower systolic pressure generated here. The inner RV surface has prominent muscular ridges (*trabeculae carneae*; Figure 1.9). A muscular band (*septomarginal trabecula*, moderator band), which carries conduction system fibers, extends from the IVS to the RV free wall. It is especially prominent in horses. A cardiomyopathy primarily affecting the RV occurs in some dogs and cats.

The tricuspid (right AV) valve separates the RA and RV. It has two distinct leaflets in dogs and cats. The lateral (parietal) leaflet is larger with incomplete commissures. The smaller

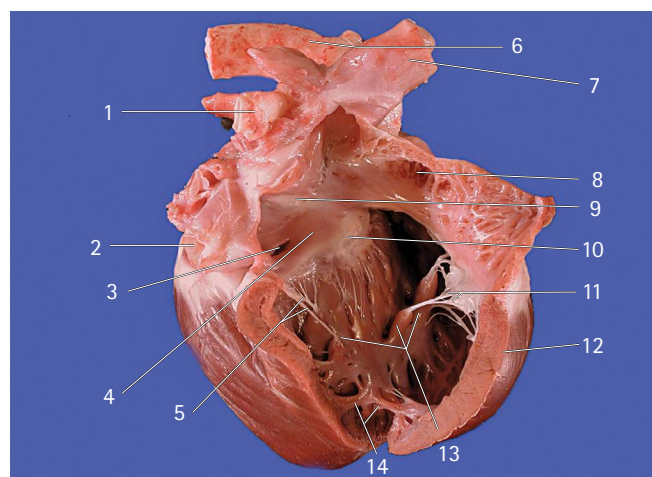


Figure 1.9 Canine heart: Right ventricular inflow tract. 1. R pulmonary a., 2. Caudal vena cava, 3. Coronary sinus, 4. Region of AV node, 5. Chordae tendineae, 6. Aorta, 7. Cranial vena cava, 8. R auricle, 9. Interatrial septum, 10. Septal tricuspid leaflet, 11. Parietal tricuspid leaflet (cut), 12. R ventricular free wall, 13. Papillary mm., 14. Trabeculae carneae. a., artery; AV, atrioventricular; mm., muscles; R, right.

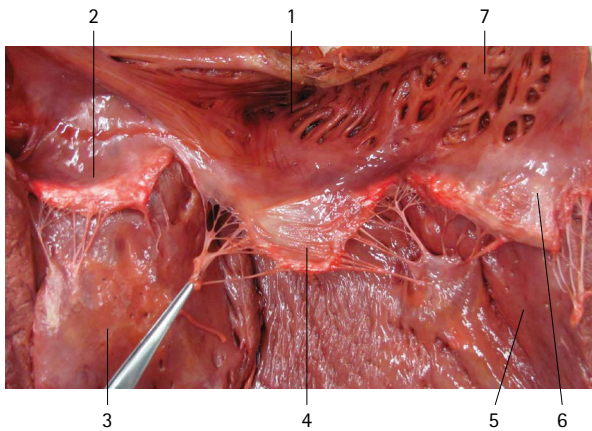


Figure 1.10 Equine heart: Right ventricular inflow tract. 1. R atrium, 2. Septal tricuspid leaflet, 3. Interventricular septum, 4. L tricuspid leaflet, 5. R ventricular free wall with papillary m., 6. R tricuspid leaflet, 7. R auricle. L, left; m., muscle; R, right.

septal (medial) leaflet inserts into the AV septum, slightly ventral to the level of the septal mitral leaflet. In horses, the tricuspid valve includes three complete leaflets (**Figure 1.10**), similar to people. The leaflets are named septal, right (along the lateral wall), and left (closest to the RV outflow tract). Generally, there are three main papillary muscles; however, their number and configuration vary and up to five (with some indistinct) papillary muscles can be present, especially in the RV conus, as evidenced by chordal attachments to the valve.

Functionally, the RV includes an inflow region, trabecular apex, and outflow tract. The muscular supraventricular crest separates the RV inflow and outflow tracts dorsally. Therefore, unlike the mitral and aortic valves, the tricuspid and pulmonic valves are not adjacent or in fibrous continuity with each other. A muscular conus (RV outflow tract) leads to the semilunar pulmonary valve, which is structurally

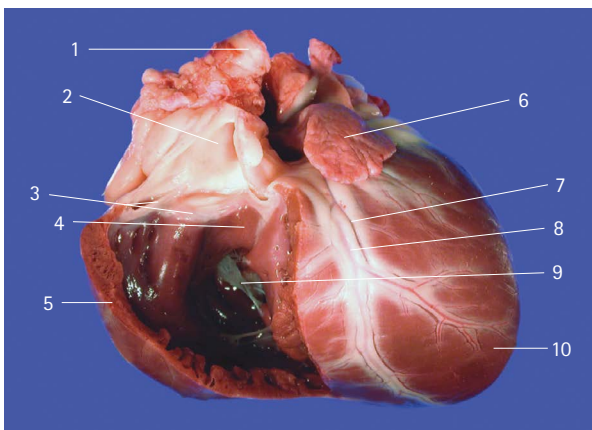


Figure 1.11 Canine heart: Right ventricular outflow tract. 1. Aorta, 2. Main pulmonary a. (pulmonary trunk), 3. Pulmonary valve, 4. Supraventricular crest, 5. R ventricle, 6. L auricle, 7. Great coronary v., 8. Cranial interventricular branch of L coronary a. (in cranial, paraconal, interventricular groove), 9. Tricuspid valve, 10. L ventricle. a., artery; L, left; R, right, v. vein.

similar but thinner than the aortic valve (**Figure 1.11**). There are no coronary ostia behind pulmonary valve cusps. Congenital malformations as well as acquired abnormalities can affect the right heart's valves.

Conduction System

Electrical activation stimulates cardiac contraction. Specialized myocardial cells ("pacemakers") spontaneously generate action potentials because they possess the property of "automaticity." These action potentials then propagate throughout the heart along an organized electrical conduction system. Electrical impulses normally originate from cells within the SA node, usually from its mid- to cranial region. Impulses then spread into the RA, LA, and via the AV conduction system, into the ventricles (**Figure 1.12**). Specialized fibers (in three internodal pathways) facilitate conduction across the RA, into the LA (via Bachmann's bundle), and to the AV node. After passing through the AV node, the electrical current quickly spreads along the His–Purkinje system into the ventricular myocardium.

The SA node is the normal pacemaker of the heart because the cells here have the fastest intrinsic rate of automaticity (spontaneous diastolic depolarization). This tissue depolarizes spontaneously because of the activity of pacemaker currents that reduce (make less negative) the transmembrane potential until a firing threshold is reached (see section "Slow-Response Action Potential"). This spontaneous depolarization occurs independent of neural control. However, autonomic effects on pacemaker currents can be profound and provide clinically important heart rate (HR) and rhythm regulation. Although primary disease of the SA node occurs sometimes, most sinus rhythm variations result from the effects of the autonomic nervous system, body temperature, endocrine status, or drugs.

The AV node is the electrical "gatekeeper" to the ventricles. Normally, no other pathway allows electrical impulses to pass from the atria to the ventricles. AV nodal cells are small and branching, and like SA nodal cells, depolarize via slow-response action potentials. These factors cause slowed (decremental) conduction across the AV node. This allows time for atrial contraction and final ventricular filling to occur before ventricular activation begins. The AV node has three regions: the dorsal-most atrionodal region, the central nodal region, and the nodal-His region. Spontaneous pacemaker activity normally occurs in the nodal region, although at a slower rate than in the SA node. Therefore, it does not become manifest unless the SA nodal rate becomes abnormally slow. As with the SA node, the conduction of impulses across the AV node is markedly affected by autonomic activity.

Electrical impulses enter a bundle of rapidly conducting (Purkinje) fibers after passing through the AV node. This "bundle of His" (AV bundle) quickly transmits impulses into the left and right bundle branches. The right bundle branch courses subendocardially down the right side of the IVS, crosses the RV within the septomarginal trabecula, and branches distally to activate the RV free wall. RV dilation that

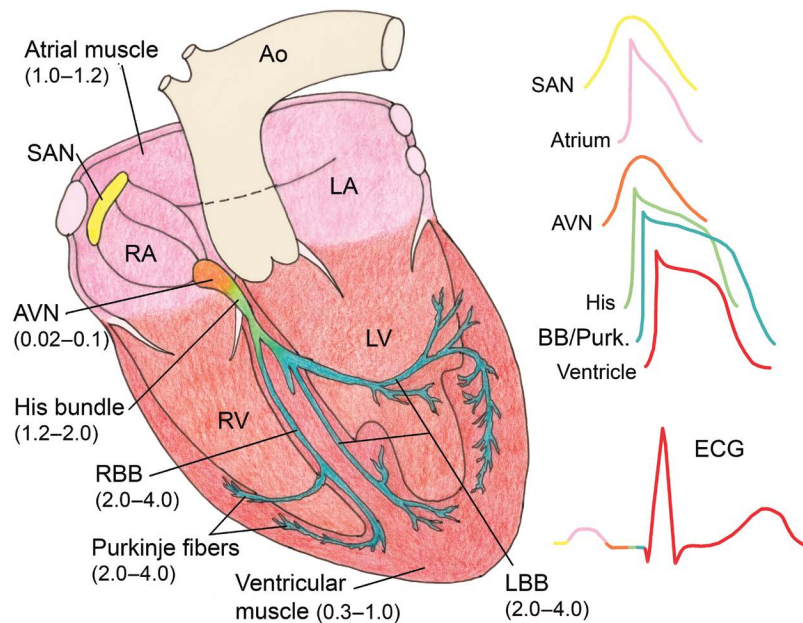


Figure 1.12 Cardiac conduction system. Major components of the conduction system are illustrated on the left, with approximate conduction speed (m/s) in parentheses. On the right, representative action potentials are color-coded to the cardiac conduction system and myocardium. A composite ECG (below) illustrates the electrical activation sequence. Ao, aorta; BB/Purk., bundle branches and Purkinje fibers; AVN, atrioventricular node; ECG, electrocardiogram; LA, left atrium; LBB, left bundle branch (posterior fascicle to the right); LV, left ventricle; RA, right atrium; RBB, right bundle branch; RV, right ventricle; SAN, sinoatrial node.

unduly stretches this muscular strand can damage the conduction fibers within and interrupt conduction to the RV free wall (known as “right bundle branch block”). On the left side of the IVS, the thick left bundle branch divides into a small septal fascicle, a posterior (caudal) fascicle serving the caudoventral aspect of the LV wall, and an anterior fascicle serving the cranio-lateral LV wall. A branching system of terminal Purkinje fibers transmits electrical impulses from the bundle branches into the ventricular myocardium. In dogs and cats, as in people, these terminal Purkinje fibers penetrate only partially into the myocardium (so-called “Type A” heart). Penetration of the terminal Purkinje fibers is deeper and more extensive throughout the ventricular myocardium in horses, as well as other large mammalian species and birds (“Type B” heart). This allows for more extensive and rapid electrical activation of the ventricles. Failure of electrical impulse transmission from atria to ventricles is referred to as AV block. This can occur at the level of the AV node, His bundle, or bilaterally in the bundle branches.

Cardiac Electrophysiology

Cardiac cells are polarized (more negative on the inside) and undergo depolarization (becoming less negative on the inside) in an organized manner. After depolarization, the cells undergo a process of repolarization. Cardiac action potentials occur in association with changes in cell membrane permeability to sodium (Na^+), potassium (K^+), and calcium (Ca^{++})

ions. Transmembrane movement of these ions depends on the opening and closing of numerous ion-specific channels, with different controls affecting opening and closing kinetics. The specific channels present in a cell membrane depend on the type and location of the cardiac cell. Furthermore, the conductance of different ions can be affected by changes in serum electrolyte concentrations, acid-base balance, autonomic influence, and tissue oxygenation, as well as by the effects of various drugs and cardiac disease states.

The duration of cardiac action potentials is much longer than that of noncardiac tissues. This allows time for myocardial relaxation and refilling between contractions. Cardiac action potentials also differ among types of heart cells, depending on cellular location and function. There are two main types of cardiac action potentials. The “fast-response” action potential is typical of atrial and ventricular muscle cells and Purkinje fibers. Depolarization of these cells must be initiated by current flow from an adjacent cell. Other cardiac cells exhibit the property of automaticity and can depolarize on their own via the “slow-response” (pacemaker) action potential. As mentioned above, this pacemaker action potential is characteristic of SA and AV nodal cells. However, diseased or ischemic myocardial cells sometimes also develop the functional characteristics of a slow-response cell.

In general, ion channels are affected by transmembrane voltage, time constants, ion concentrations, ligands (such as norepinephrine [NE] or other beta-agonists and acetylcholine [ACh]), pH, adenosine, and drugs. Cardiac arrhythmias can result from changes in these various factors. The efficacy of

different antiarrhythmic drugs relates to their effect on different ion channels, as well as the arrhythmia's underlying mechanism (see [Chapters 23](#) and [24](#)). For example, a calcium channel blocker such as diltiazem will affect phase 0 depolarization in nodal (slow-response) cells, but is less likely to affect ventricular myocytes or Purkinje cells. Conversely, a sodium channel blocker like lidocaine will have minimal effect on nodal cells, which depend on Ca^{++} entry for their activation.

Resting Membrane Potential The cardiac cell membrane (sarcolemma) maintains a gradient of ions between the intra- and extracellular environment. In normal myocardial cells at rest, the electrical potential difference across the sarcolemma is about -90 mV; inside the cell is negative compared with the outside. This resting membrane potential (RMP) is largely determined by the equilibrium between chemical and electrostatic forces for K^+ (as described by the Nernst equation¹ and the concept of the Gibbs–Donnan equilibrium). The concentration of K^+ inside the cell is much greater than that outside; conversely, extracellular Na^+ and Ca^{++} concentrations far exceed intracellular concentrations. The resting sarcolemma is relatively permeable to K^+ , but largely blocks migration of Na^+ and Ca^{++} as well as negatively charged intracellular proteins. K^+ tends to diffuse outward along its concentration gradient through K^+ -specific channels despite an opposing electrostatic force attracting the positive ions into the cell. A tiny inward leak of Na^+ also occurs. Normal RMP and ionic concentrations are maintained by the membrane's electrogenic Na^+ , K^+ -ATPase pump, which moves three Na^+ ions out for every two K^+ ions in. Digoxin is a drug that blocks (“poisons”) this pump, which partially relates to the drug’s mechanism of action.

Fast-Response Action Potential When a stimulus reduces the membrane potential to a less negative “threshold” level, activation of Na^+ -specific membrane channels allows a rapid Na^+ influx that initiates an action potential (phase 0; [Figure 1.13](#)). A small amount of ionic current moving from adjacent cells across gap junctions often provides this stimulus. Activation (as well as subsequent inactivation) of these channels depends on the level of membrane potential (voltage-dependence), and this inward Na^+ current (I_{Na}) occurs only briefly (time-dependence). Inactivation (closure) of the Na^+ channels produces an effective refractory period. A return toward RMP, as well as time, is necessary for Na^+ channels to recover from inactivation and become responsive to another stimulus. The steepness of the phase 0 upstroke, as well as its amplitude, influences the velocity of impulse conduction along the myocardial membranes. This largely explains the fast conduction velocity in fast-response cells; conversely, nodal (slow-response) cells have a gradual phase 0 slope and relatively slow conduction velocity. If fast-response cells are stimulated when membrane potential is less negative than

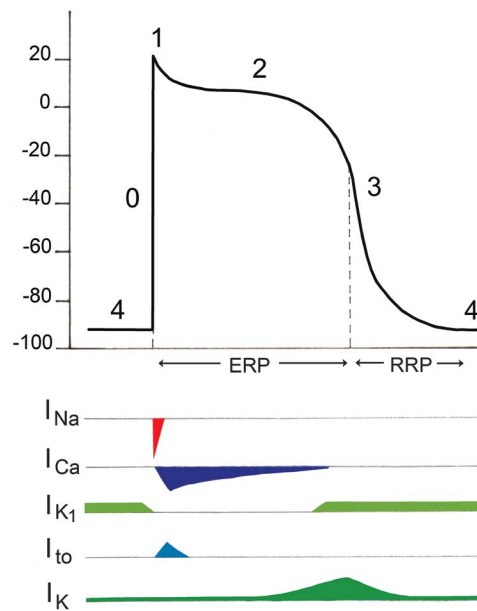


Figure 1.13 Fast-response action potential. Phases of the action potential are indicated, with the timing and direction of some important ion currents shown below; inward currents depicted below the baseline, outward currents, above. I_{Ca} represents the L-type Ca^{++} current, I_{K1} is the inward rectifier (important for maintaining resting membrane potential), and I_{K} includes the rapid and slow components of the delayed rectifier current (important for repolarization). See section “Fast-Response Action Potential” for further explanation. ERP, effective refractory period; RRP, relative refractory period.

normal RMP, Na^+ channels are partially inactivated and conduction velocity of the resulting action potential (if it even occurs) is slowed. Regions of slowed conduction and unidirectional conduction block predispose to reentrant arrhythmias (p. 365). A number of antiarrhythmic drugs, such as lidocaine and quinidine, block I_{Na} .

The rapid upstroke of the fast-response action potential is followed by a brief partial repolarization (phase 1) caused by a transient outward K^+ current (I_{to}) in some cardiac cells. Voltage-activated membrane Ca^{++} channels (L-type) slowly open during the latter part of phase 0, allowing an inward Ca^{++} current (I_{Ca}), which is responsible for phase 2 (the plateau). The duration of phase 2 is longer in ventricular myocardial cells than those in the atria. The Ca^{++} that enters the myocardial cells during phase 2 induces electrical–mechanical coupling (see section “Electrical–Mechanical Coupling”). As the Ca^{++} channels slowly inactivate, the inward Ca^{++} flux decreases and outward movement of K^+ increases, leading into repolarization (phase 3). Several types of K^+ channels are important in this process, especially the slow (I_{Ks}) and rapid (I_{Kr}) components of the I_{K} (delayed rectifier) current. The inwardly rectifying K^+ current (I_{K1}) also contributes at the end of the repolarization period and helps maintain RMP (phase 4) as well. Reduced outward K^+ flux during phases 2 and 3, or enhanced inward Ca^{++} flux, can delay repolarization and predispose to serious and potentially fatal arrhythmias.

Some antiarrhythmic drugs block (certain) potassium channels; they can exert both antiarrhythmic and proarrhythmic effects, depending on the situation.

The effective refractory period (from phase 0 until membrane potential reaches about -50 mV during phase 3) is a time when the cell cannot be re-excited. Immediately following is the relative refractory period, when a stronger than normal stimulus might elicit another action potential, although conduction velocity is likely to be slowed because of partial Na^+ channel inactivation. Normal excitability is achieved only after full repolarization.

Slow-Response Action Potential Two important properties of the heart are automaticity (the ability to initiate a heartbeat) and rhythmicity (the regularity of this activity). Cells with slow-response action potentials allow the heart to beat spontaneously because, instead of a consistent RMP, they undergo spontaneous diastolic (phase 4) depolarization (**Figure 1.14**). Spontaneous depolarization is characteristic of SA and AV nodal cells. These cells also have a less negative maximum diastolic membrane potential than cells characterized by the fast-response action potential.

The process of spontaneous (phase 4) diastolic depolarization results from the combined effects of: activation of the so-called “funny” current (I_f , carried by inward Na^+ and K^+ movement, especially at more negative levels of membrane potential and under beta-receptor, sympathetic stimulation); cessation of outward K^+ leak; transmembrane $\text{Na}^+-\text{Ca}^{++}$ exchange, and activation of a transient (T-type) Ca^{++} influx. The process of spontaneous depolarization involves the concept of a SA nodal “membrane (or voltage) clock” and a “ Ca^{++}

clock” that work together to control SA node activation. The slow-response action potential upstroke (phase 0) and also the peak of phase 2 depend on slow (L-type) Ca^{++} channel activation; there is no recognizable phase 1 or plateau. Phase 3 (repolarization) depends on outward K^+ currents (I_K). Conduction velocity also is much slower along cells characterized by slow-response action potentials and the refractory period is longer. Consequently, conduction is more easily blocked in these cells.

The SA nodal cells normally have the most rapid intrinsic rate of spontaneous diastolic depolarization. Therefore, they usually reach threshold first and control the heartbeat. If the sinus rate slows or stops, other slow-response fibers lower in the conduction system (so-called “subsidiary pacemakers”) can initiate a heartbeat. This is termed “escape” pacemaker activity (also see p. 141) and is a normal cardiac rescue mechanism. Subsidiary pacemakers are located mostly in the His–Purkinje system. Ultimately, the rate at which SA (or other automatic) cells activate the heart depends on the slope of their spontaneous phase 4 depolarization, as well as maximal diastolic potential and threshold potential.

Myocardial Contraction

Cardiac myocytes act as a “functional syncytium,” or as if they were a single cellular unit, unlike skeletal muscle. Gap junctions (nexi) within the intercalated disks that separate adjacent myocytes promote cell-to-cell conduction and communication (**Figure 1.15**). Gap junctions, as points of contact

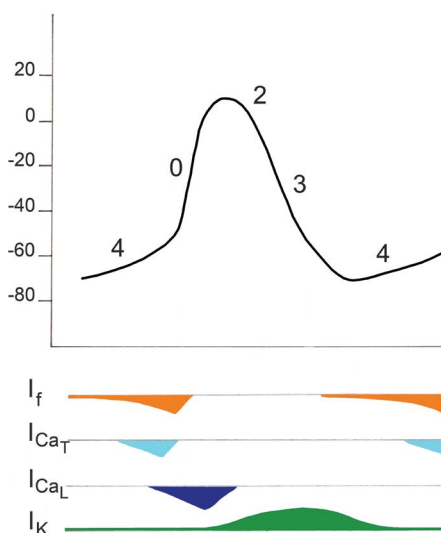


Figure 1.14 Slow-response action potential. Phases of the action potential are indicated, with the timing and direction of some important ion currents shown below; inward currents depicted below the baseline, outward currents, above. See section “Slow-Response Action Potential” for further explanation.



Figure 1.15 Ultrastructure of myocardial intercalated disks. This image is centered on a Z disk (Z line) between two sarcomeres. Gap junctions (light blue arrowheads) allow transfer of chemical signals between adjacent cells. Desmosomes (bright pink asterisks) have filaments that extend into the cytoplasm and are important in attaching adjacent cells together. The fascia adherens (yellow brackets) are located between desmosomes and anchor the actin filaments. (From Frappier BL, Eurell JA (editors). *Dellman's Textbook of Veterinary Histology*. 6th edition. 2006. p. 90.)

between the intracellular fluid of adjacent cells, facilitate local ionic current flow and action potential propagation. This allows coordinated contraction and relaxation, as if the cardiac muscle cells were a single entity.

At the subcellular level, sarcomeres (demarcated by Z lines or disks) are the basic contractile units within myocytes (**Figure 1.16**). Thin actin filaments attach to the Z lines and interdigitate with thick myosin filaments. Contraction (sarcomere shortening) occurs as these filaments slide along each other by the cycling of cross-bridges (formed by heavy meromyosin heads interacting with sites on the actin filaments). This cycling requires the presence of adenosine triphosphate (ATP) and Ca^{++} . The actin filaments are composed of two helical chains attached to a twisting tropomyosin support molecule. The troponin complexes consist of proteins (troponins I, C, and T), which regulate contraction. They are attached to the tropomyosin backbone of the actin filaments. Troponin I, in conjunction with tropomyosin, inhibits cross-bridge formation during diastole when intracellular free Ca^{++} is low. When Ca^{++} becomes available in systole (see next paragraph), it activates troponin C, which then binds to troponin I. This induces a conformational change

that exposes myosin binding sites on the actin strand and subsequently allows interaction between adjacent actin and myosin filaments. Myocardial injury causes leakage of troponin proteins; clinical assays for circulating troponin I and T can provide a sensitive and specific test for cardiac muscle damage.

Electrical–Mechanical Coupling The Ca^{++} influx that occurs during phase 2 of cardiac cell activation triggers the intracellular release of more Ca^{++} from the sarcoplasmic reticulum (SR) via the calcium release (ryanodine; RyR2) receptor (**Figure 1.17**). This process is known as electrical–mechanical or excitation–contraction coupling. It is this increase in free intracellular Ca^{++} from the SR that allows contraction to proceed. The SR is an intracellular network of tubules surrounding the myofibrils that sequesters and releases Ca^{++} (**Figure 1.16**). Invaginations of the cell membrane (T tubule system) facilitate action potential propagation along the cells. Coupling of electrical excitation to mechanical contraction is enhanced by the close proximity of T tubules to parts of the SR. Sympathetic (beta-receptor) activation increases

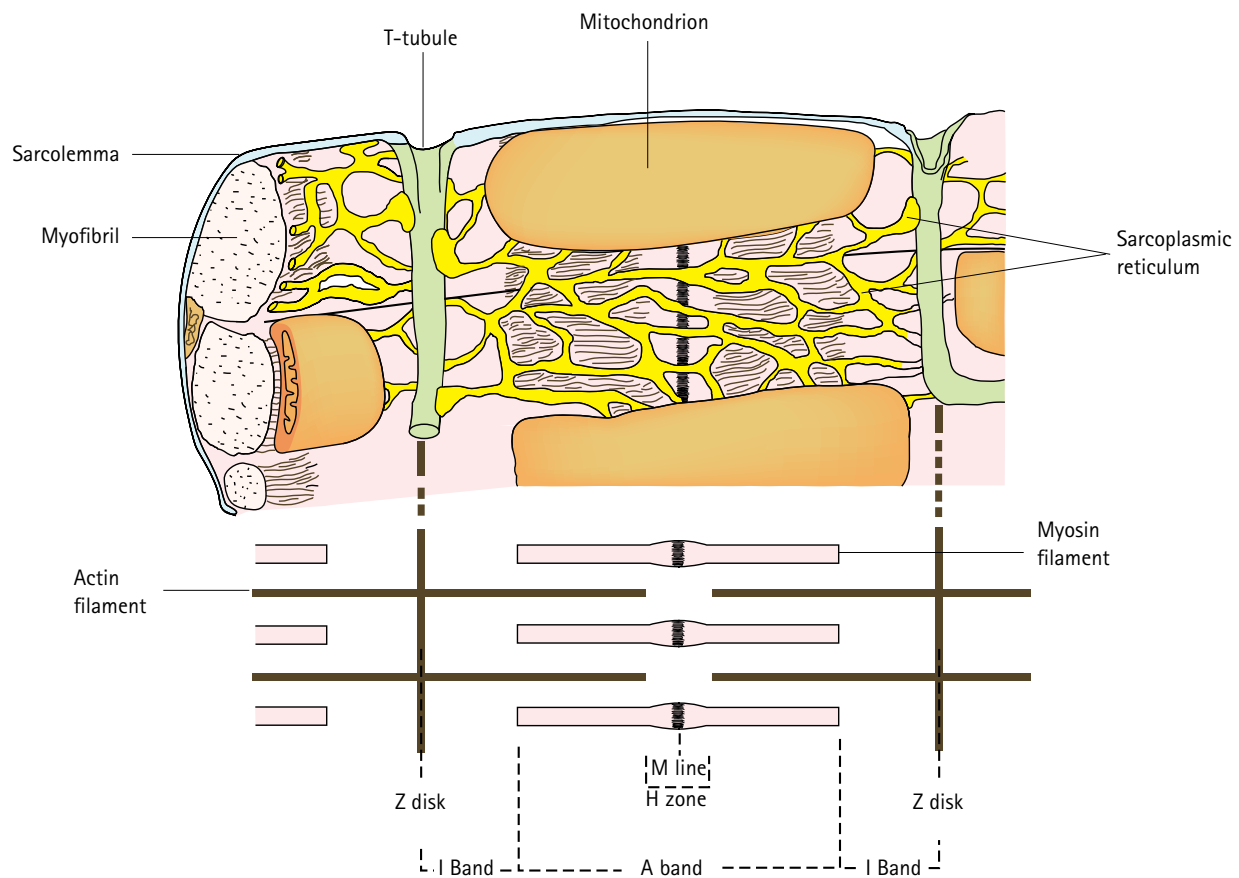


Figure 1.16 Diagram of myocardial cell components involved with excitation and contraction (above) and schematic illustration of the contractile elements (below). Location of isotropic (I) bands and anisotropic (A) band between the Z disks is indicated. See section “Myocardial Contraction” for more information.

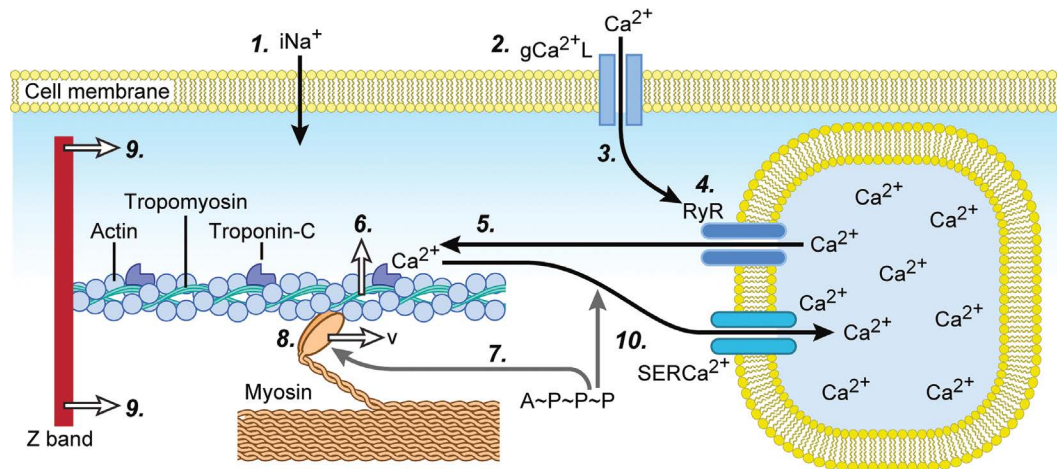


Figure 1.17 Schematic illustration of the excitation–contraction coupling process. 1. Inward Na^+ current (phase 0) of the fast-response action potential (AP) depolarizes the myocardial cell membrane. 2. Voltage-gated Ca^{2+} channels in the membrane open as the membrane depolarizes. 3. A small amount of extracellular Ca^{2+} enters through these open channels (during phase 2 of AP). 4. This Ca^{2+} activates ryanodine receptors (RyR) and triggers the release of Ca^{2+} stored within the (intracellular) sarcoplasmic reticulum (SR). 5. A large amount of Ca^{2+} leaves the SR, becoming available to interact with troponin-C. 6. The Ca^{2+} –troponin-C complex removes the inhibition of troponin-I (not shown), which then allows the heavy meromyosin heads to bind with actin. 7. The hydrolysis of adenosine triphosphate (ATP) releases energy, which fuels the movement of the myosin heads. 8. The myosin heads, bound to actin, now cycle (ratchet) and pull the actin filaments inward. 9. The Z bands move toward each other as the sarcomeres (Z-to-Z distance) shorten during contraction. 10. Energy from ATP hydrolysis also fuels the sarcoendoplasmic reticulum Ca^{2+} ATPase (SERCA) Ca^{2+} reuptake pump of the SR membrane; this resequesters free intracytoplasmic Ca^{2+} into the SR. The rapid drop in free Ca^{2+} causes actin–myosin disengagement and myocardial relaxation. (Diagram courtesy of Dr. RL Hamlin.)⁸

SR Ca^{2+} release, as well as indirectly promotes Ca^{2+} reuptake to facilitate relaxation.

Myocardial Relaxation During cell repolarization, Ca^{2+} influx falls off as the membrane again becomes impermeable to Ca^{2+} . The SR is not stimulated to release further Ca^{2+} into the cytosol and now actively takes Ca^{2+} back up via a pump called sarcoendoplasmic reticulum Ca^{2+} ATPase (SERCA). This pump is regulated by the protein phospholamban. The rapid resequencing of cytosolic Ca^{2+} makes this ion unavailable to the contractile apparatus and leads to inhibition of cross-bridge formation. Although the SR is the major site of Ca^{2+} reuptake, some Ca^{2+} is transported out of the cell via membrane Na/Ca exchange and Ca^{2+} pump mechanisms. Mitochondrial uptake of free Ca^{2+} becomes important when intracellular Ca^{2+} levels are pathologically high. Slowed or incomplete reuptake of Ca^{2+} in diastole increases cardiac stiffness and adversely affects filling. Impaired myocardial relaxation can develop acutely with myocardial ischemia; chronically it can contribute to heart failure, especially in cats with hypertrophic cardiomyopathy. Catecholamines accelerate relaxation in normal myocardium by phosphorylating phospholamban and removing its inhibition of SERCA.

The Heart as a Pump

The ventricles fill during diastole and eject during systole. This occurs over 100,000 times each day in a normal canine heart. Cardiac pump function can be described in a number of

ways. The stroke volume (SV) is the volume of blood pumped from either ventricle with each heart contraction. The HR is the frequency of cardiac contractions per minute. The CO is the volume of blood pumped from either ventricle over one minute. Systemic arterial blood pressure is another variable of CV function that depends on the interaction between CO and vascular resistance.

The heart's ability to function as a pump is based on interrelationships among the sequence of electrical activation, ventricular diastolic function, and ventricular systolic function. Abnormalities in any of these determinants can reduce CO. Diastolic function is complicated and ventricular filling is influenced by multiple factors. Conceptually, diastolic function can be envisioned as an interaction among ventricular relaxation, venous (filling) pressures, and ventricular compliance (or distensibility). In early diastole, active relaxation of the myocardium (an energy-dependent process) is important for rapidly reducing intraventricular pressure. In addition, the recoil and untwisting of the ventricles greatly affect early ventricular filling. Then the combined effects of blood return from the venous system, atrial pressure, ventricular compliance, the duration of diastole, and atrial contraction strength contribute to the ventricular volume achieved by the end of diastole (also known as preload). Ventricular compliance (defined as change in volume/change in pressure, which is the reciprocal of stiffness) becomes increasingly important as diastole and ventricular filling progress. Venous pressure and venous return to the heart are affected by numerous factors, as summarized later in this chapter (section "Venous System"). The duration

of diastole depends on the HR. As HR increases, diastole becomes shorter and atrial contraction contributes a proportionately greater amount to EDV. If atrial contraction is lost (as with atrial fibrillation), serious negative effects on cardiac performance can result, especially at higher HRs.

Systolic function depends on myocardial contractility (inotropy) as well as the loading conditions (preload and afterload) imposed on the ventricular fibers. Abnormal valvular function can negatively affect ventricular function in the setting of heart disease. The synchronization of ventricular filling and contraction also is important and involves at least three different aspects of electromechanical coordination. The first is AV synchrony, which mainly depends on heart rhythm and the timing between atrial and ventricular activation (PR interval on ECG; see section “Cardiac Cycle and Generation of Heart Sounds”). Intraventricular synchrony of contraction relates to the sequence of mechanical activation and relaxation within a ventricular chamber. Interventricular synchrony compares the ejection periods of the left and right ventricles. Synchrony can be altered by arrhythmias, conduction disturbances, and various cardiac diseases.

Cardiac Output CO is calculated as the product of HR and SV. It generally is expressed as liters or mL/minute. Thus $CO = HR \text{ (beats per minute)} \times SV \text{ (in L or mL per beat)}$. Frequently, CO is indexed to body size (the “cardiac index”). The normal cardiac index for a resting dog is about 3.1–4.7 liters/minute/m². Because the right heart and left heart are in series, CO from the RV equals CO from the LV. However, minor variation between ventricles does occur over brief time periods, such as during phases of respiration. Because CO depends on both frequency of contraction and ventricular function, it is considered a global estimate of the heart as a pump. Invasive methods used to estimate CO are based on the Fick principle² and include thermodilution, lithium-based indicator techniques, and other methods. These rarely are used in patients. Noninvasive CO estimation can be done with echocardiography, especially Doppler methods (p. 127).

Normal SV is about 55–65% of the ventricular end-diastolic volume (EDV). The blood remaining in the ventricles after ejection is known as the residual, or end-systolic, volume. This ratio of SV/EDV is termed ejection fraction (EF) and is a global estimate of ventricular function. The ventricular SV and EF are related directly to myocardial contractility and ventricular preload, and related inversely to ventricular afterload.

Contractility The term “contractility” refers to the intrinsic strength of contraction at a given preload and afterload. Contractility also is known as inotropic state or inotropy. Contractility primarily depends on the amount of free intracellular Ca⁺⁺ available during systole, although ATP availability and the sensitivity of the contractile proteins to Ca⁺⁺

also are important. Changes in autonomic nervous activity or HR (the Bowditch, also known as the “treppe” or “staircase,” effect) can influence contractility in a positive manner. Positive inotropic agents such as catecholamines and digoxin increase peak contractile force and SV by increasing intracellular Ca⁺⁺ availability. Because the ventricle empties to a greater degree, this can reduce ventricular end-systolic volume. Calcium-sensitizing agents (such as pimobendan) increase myocardial contractility without substantially increasing free Ca⁺⁺ concentration. Negative inotropic agents (such as beta-blockers or calcium-channel blockers) impair Ca⁺⁺ entry across L-type channels, reduce available Ca⁺⁺ and depress contractility.

Impaired myocardial contractility is a defining feature of dilated cardiomyopathy. Reduced contractility also can develop from chronic ventricular volume and pressure overloads. With little exception, anesthetic drugs markedly decrease contractile and overall systolic function. Accurate assessment of systolic (contractile) function is challenging in the setting of valvular heart disease, especially in cases of mitral regurgitation.

Preload The concept of preload refers to the degree of diastolic sarcomere stretch just prior to contraction. This is related to ventricular EDV and end-diastolic pressure (EDP). Diastolic sarcomere stretch (to an optimal length) will increase the force of the subsequent contraction by favorably aligning the contractile elements, and increasing Ca⁺⁺ release and affinity. In the intact heart, as EDV (preload) increases, the volume ejected with each contraction increases. This is the Frank–Starling relationship or Starling’s law of the heart (sometimes called “heterometric autoregulation”; **Figure 1.18**, left middle). This mechanism is crucial for beat-to-beat adjustments in SV and for balancing the output of the RVs and LVs.

Although preload directly influences ventricular systolic function, ventricular filling and stretch are determined by factors related to diastolic function (see section “The Heart as a Pump”). Ventricular preload is clinically important. Volume depletion (as from vomiting, diarrhea, urinary loss, or hemorrhage) is likely to reduce preload and CO. Prerenal azotemia, impaired perfusion of other organs, and hypotension can result. Myocardial hypertrophy or infiltration with fibrous tissue also impedes filling by increasing myocardial stiffness. External compression of the heart, as with pericardial disease, is another cause of impaired ventricular filling. When ventricular distensibility is reduced, higher filling pressures are required for any given diastolic volume; this is an operative definition of ventricular “diastolic dysfunction.” Consequences of impaired ventricular filling are a smaller EDV and increased venous pressure behind the affected ventricle. Perhaps surprisingly, ventricular dilation also can increase end-diastolic ventricular stiffness, as well as preload (**Figure 1.19**). In either situation, excessively

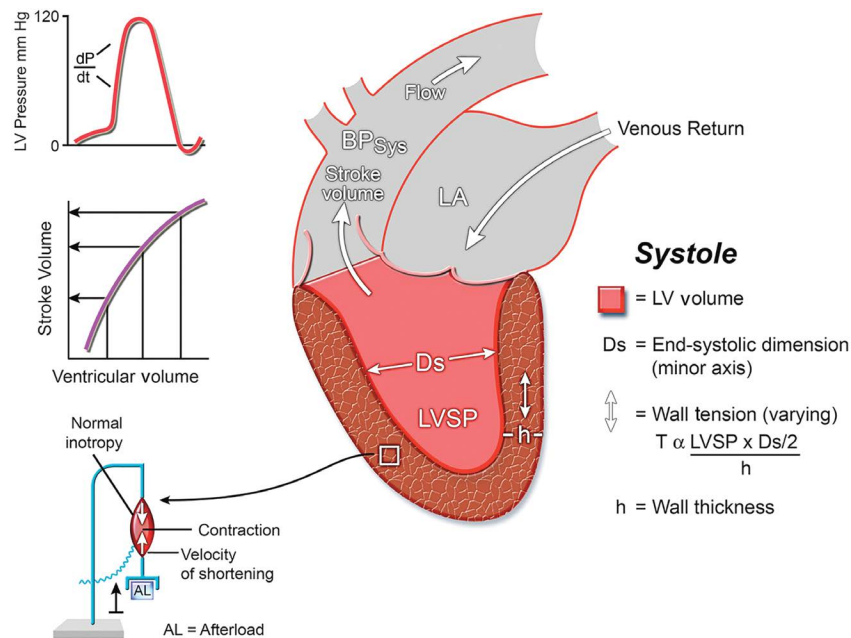


Figure 1.18 Schematic illustration of important concepts of left ventricular (LV) systole; analogous events occur in the right heart. After electrical activation, the LV myocardium contracts and the rapidly developing wall tension increases intraventricular pressure (LVSP, LV systolic pressure), squeezing the blood within the chamber. The upper figure on the left depicts the extremely rapid increase in LVSP. LV wall tension varies throughout systole as pressure increases, blood is ejected from the ventricle, and the ventricular walls thicken during ejection. Maximal wall tension occurs at the instant of aortic valve opening, at which point blood (stroke volume) is ejected into the aorta and systolic blood pressure (BP_{sys}) increases. The wall tension needed to overcome the aortic pressure and arterial impedance is called the “afterload (AL).” This word is based on muscle strip experiments (diagram at lower left) where the AL was literally a weight that had to be lifted and moved by the contracting muscle. Unlike increasing preload, which enhances ventricular function, AL opposes it, reducing the velocity and duration of shortening in the muscle and the stroke volume in the LV. Based on the Laplace relationship (right), the LV wall tension increases with a higher LVSP and with ventricular dilation ($D_s/2$) but is normalized (reduced) by ventricular hypertrophy that increases wall thickness. This wall thickening explains in part how the LV adapts to systemic hypertension and to aortic stenosis (two disorders that require higher LVSP). The other “loading” condition on the ventricle is preload (also see [Figure 1.19](#), diastole). Preload relates the end-diastolic sarcomere stretch (and LV volume) prior to contraction to LV’s ability to develop tension and eject a stroke volume. Increasing preload optimizes sarcomere length, which increases the force of contraction and stroke volume (left, middle figure). This is known as the Frank–Starling relationship. Thus, reduced ventricular diastolic volume (such as from dehydration) decreases LV stroke volume, while an increased preload produces a greater stroke volume, even accounting for its effects on afterload. In upper left diagram: dP/dt , change in pressure/change in time (1st derivative of LV pressure).⁸

high ventricular filling pressures promote venous congestion upstream from the affected chamber, leading to edema and cavity effusions.

Afterload Ventricular afterload is a complicated variable. It relates to the contractile force that must be achieved before sarcomeres can shorten and the ventricle ejects blood. Increased afterload has a negative effect on SV. One estimate of afterload is peak wall stress at the instant of aortic valve opening. After ejection has begun, the aorta and vascular system continue to oppose contraction. Impedance is another measure of afterload. Impedance is defined for the LV as the instantaneous change in aortic pressure/aortic flow. Because impedance varies throughout ejection, it cannot be measured practically in patients. From a clinical standpoint, afterload is often equated to arterial blood pressure, however this is an oversimplification. Factors that impede aortic flow, such as elevated blood pressure, (sub)aortic stenosis, reduced arterial compliance, increased vascular resistance, and reflected

arterial waves increase impedance afterload. Ventricular wall thickening actually reduces wall stress; whereas, ventricular dilation without sufficient wall hypertrophy increases afterload.

Response to Pressure or Volume Loading A chronic increase in ventricular volume (preload) or systolic pressure generation (afterload) creates greater wall tension (stress) according to the Laplace relationship.³ Increased wall stress demands greater energy (ATP) and O₂ consumption. As a compensatory response, myocardial hypertrophy develops via an increase in number of sarcomeres. In general, the pattern of hypertrophy depends on the type of overload. Chronic increase in ventricular volume stimulates the formation of new sarcomeres in series, lengthening the myofibers and creating a larger ventricle of normal wall thickness—so-called “eccentric hypertrophy.” A classic example is the LV dilation that develops with chronic degenerative (myxomatous) mitral valve disease in the dog ([Chapter 29](#)). Diseases

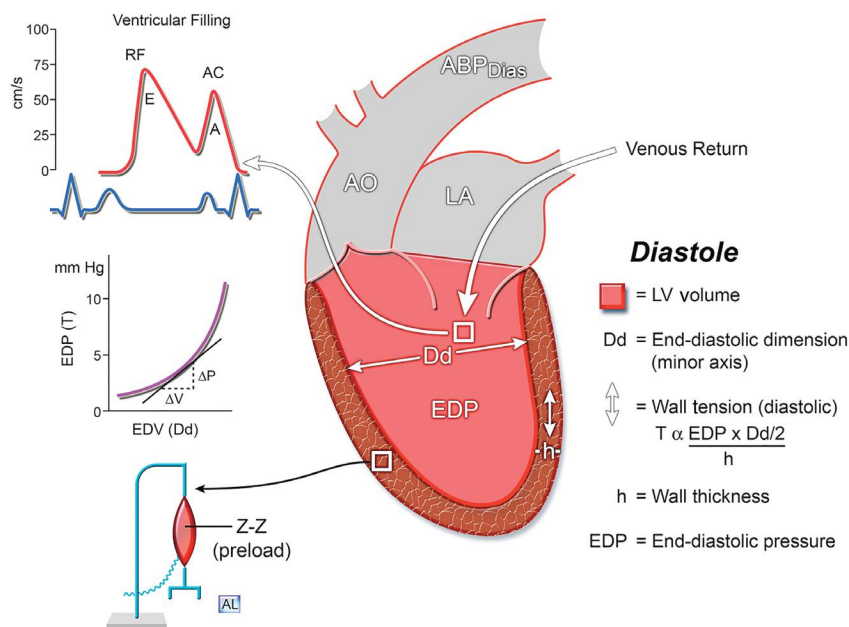


Figure 1.19 Schematic illustration of important concepts of left ventricular (LV) diastole; analogous events occur in the right heart. The volume that distends the ventricle sets the sarcomere length prior to contraction and strongly influences ventricular contractility. This sarcomere length, termed the “preload,” is based on muscle strip experiments that prestretched the muscle before stimulation (lower left diagram). The actual end-diastolic ventricular volume (EDV) and diameter (Dd, often measured by echocardiography) depend on the distending effect of end-diastolic pressure (EDP), as well as the stiffness of the muscle and compliance of the ventricular chamber. As venous return increases the LV volume, wall tension develops based on the law of Laplace (right). Tension is directly proportional to the distending pressure and chamber radius (Dd/2) and inversely proportional to wall thickness. The slope of the tangent of the diastolic volume to pressure relationship ($\Delta V/\Delta P$) relates to the compliance of the ventricle and explains in part why severe ventricular dilation is associated with higher filling pressures and risk of pulmonary edema (left, middle figure). As EDV increases, the increasing wall tension resists filling and requires a relatively higher end-diastolic pressure for filling. Furthermore, if a ventricle is stiffer than normal, the diastolic volume–pressure relationship shifts leftward, resulting in less filling at any level of EDP. Diastole is complicated to measure clinically; however, pulsed wave Doppler methods (upper left) can record the two main filling waves of the ventricle. Rapid ventricular filling (RF) in early diastole generates the E wave, while the late diastolic atrial contraction (AC) generates the A wave. The size and contour of these waveforms can reflect changes in diastolic function and ventricular filling pressure.⁸

that demand excessive systolic pressure generation stimulate formation of new sarcomeres in parallel, increasing myofiber diameter and ventricular wall thickness—so-called “concentric hypertrophy.” Severe pulmonic or (sub)aortic stenosis provides examples of this (Chapter 27).

Increased myocardial mass could normalize wall stress. However, with progressive cardiac disease, wall stress normalization might not be achieved or sustained despite myocardial hypertrophy. The “cardiomyopathy of overload” is a situation where a chronic workload has led to depressed contractility and systolic heart failure (heart failure with reduced EF). Diastolic heart failure (heart failure with preserved EF) also can develop from chronic workload, especially when the ventricle becomes thick, fibrotic, or ischemic.

Ventricular Function Assessment Overall CV function could be estimated by measuring CO or systemic blood pressure, as noted previously. Ventricular function can be assessed by invasive (catheter-based) or noninvasive methods. Most noninvasive methods used currently are ultrasound-based, including M-mode, 2D and Doppler echocardiography, as well as more sophisticated automated methods. A number of

indices can be used to estimate systolic function. Although inotropy is defined in muscle strip experiments by the maximal velocity of fiber shortening ($V_{\max}$), indices of ventricular contractility in the intact heart are imperfect. The slope of the end-systolic pressure–volume relationship (E_s , $E_{\max}$, maximal end-systolic elastance) provides a good estimate of contractility, and preload-recrutable stroke work is considered another index of contractile function. Unfortunately, neither are practical to measure in patients. The maximal rate of LV pressure generation during isovolumic contraction ($dp/dt_{\max}$) can be determined invasively from a catheter placed into the LV, and noninvasively in some cases using echocardiography. Although $dp/dt_{\max}$ has been considered a gold standard index of LV contractility, it is heavily influenced by preload.

The ventricular EF and the percent reduction in LV diameter or short-axis area from diastole to systole (fractional shortening, FS; and fractional area change, FAC) are common LV function indices measured by echocardiography. These mainly represent global systolic function, as opposed to contractility per se, because these ejection phase indices are especially influenced by loading conditions (preload and afterload), as well as heart rate. Right ventricular function

can be estimated echocardiographically by the distance of apical-basilar contraction, area change of the cavity over the cardiac cycle, and by tissue Doppler and special techniques that measure velocity or deformation of the myocardium. Unfortunately, when there is moderate to severe mitral regurgitation, both systolic and diastolic ventricular function indices tend to become hyperdynamic and unreliable related to changes in ventricular load (Chapter 4).

Invasively measured indices of ventricular relaxation include the maximal rate ($-dP/dt_{\max}$), and the time constant (τ), of LV pressure decline during isovolumic relaxation. Doppler indices offer noninvasive clues about ventricular filling but are rarely specific for relaxation. The isovolumic relaxation time (IVRT), mitral inflow patterns, and tissue Doppler velocity measurements are in popular use (p. 127).

Cardiac Cycle and Generation of Heart Sounds

Understanding the interrelations among electrical, mechanical, and acoustic events during the cardiac cycle is fundamental to understanding both normal and abnormal cardiac function (Figure 1.20). Accurate interpretation of CV examination findings also depends on knowledge of these events. Electrical activation (depolarization) always precedes mechanical activation (contraction).

Atrial electrical activation, indicated by the P wave on ECG, triggers atrial contraction (the “atrial kick”). This provides final ventricular filling (preload) at the end of ventricular diastole. At resting HRs, this represents only 10–20% of the total ventricular EDV. However, at fast HRs, atrial contraction can contribute up to 30% (or more) of the final ventricular volume. Therefore, loss of atrial contraction combined with

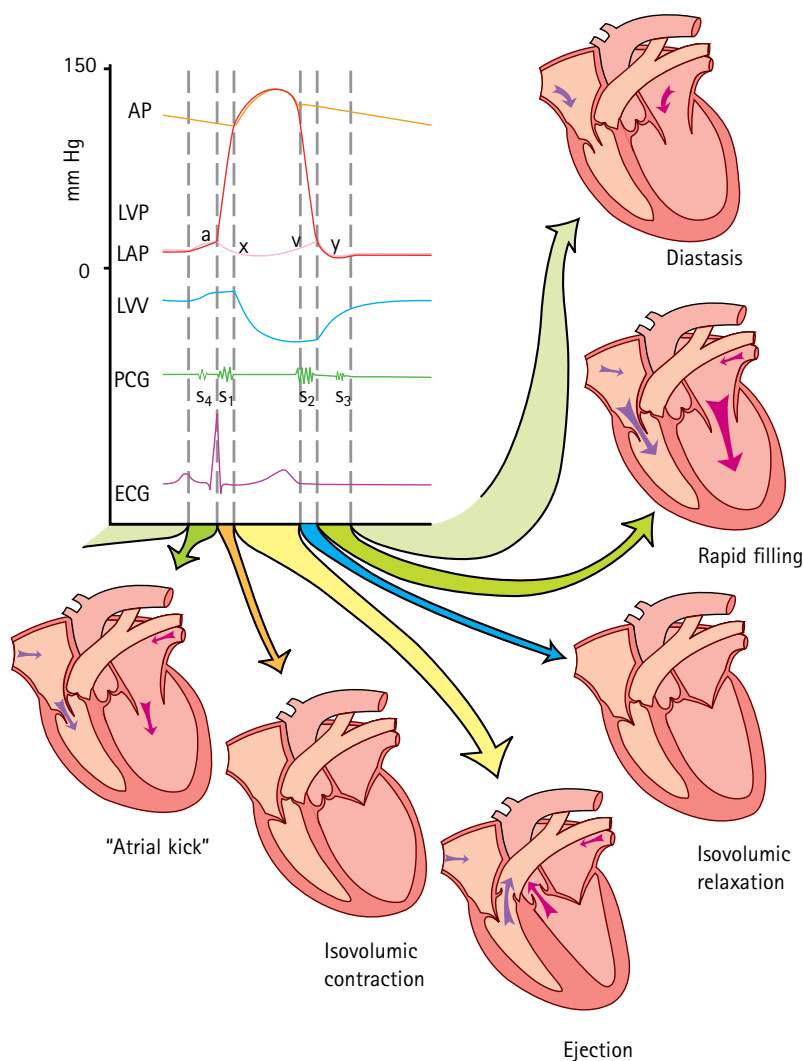


Figure 1.20 Cardiac cycle diagram showing interrelationships among electrical activation; pressures within atrium, ventricle, and associated great vessel; changes in ventricular volume; and heart sounds. Phases of the cardiac cycle are indicated by colored arrows correlating their time of occurrence on the graph with pictorial illustrations of the cardiac events. The timing of the sounds S₃ and S₄ is illustrated, although these sounds are not heard in normal dogs and cats. Similar pressure and volume changes occur in the right heart. (See section “Cardiac Cycle and Generation of Heart Sounds” for explanation of atrial pressure waves.) AP, aortic pressure; ECG, electrocardiogram; LAP, left atrial pressure; LVP, left ventricular pressure; LVV, left ventricular volume; PCG, phonocardiogram.

high HR (as can occur with atrial fibrillation) can markedly impair cardiac filling and output.

Ventricular electrical activation, signaled by the QRS complex on ECG, precedes ventricular contraction (systole). Ventricular pressure is low at the onset of the QRS complex (end-diastole); however, it quickly begins to rise. When ventricular pressure exceeds atrial pressure (also quite low), the AV valves close. Vibrations associated with valve closing and tensing are heard as the first heart sound (S_1 , “lub”). From a clinical perspective, this signals the beginning of ventricular systole. Ventricular pressure continues its rapid increase. The brief time from AV valve closure until ventricular pressure rises enough to open the semilunar valves is known as isovolumic (isovolumetric) contraction. After the aortic and pulmonary valves open, ventricular ejection proceeds rapidly as the contracting ventricular walls thicken and shorten. Then the rate of ejection slows as myocardial relaxation begins to occur. These velocity changes can be appreciated on an aortic (or pulmonary) Doppler flow recording.

Ventricular pressure falls quickly as relaxation occurs. When ventricular pressure drops below that in the associated great artery, ejection ceases (after a brief time lag caused by the momentum of blood flow) and the semilunar valves close. Vibrations associated with closing and tensing of these valves create the second heart sound (S_2 , “dub”). From a clinical perspective, this signals the end of ventricular systole and the beginning of ventricular diastole. The initial phase of diastole is isovolumic (isovolumetric) relaxation. During this brief period, the ventricular myocardium is actively relaxing and ventricular pressure falls rapidly with no change in volume. When intraventricular pressure drops below that in the atria, the AV valves open and rapid (early) ventricular filling occurs. The greatest increase in ventricular volume occurs during this rapid filling phase, typically to about 80% of final ventricular volume at normal HRs. A slower filling phase (diastasis) follows, although little volume is added here. The duration of diastasis is inversely related to HR. The final phase of ventricular diastole occurs with atrial contraction, as the cycle begins again.

Atrial contraction, at the end of ventricular diastole, produces an increase in atrial pressure called the “a wave.” Sometimes a smaller “c wave” also is evident following the “a wave,” as ventricular contraction begins (not shown in [Figure 1.20](#), see [Figure 1.23](#)). During initial ventricular ejection, there is a drop in atrial pressure as the atrium relaxes and the AV junction moves downward during ventricular contraction (the “x descent”; [Figure 1.20](#)). A gradual rise in atrial pressure (“v wave”) follows, as blood continues to flow into the atria during ventricular systole. Atrial pressure falls again (“y descent”) when the AV valves open in early diastole. Continued filling during diastasis produces a gradual, small rise in atrial (and ventricular) pressures.

Only two heart sounds (S_1 and S_2) are heard in normal dogs and cats. However, two other sounds might become audible with certain myocardial abnormalities. The S_3 (ventricular gallop sound) results from accentuated low-frequency vibrations

associated with the end of early (rapid) diastolic filling. The S_3 is most likely to be heard in dogs (or cats) with LV dilation and failure (as from dilated cardiomyopathy with elevated filling pressures). The S_4 (atrial gallop sound) is associated with blood and tissue oscillations at the time of atrial contraction. The S_4 might be heard with an abnormally stiff LV (such as from hypertrophic cardiomyopathy). Normal horses, in contrast to small animals, have an audible S_4 , and often an S_3 or ventricular sound, as well. These sounds become more accentuated with myocardial disease, as in small animals. In horses with physiological (or pathological) AV block, an isolated S_4 sound heard during pauses in the rhythm indicates that atrial, but not ventricular, contraction has occurred.

Pressure–Volume Loops The changes in LV pressure and volume that occur during the cardiac cycle can be depicted in a loop without regard to timing; this helps illustrate functional abnormalities. [Figure 1.21](#) shows a normal pressure–volume loop compared with the changes induced by systolic dysfunction (poor myocardial contractility), diastolic dysfunction (impaired ventricular filling), and chronic volume overload. Such changes underlie

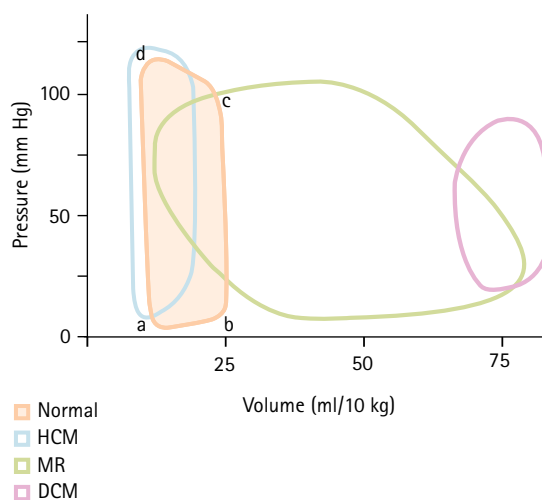


Figure 1.21 The normal left ventricular pressure–volume relationship is illustrated in orange. Ventricular filling occurs from “a” to “b.” Mitral valve closure and end-diastolic volume and pressure occur at point “b.” From “b” to “c” is isovolumic contraction and from “c” to “d” is ejection. The change in ventricular volume from “c” to “d” represents the stroke volume. Isovolumic relaxation occurs from “d” to “a,” where the mitral valve opens. Changes typical of various chronic heart diseases also are depicted. Hypertrophic cardiomyopathy (HCM, blue loop) is associated with increased ventricular stiffness, elevated end-diastolic pressure, and reduced volume. Large end-diastolic and stroke volumes are typical for severe, chronic mitral regurgitation (MR, green loop). There is no true isovolumic contraction because of the MR. Likewise for isovolumic relaxation because MR continues after aortic valve closure; elevated atrial pressure causes rapid inflow shortly thereafter. In dilated cardiomyopathy (DCM, red loop), both end-diastolic and end-systolic volumes are large and stroke volume is small because of the chronically poor contractility and secondary volume retention. Elevated filling pressure develops as ventricular dilation and stiffness increase.

the clinical, radiographic, and echocardiographic findings associated with various heart diseases.

Autonomic Control of the Heart

Although cardiac innervation is not necessary for action potential generation and contraction, parasympathetic and sympathetic nerves play an important role in modulating cardiac activity (**Figure 1.22**). NE released at the sympathetic nerve terminals, and also circulating epinephrine and NE, act as adrenergic agonists. Ach is the neurotransmitter released by parasympathetic neurons. Varying levels of sympathetic and parasympathetic (vagal) “tone” combine to regulate cardiac responses under a wide variety of conditions. Arterial baroreceptor reflexes have a profound influence on efferent autonomic traffic.

Effects of Sympathetic Stimulation Adrenergic receptors are widespread throughout the heart and are mainly of the β_1 subtype. Stimulation of these receptors increases HR (*chronotropy*) and conduction velocity (*dromotropy*), shortens the refractory period, and enhances myocardial contractility (*inotropy*) and relaxation (*lusitropy*). Beta-adrenergic stimulation enhances L-type calcium channel opening, which increases contractility because more Ca^{++} enters the myocytes during depolarization and more Ca^{++} is released from the SR. Beta-receptor stimulation also accelerates myocardial relaxation by reducing troponin's affinity for Ca^{++} and accelerating SR reuptake of Ca^{++} via the phospholamban-SERCA regulatory system. Sympathetic stimulation of the SA node hyperpolarizes these cells, thus activating an inward flux of Na^+ and K^+ (I_f) which causes faster spontaneous diastolic (phase 4)

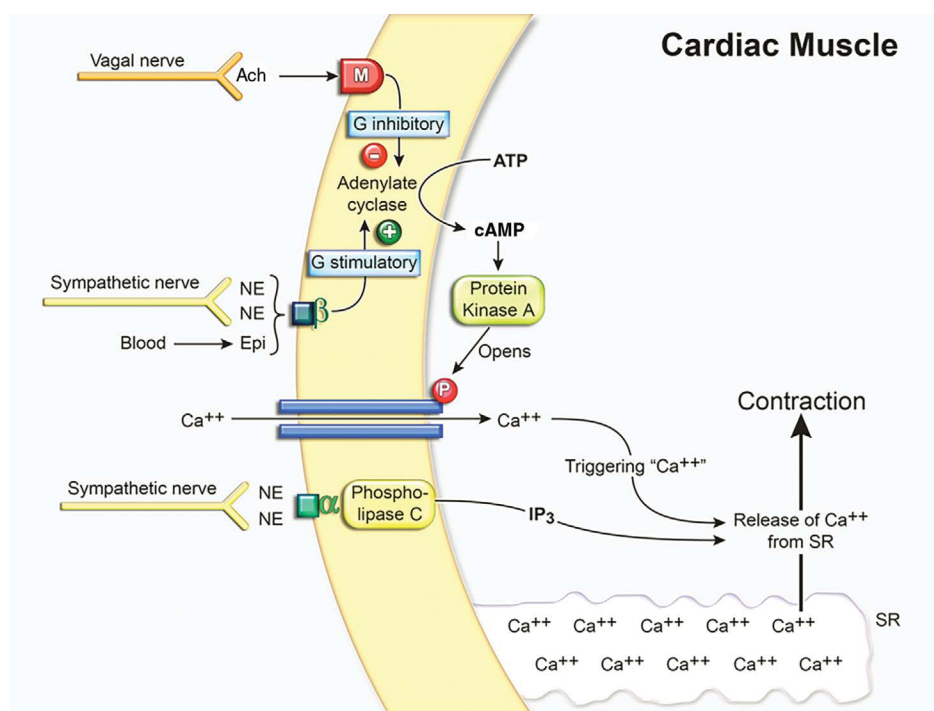


Figure 1.22 Autonomic control in the heart. Most beta-adrenergic receptors in the heart are myocardial β_1 receptors, with some β_2 receptors. There are few alpha-adrenergic receptors in companion animal species. The agonists for beta- and alpha-receptors are norepinephrine (NE, released from sympathetic nerves) and epinephrine (Epi, released by the adrenal medulla). Simply put, the essence of cardiac beta-stimulation is faster, stronger, and quicker. Under sympathetic stimulation of the beta-receptors, the heart beats faster (positive chronotropy), conducts current more rapidly (positive dromotropy), contracts more vigorously (positive inotropy), relaxes faster (positive lusitropy), and becomes more excitable (positive bathmotropy). Beta-receptors link by a stimulatory G protein to the adenylate cyclase system, which generates cyclic adenosine monophosphate (cAMP), as well as other messengers such as protein kinase A. cAMP works via protein kinase A to increase calcium channel opening, which increases Ca^{++} entry across its L-type channel; this increases the strength of contraction. It also acts to phosphorylate the membrane protein phospholamban. This reduces the braking (depressing) effect of phospholamban on the Ca^{++} reuptake pump (SERCA), which in turn increases the rate of Ca^{++} uptake into the sarcoplasmic reticulum (SR) and therefore, relaxation (lusitropic effect).

The alpha-receptors are less prominent in cardiac muscle; some species have little or none. Their main agonist is NE released from sympathetic nerves. The alpha-receptor's signaling system is different; the receptor is coupled to phospholipase C, which generates inositol triphosphate (IP_3), a second messenger that increases Ca^{++} release from the SR to create a positive inotropic effect.

Muscarinic (M) receptors are widely distributed in atrial myocardium, the SA node, and the AV node. They are less numerous in ventricular muscle, although some are present. Vagal stimulation releases the agonist, acetylcholine (ACh), from parasympathetic nerves. ACh stimulates the M2 receptor, which is coupled to an inhibitory G protein. This in turn inhibits adenylate cyclase. Thus, vagal stimulation depresses contractile function, especially in the atria where vagal innervation is most prominent.⁸

depolarization. Therefore, these cells reach threshold and generate the next action potential sooner, leading to an increase in heart (sinus) rate. This also decreases beat-to-beat HR variability, in contrast to the influence of vagal activity. Enhanced opening of L-type calcium channels also speeds AV conduction velocity besides facilitating pacemaker activity. Drugs that block beta-receptors antagonize these sympathetic effects.

Effects of Parasympathetic (Vagal) Stimulation Vagal (muscarinic) innervation to the heart is much more prominent in SA and AV nodal tissue and atrial myocardium, compared to the ventricular tissues. Vagal stimulation slows the SA node rate by antagonizing sympathetic activity and by reducing the slope of diastolic depolarization via an Ach-activated outward K^+ current (I_{KACh}). AV conduction also is slowed. Thus, the physiologic control of HR is mediated by the autonomic nervous system mainly by changes in the slope of diastolic (phase 4) depolarization in SA nodal cells. Vagal stimulation also accelerates repolarization; this effect is more pronounced in atrial myocardial cells. Normally, vagal influences predominate at rest.

Periodic variation in the sinus rate is called sinus arrhythmia. This is related to reflex-mediated fluctuations in the degree of vagal tone and usually is associated with the respiratory cycle (respiratory sinus arrhythmia). HR increases with inspiration (as vagal tone diminishes) and decreases during expiration (as vagal tone rises). Sinus arrhythmia can be quite pronounced in resting dogs and horses. Physiological second-degree AV block often occurs in horses during periods of HR slowing, as a further manifestation of increasing vagal tone. Sinus arrhythmia also occurs in resting cats, although the HR variability is more subtle.

Measurement of HR variability can indicate an underlying imbalance in autonomic activity. HR variability decreases in situations of stress, as sympathetic activity increases and vagal influence diminishes. Low HR variability has been associated with reduced survival in various disease conditions. HR variability can be measured over various durations of time and in several ways. These include time-domain indices (which quantify the variability among interbeat intervals), frequency-domain indices (which measure signal energy or power within several frequency bands), and nonlinear measurements of the unpredictability of a time series (for example, with Poincaré plots).

Parasympathetic nerves produce an antisympathetic effect on atrial myocardial cells. Because few ventricular cells receive direct vagal innervation, this effect is less prominent in the ventricular myocardium. However, parasympathetic neurons indirectly affect the myocardium through Ach-mediated activation of muscarinic cholinergic receptors located on sympathetic nerve terminals. This inhibits NE release from these terminals, which weakens the effects of sympathetic activation on ventricular cells.

Cardiac Energy Supply

The heart requires a high level of energy to support contraction, as well as other cellular functions. Myocardial O_2 needs rise when HR, contractility, and wall tension increase, as occurs with sympathetic activation. Ironically, higher HR also reduces the diastolic period when most coronary flow occurs.

Coronary arterioles deliver O_2 to the cells via a dense myocardial capillary network. Regulation of coronary arteriolar tone is tightly coupled to the myocytes' energy status and metabolic vasodilation is the most important control. The myocardium contains many mitochondria, which produce ATP by oxidative phosphorylation; fatty acids are the major source of energy for the heart. Mitochondrial ATP production is impaired when excess intracellular Ca^{++} leads to mitochondrial Ca^{++} overloading.

Coronary Blood Flow Overall, coronary blood flow is proportional to the driving pressure across the coronary circulation and is expressed by the following relationship: (aortic pressure – coronary sinus [or RA] pressure)/coronary vascular resistance. Coronary flow varies throughout the cardiac cycle because of pressure fluctuations within the chambers and ventricular walls. Because the major coronary arteries lie on the external surface of the heart, flow moves in an epicardial-to-endocardial direction. During systole, when intraventricular pressure rises, coronary flow in subendocardial regions diminishes or ceases. It may even reverse direction when intraventricular pressure is abnormally high (as with severe subaortic stenosis). Thus, most coronary flow occurs during diastole. Situations that shorten diastole or impair ventricular relaxation can negatively affect coronary blood flow. For example, when the active phase of myocardial relaxation is slowed, as occurs with ischemia, the early diastolic rise in coronary flow is impaired. At fast HRs, coronary flow (as well as ventricular filling) diminishes because diastole is abbreviated. When myocardial stiffness also is increased, tachycardia further compromises ventricular filling and perfusion.

Because coronary flow moves in the epicardial-to-endocardial direction, the subendocardial myocardium is most susceptible to ischemia when coronary flow is inadequate. At the same time, the subendocardial myocardium also undergoes greater mechanical stress and requires greater O_2 uptake, especially when myocardial energy needs increase (as with high afterload or sympathetic stimulation). A rough estimate of LV myocardial O_2 demand is provided by multiplying HR by arterial BP (as a proxy for afterload); this is known as the “double product.” Coronary blood flow that is insufficient for the myocardial demand promotes myocardial ischemia, cell death, and replacement fibrosis. This contributes to the ventricular dysfunction associated with diseases such as hypertrophic cardiomyopathy and severe subaortic stenosis.

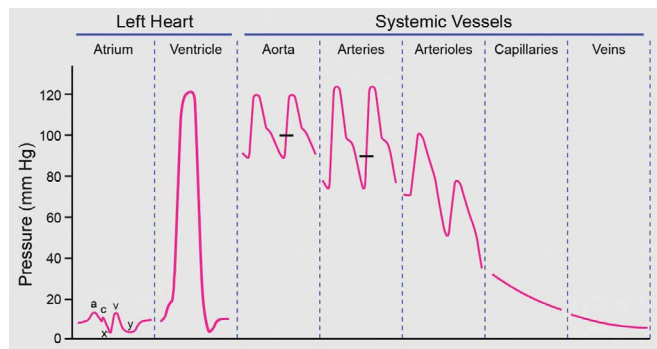


Figure 1.23 Schematic example of normal pressures and waveform contours across the systemic circulation. Left atrial pressure variations occur during the cardiac cycle from atrial contraction (“a wave”), onset of ventricular contraction (“c wave”), atrial relaxation and downward AV junction movement during ventricular systole (“x descent”), continued atrial filling during ventricular systole (“v wave”), and atrial emptying as the AV valves open in early diastole (“y descent”). Two cardiac cycles are shown for aorta, (large) arteries, and arterioles. The horizontal black bars indicate mean pressure, in the aorta and large peripheral arteries. Note that peak systolic pressure in the latter exceeds that in the aorta; this is caused by the effect of reflected pressure waves from the more peripheral smaller and stiffer arteries. Pulsatile arterial pressure waves become damped as blood travels through ever smaller arteries and arterioles. Capillary flow is nonpulsatile, as is venous flow. However, especially when right heart filling pressure is elevated, right atrial pressure waves can reflect backward into the large veins (see Chapter 15).⁸

The Circulation

Total blood volume is about 8–10% of body weight (80–100 ml/kg) in the dog and about 10% of body weight in the horse. The systemic circulation contains about 75% of the total blood volume at any one time, compared with 25% in the pulmonary circulation. Systemic veins act as storage (capacitance) vessels and usually contain about 70–80% of the systemic blood volume. The spleen serves as another important blood reservoir, particularly in the horse and dog. About 11–15% of blood in the systemic circulation is contained within arterial vessels and 5% within the capillary beds. In contrast, blood within the pulmonary circulation is distributed evenly among arterial, capillary, and venous vessels. **Figure 1.23** shows normal pressures and waveform contours across the systemic circulation. Pressure waveforms in the pulmonary circulation are similar; however, mean blood pressure in the pulmonary circulation is about one-seventh of that in the systemic circuit. A complex system of regulatory mechanisms controls systemic perfusion pressure, as well as the distribution of blood flow among body systems according to their changing metabolic needs.

Hemodynamic Concepts

Flow, Pressure, Resistance Relationships Blood flow (volume/unit time) through any part of the circulation depends directly on the driving (perfusion) pressure and inversely on vascular resistance. These fundamental relationships are

summarized by the equation: $Q = \Delta P/R$, where Q = blood flow, ΔP = pressure difference across the vessel(s) in question (that is, perfusion pressure), and R = vascular resistance. When referring to the output from either the left or right heart, $Q = CO$.

In the systemic circulation, ΔP is the difference between mean aortic pressure and mean RA pressure; R is total peripheral (systemic vascular) resistance. Sometimes left heart CO is estimated only as mean aortic pressure/ R , ignoring mean RA pressure because normally it is quite low. For the pulmonary circulation, ΔP is the difference between mean pulmonary arterial and LA pressures; R is pulmonary vascular resistance. Because the pulmonary and systemic circulations are in series, the output from each ventricle must be balanced over time (left heart CO = right heart CO). Resistance in the normal pulmonary circulation is about one-seventh that in the systemic circulation. This allows lung perfusion to occur at relatively low pressures (**Figure 1.1**). While perfusion P (ΔP) is the force that pushes blood through the vasculature, the term “blood pressure (BP)” refers to the transmural pressure in a vessel, or the distending force/unit area of vessel wall.

Resistance Vascular resistance, or impediment to flow, is an important variable that affects blood flow rate and the distribution of that flow among various vascular beds. The reciprocal of resistance is conductance, a measure of flow for a given pressure difference. Blood vessel radius has the greatest impact on resistance and flow. Poiseuille's law summarizes the effects of vessel dimension, flow velocity, pressure, and viscosity on blood flow.⁴ According to the relationships described by this law, resistance is inversely proportional to vessel radius to the fourth power (r^4), and directly proportional to blood viscosity. The exponential effect of vessel radius on resistance has important implications with regard to CV pathophysiology and therapy.

Within the systemic circulation as a whole, the highest vascular resistance is at the level of the arterioles. Widespread arteriolar dilation or constriction can lead to systemic hypotension or hypertension, respectively. For example, in patients with septic shock, hypotension might persist despite fluid volume resuscitation and increased CO because of widespread arteriolar vasodilation caused by metabolic acidosis and continued production of nitric oxide (NO) and other vasodilating factors. Catecholamine and vasopressin therapy might be needed to stimulate arteriolar constriction, increase systemic resistance, and maintain BP.

In the pulmonary circulation, there are three general levels of resistance to flow: pulmonary arterioles, pulmonary capillaries, and LA (essentially, pulmonary venous) pressure. Widespread compression of alveoli can promote increased pulmonary vascular resistance. Left-sided heart failure increases pressure in the LA, which impedes pulmonary flow to the left heart and raises pulmonary venous and

capillary pressures. In contrast, RA pressure and systemic capillary pressure or compression do not influence systemic vascular resistance.

Viscosity Viscosity is a measure of resistance to flow. The apparent viscosity of blood is determined mainly by the hematocrit. At higher hematocrit values, there is greater friction between successive layers of blood flowing within vessels, and therefore greater viscosity. A normal hematocrit value provides the best balance between ease of flow and ability to deliver O_2 to the tissues.

Blood Flow Velocity Blood flow velocity at any level of the circulation is related to the total cross-sectional area at that level, as well as to flow rate. For a given flow (or CO), as cross-sectional area decreases, velocity increases; this is known as the continuity relationship. For this reason, a narrowed valve abruptly accelerates blood flow velocity. Conversely, blood flow velocity is slowest in the systemic capillary beds because total capillary cross-sectional area is huge, compared to that of the aorta, where velocity is fastest.

Laminar and Turbulent Flow Blood flowing in smooth, straight vessels tends to form layers (streamlines) that slip over each other; flow is faster toward the center of the vessel, while the outer layers drag along the vessel wall. This laminar flow can easily be disrupted and become turbulent (disorganized). Turbulent flow is characterized by the formation of whorls or “eddy currents.” Factors that promote turbulence include high flow velocity (as with ventricular outflow obstruction), low blood viscosity (from anemia), wide vessel diameter, sudden change in vessel diameter or direction, and pulsatile flow. A measure of the tendency for turbulence to occur is described by Reynold’s

number.⁵ Reynold’s numbers over a so-called “critical” level ($\sim 2,000$ – $2,300$) are likely to be associated with an audible murmur. Resistance to blood flow increases when flow is turbulent.

The Vasculature

Arterial System Arteries provide a high-pressure reservoir for the pulsatile CO, as well as a conduit for blood to the body’s tissues. The strong elastic walls of the large arteries keep systolic pressure from becoming excessively high. Their recoil maintains pressure during diastole, which drives blood toward the peripheral tissues (**Figure 1.24**). Smaller arteries are less compliant as the proportion of elastin in their walls is less (**Figure 1.25**). Arterioles have more muscular walls, with an increased wall thickness/lumen ratio. As noted above, the greatest increase in systemic vascular resistance occurs at the level of the arterioles, which act as “control valves” to the microcirculation. There is rich sympathetic innervation to the smooth muscle within arteriolar walls, which allows the arterioles control over blood flow distribution to the different tissues according to metabolic needs.

The pulsatile pressure within the great arteries gradually is dampened by the elastic recoil of the arterial walls and the progressively increasing resistance of the arterial tree. Blood flow in the capillary beds is nonpulsatile.

Arterial Blood Pressure Arterial blood pressure is expressed as systolic pressure/diastolic pressure, in mm Hg. “Systolic pressure” is the highest pressure that occurs with each cardiac ejection. In the great arteries, a small pressure deviation (the “incisura” or “dicrotic notch”) occurs following the systolic pressure peak; this is associated with semilunar valve closure. “Diastolic pressure” is the lowest arterial pressure, attained just before the next ejection. “Pulse pressure”

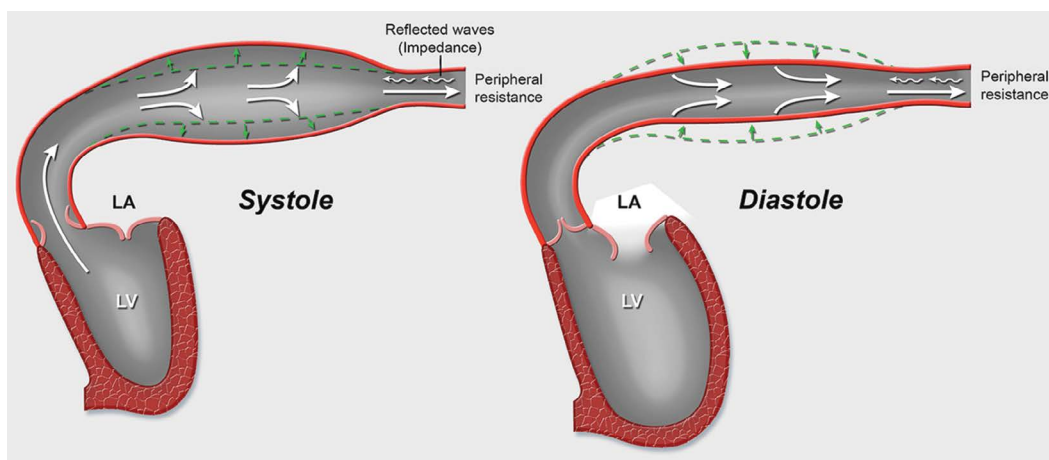


Figure 1.24 The large elastic arteries expand during systole to accept the ejected stroke volume without excessive increase in arterial pressure. During diastole, recoil of their elastic walls maintains arterial pressure, which helps drive blood flow (larger white arrows) through the circulation. LA, left atrium; LV, left ventricle.⁸

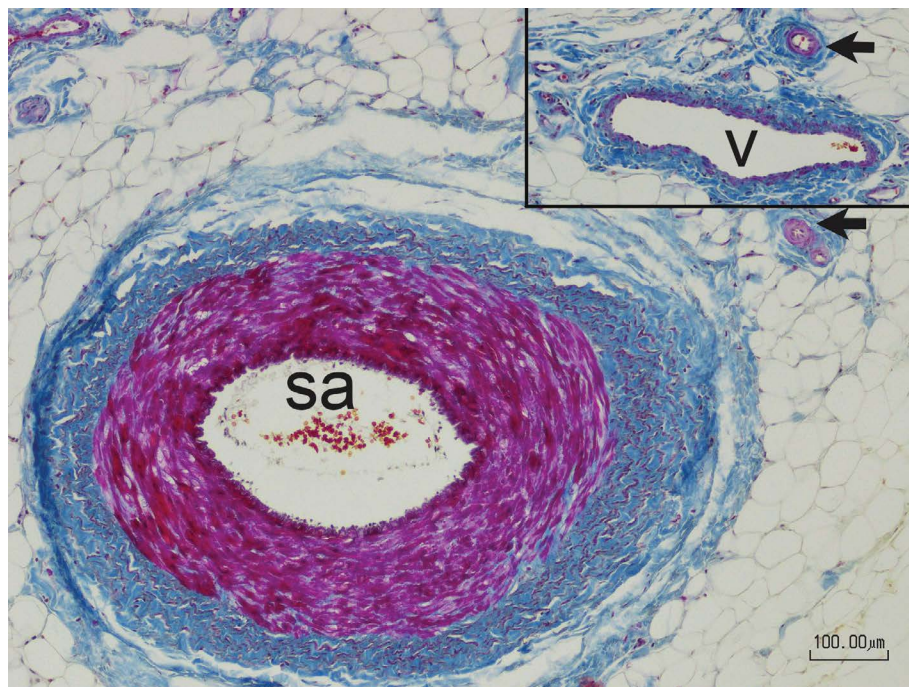


Figure 1.25 Photomicrograph showing cross-section of a small artery (sa). The tunica intima (interna) consists of an endothelial cell layer covering a small amount of subendothelial connective tissue and an inner elastic membrane (which appears plicated as an artifact of fixation). The relatively thick tunica media consists mainly of smooth muscle cells (stained deep pink here), arranged perpendicular to the long axis of the vessel. The outer tunica externa (adventitia) is mostly collagen fibers (blue), with fibroblasts and some wavy elastic fibers (purple) interspersed. The inset shows a smaller vein (v), an arteriole (arrow; two arterioles are indicated in the main image also), and several tiny venules. The walls of veins are quite thin compared to their lumen size (seen partially collapsed here), but do contain a small number of smooth muscle cells. Mallory stain; 10× magnification. (Image courtesy of Dr. E Uemura.)

is the difference between systolic and diastolic arterial pressures (**Figure 1.26**). The pulse pressure is the major determinant of how strong the peripheral arterial pulse feels on palpation. Several factors influence pulse pressure, especially the SV, the compliance of the arterial system, the rapidity of diastolic blood run-off into the peripheral vasculature, and, to a lesser degree, the character of ventricular ejection. When

SV increases, the rise in arterial pressure is greater because a larger volume must be accommodated in the arterial tree with each heartbeat. Pulse pressure also is wider at a slow HR because diastolic blood pressure falls lower (there is more time for pressure decline as blood flows from aorta into the periphery) and subsequent SV is greater (there is more time for ventricular filling). When the compliance (distensibility) of the arterial tree is greater, there is less pressure rise with each ejection. Pulse pressure is, therefore, directly related to SV and inversely related to arterial compliance.

Mean arterial pressure (MAP) is closer to diastolic pressure because diastole has a longer duration than systole. MAP can be estimated as: $\text{MAP} = \text{diastolic arterial pressure} + \frac{1}{3} \text{ pulse pressure}$. The MAP usually provides the best estimate of organ perfusion pressure. MAP values <60 mm Hg, generally, are considered critically low in patients.

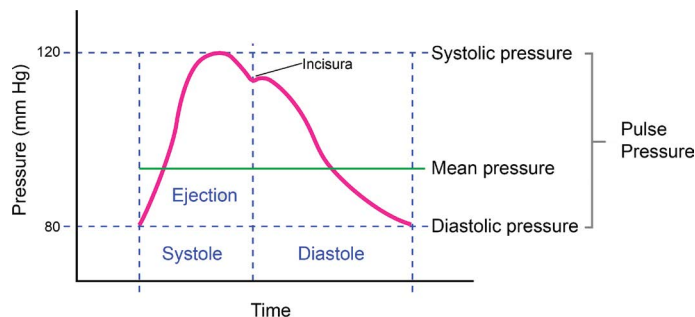


Figure 1.26 Illustration of an arterial (aortic) pressure waveform. “Systolic pressure” is the peak pressure reached following ventricular ejection. “Diastolic pressure” is the lowest pressure, just before the next ejection. The incisura indicates the time of aortic valve closure. The “pulse pressure” is the difference between the systolic and diastolic pressures. “Mean pressure” is often estimated as diastolic pressure + 1/3 of the pulse pressure.⁸

Microcirculation and Lymphatics Blood flow to each tissue bed is controlled by the constriction or dilation of the arterioles serving that bed. The level of sympathetic tone, and sometimes hormonal factors, influence the degree of vasoconstriction. However, precapillary arterioles are influenced greatly by local metabolic (vasodilatory) factors because of their close contact with the tissues they serve. Capillaries, with their single endothelial cell layer, are where

nutrient and waste exchange occur. Fick's Law of Diffusion⁶ describes factors that influence the rate of transfer of substances between the capillary and the interstitium surrounding the body's cells. Increases in cell metabolic rate lead to enhanced delivery of O₂ and various nutrients by alterations in all these factors except the diffusion coefficient. This is accomplished via increased capillary recruitment and blood flow, and increased concentration gradients between capillary and interstitium.

Fluid movement across the capillary membrane depends on the relationship between hydrostatic and oncotic pressures in both capillary and interstitium (Starling's forces).⁷ This concept is of paramount clinical relevance because it explains the mechanism of edema (or effusion) formation in many diseases. Recent evidence highlights the importance of the tissue interstitium in regulating plasma volume in health and disease, generating cellular signals, and preventing edema. Hydrostatic pressure within capillaries tends to push fluid through the membrane pores into the interstitium, especially at the arteriolar end of the capillary. Plasma proteins are too large to pass through pores in the normal capillary membrane (there is high colloid oncotic pressure within the capillary). Usually, the capillary oncotic pressure tending to hold fluid within the vessel almost balances the outward hydrostatic force (pressure) tending to push fluid into the interstitium, so that there is a small net flow into the interstitium. Most of the filtered fluid is reabsorbed by the venous side of the capillaries; the rest is removed by lymphatics.

Lymph vessels mobilize excess fluid from the interstitial space. Some interstitial proteins also are removed, which reduces net fluid flow out of the capillaries. Lymph fluid from most of the body returns to the cranial vena cava via the thoracic duct; return from the right forelimb, neck, and head is by the right lymphatic duct. The rate of lymph flow increases when interstitial free fluid pressure rises. This can result from increased capillary hydrostatic pressure (as with heart failure, venous obstruction, or overinfusion of IV fluids), decreased plasma colloid oncotic pressure (from severe hypoproteinemia), and increased interstitial protein accumulation (usually from increased capillary permeability, as with inflammatory disorders). Tissue edema develops when the rate of interstitial fluid accumulation exceeds the maximal rate of lymph flow. This is more likely to occur in acute settings, because lymphatic drainage can dramatically increase over time. For example, in dogs, pulmonary edema is likely to develop when mean LA pressure rises rapidly to over 18 mm Hg. However, with chronic progressive LA pressure elevation, values of up to 40 mm Hg might not cause overt pulmonary edema.

Venous System Veins return blood to the heart; one-way valves help prevent backflow. Because virtually all systemic venous blood eventually reaches the RA (there is a small venous admixture in the lungs and in the heart), systemic venous return essentially equals CO. Mean systemic venous

pressure depends on sympathetic tone (venoconstriction) as well as blood volume. Pressure in the RA and adjoining segments of the vena cavae, also known as central venous pressure (CVP), influences pressure in all systemic veins. CVP usually is measured clinically in cm H₂O, although sometimes it is measured in mm Hg (1 mm Hg = 1.36 cm H₂O). In normal dogs and cats, CVP ranges from 0 to 10 cm H₂O, with trends up or down carrying the greatest clinical relevancy.

Systemic veins can expand to store some blood volume, or constrict to return it to the central circulation. Functionally, these are termed unstressed and stressed venous volumes, representing the volumes filling the systemic veins and the volume available to increase venous return to the heart. Fluid therapy can increase both, while venoconstriction is likely to affect the stressed volume and facilitate venous return. The compliance of veins is about 24 times greater than that of arteries, so a large increase in venous volume can occur with little change in pressure or stressed volume. Systemic venous constriction can maintain arterial flow and pressure when up to 20% of the total blood volume is lost. The spleen also acts as an important blood reservoir in the horse and dog; splenic contraction increases the amount of blood in circulation and therefore, venous return to the heart.

Systemic veins are the major blood reservoir for the body. Increasing venous return is associated with both an increase in cardiac output, due to improved preload, and impairment of venous return at RA pressure increases. Eventually, a classic Guytonian equilibrium is achieved between venous return and cardiac output. In contrast to systemic veins, pulmonary venous capacitance is small and increased venous volume can predispose to pulmonary edema.

Normally, no pulsations are seen in veins because pressure pulses are not transmitted forward from the arteries through the capillaries. However, pressure waves can be transmitted backward from the right heart into the large veins, especially when RA pressure is elevated (see section "Cardiac Cycle and Generation of Heart Sounds," and [Chapter 15](#)).

Control of the Circulation

Fairly constant arterial blood pressure is needed for normal tissue perfusion. The rapidly acting BP regulatory mechanisms are primarily neural and hormonal in origin. The arterial baroreceptor reflexes are most important. However, long-term arterial BP control depends on blood volume also, which involves renal regulation of sodium and water balance. In addition, a host of local factors influences the degree of vascular constriction or dilation within different regional circulations.

Blood flow regulation in the peripheral circulation depends on three general mechanisms: neural (autonomic) regulation, hormonal factors, and local control systems that include endothelial-derived factors, paracrine controls, and

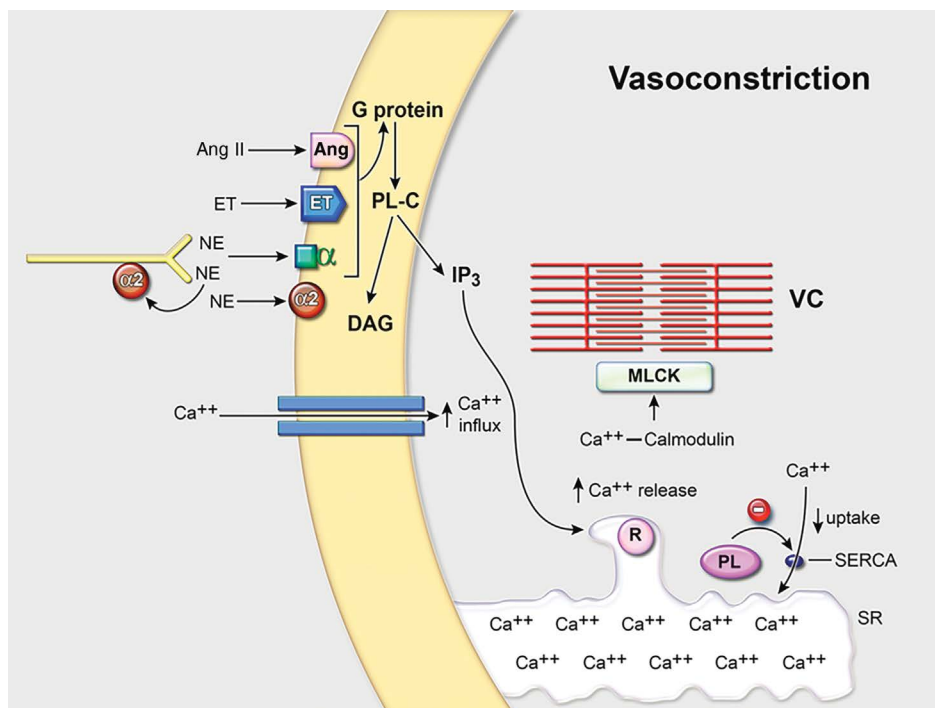


Figure 1.27 Vasoconstriction. Extracellular Ca^{++} enters the vascular smooth muscle (VSM) cell via the long-lasting (L-type) Ca^{++} channels. Various receptors modulate the ion's entry, including α -adrenergic receptors (stimulated by norepinephrine, NE), and also receptors for angiotensin (Ang) II and endothelin (ET), as well as vasopressin (not depicted). These receptors interact with the G protein that regulates Ca^{++} entry, via phospholipase-C (PL-C)-mediated formation of the second messenger, inositol triphosphate (IP_3). Ca^{++} entry stimulates the sarcoplasmic reticulum (SR) to release stored Ca^{++} via the calcium release channel (R). Diacyl glycerol (DAG) also is formed, which can increase Ca^{++} sensitivity and enhance vasoconstriction. Ca^{++} released by the SR (and complexed with calmodulin) binds to the enzyme myosin light chain kinase (MLCK). The activated MLCK phosphorylates myosin light chains, allowing these to interact with thin actin filaments of the VSM cell sarcomere. Actin-myosin interaction leads to VSM contraction and vasoconstriction. Unlike cardiac muscle (which quickly contracts and relaxes), VSM maintains a tonic contraction for long periods.⁸

cellular metabolites (Figures 1.27 and 1.28). The relative importance of central compared to local control is not uniform across the circulation. For example, neural control predominates in splanchnic tissues, however local metabolic factors are most important in the heart. Ultimately, it is constriction and relaxation of arteriolar smooth muscle that regulates blood flow distribution throughout the body, total peripheral resistance, and BP. Vascular smooth muscle in most tissues is innervated only by sympathetic fibers. A level of partial contraction (vascular "tone") exists that appears to be independent of nervous system control. An increase in sympathetic nerve activity stimulates further contraction, while reduced sympathetic nerve traffic allows dilation.

Vascular smooth muscle contraction is mediated by increased intracellular Ca^{++} , most often via agonist binding to membrane receptor-operated Ca^{++} channels. Intracellular Ca^{++} release from the SR also contributes. Agonists include catecholamines, angiotensin (Ang)II, and vasopressin. Voltage-operated Ca^{++} entry also can stimulate contraction. In contrast to cardiac muscle, where Ca^{++} -troponin interaction (on actin filaments) controls contraction, vascular smooth muscle contraction depends on myosin activation by Ca^{++} complexed to calmodulin and interacting with myosin light chain kinase.

When these regulatory systems are activated acutely, it is generally for correction of abnormal BP. Chronic activation of vasoconstrictor systems occurs in disorders such as heart failure. Chronic activation also is associated with renal sodium retention as well as mechanisms that promote tissue hypertrophy and fibrosis.

Local (Intrinsic) Control Several mechanisms influence blood flow at the local tissue level. A major one is the concentration of vasodilator metabolites produced by the tissue's cells, which adjusts blood flow according to local metabolic needs (metabolic regulation). Examples of local vasodilator substances include K^+ , adenosine, CO_2 , and metabolic acids including lactic acid. Local vasodilation also occurs from a number of paracrine and inflammatory mediators including NO, prostacyclin (PGI_2), kinins, and histamine. Examples of local vasoconstrictor substances include O_2 (relevant to the treatment of cerebral edema) and the prostaglandin thromboxane A_2 , which also causes platelet aggregation.

Many arterioles have the intrinsic ability to constrict (or dilate) in response to increased (or decreased) pressure and stretch, so that a steady flow rate is maintained. This is known as autoregulation. Another local mechanism is

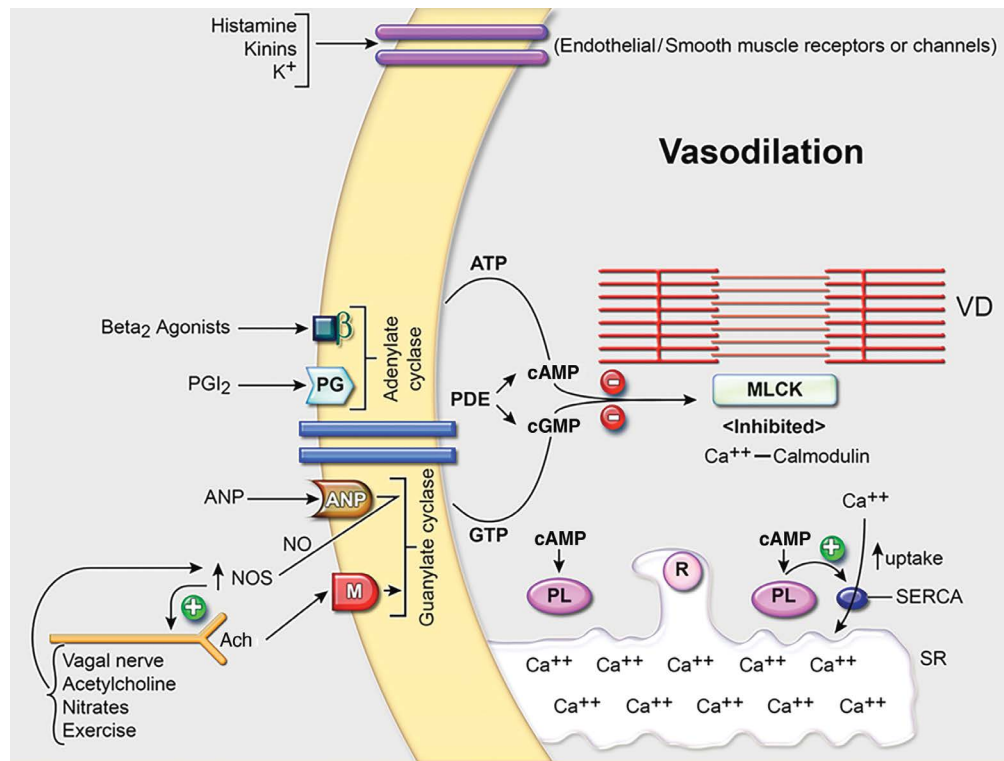


Figure 1.28 Vasodilation occurs mainly by reduction in cytosolic Ca^{++} concentration, which reduces the degree of vascular smooth muscle constriction. Factors or drugs that decrease cytosolic Ca^{++} concentration, or promote increased reuptake into the sarcoplasmic reticulum (SR), reduce tonic constriction and therefore, allow vasodilation. In addition, there are membrane-associated vasodilator systems. These include β_2 -adrenergic receptors, and receptors for prostacyclin (PGI_2), A- and B-type natriuretic peptides (ANP, shown), and acetylcholine (ACh; muscarinic receptor, M). These receptors signal through the second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Both of these messengers inhibit the Ca^{++} -myosin light chain kinase (MLCK) interaction, leading to vasodilation. Nitric oxide (NO), derived from nerves and endothelial cells via NO synthase (NOS), also signals the guanylate cyclase system to increase intracellular cGMP. NO production is increased by parasympathetic activity, exercise (shear stress in the endothelium), and nitrate drugs. Reuptake of Ca^{++} into the SR is influenced by the sarcoendoplasmic reticulum Ca^{++} -ATPase (SERCA). Increased SERCA activity leads to vasodilation; inhibition promotes continued vasoconstriction. Phospholamban (PL) is a membrane protein that inhibits SERCA. When phospholamban is inhibited (for example, by the action of cAMP), Ca^{++} reuptake leads to vasodilation. Various intracellular phosphodiesterase (PDE) enzymes degrade cAMP and cGMP. PDE-inhibitor drugs (such as pimobendan, which inhibits PDE-3, or sildenafil, which inhibits PDE-5) function as vasodilators.⁸

endothelial-mediated regulation. This can promote vasodilation (as with NO release in response to increased blood flow and shear stress), or vasoconstriction (as when endothelin, ETN-1 is released from injured endothelium). The ETNs are a family of potent vasoconstrictors released from endothelial cells. When produced in increased amounts, they can act as hormones as well as local paracrine factors. ETN A and B are thought to be important in pulmonary disease and pulmonary hypertension.

Neurohormonal (Extrinsic) Control Control of the circulation as a whole, including the regulation of systemic arterial BP within narrow limits, is mediated centrally by the autonomic nervous system. Hormonal (humoral) controls also contribute to some extent, as well as play an important role in blood volume regulation. The sympathetic (adrenergic) nervous system (SNS) activates the CV system (pressor response) via the neurotransmitter NE. Sympathetic innervation extends to the veins (capacitance vessels) as well as arteries and arterioles

throughout the body. Capillaries are not innervated. Vascular reflexes, or hormonal stimuli, that activate the central pressor region increase the number of efferent sympathetic impulses. This increases NE release at the vascular nerve terminals and, thus, the degree of vasoconstriction. Sympathetic innervation is greater in the small arteries, arterioles, and veins than in larger arteries. Inhibition of the central pressor region reduces sympathetic efferent traffic and results in vasodilation.

The parasympathetic (cholinergic) nervous system (PNS) has inhibitory effects on the heart. However, parasympathetic activation has minimal effect on total peripheral resistance because the PNS innervates only vasculature in the head and some viscera, not skeletal muscle or skin. ACh is its neurotransmitter.

Vascular Receptors The density and distribution of different receptors within the vasculature varies depending on the organ system and tissue. Postsynaptic α_1 -receptors are most

important; stimulation by NE causes vasoconstriction. Vascular wall α_2 -receptors are extrasynaptic and usually are stimulated by circulating (adrenal-released) catecholamines; they also mediate vasoconstriction. Thus, stimulation of vascular $\alpha_{1 \text{ or } 2}$ -receptors increases vascular resistance, reduces compliance, increases venous return to the heart, and ultimately raises systemic arterial pressure. NE within the synaptic clefts also stimulates presynaptic α_2 -receptors, which inhibit further NE release.

There are extrasynaptic vascular β_2 -receptors in many tissues (such as skeletal muscle); when stimulated by low levels of circulating epinephrine, they mediate vasodilation. They also respond to NE. Epinephrine also can activate α -receptors and cause constriction. Some vascular beds (especially renal) contain dopaminergic receptors that mediate vasodilation. Overall, however, when vasodilation occurs as a function of an autonomic reflex, it is achieved by withdrawal of sympathetic tone and decreased stimulation of α -receptors, rather than by stimulation of vascular β_2 -receptors. Local vasodilator substances might contribute as well.

Vascular Reflexes Central sympathetic and parasympathetic output is influenced by afferent signals from baroreceptors, chemoreceptors, other brain centers, and skin receptors. Widespread activation of sympathetic vasoconstrictor fibers

increases peripheral vascular resistance and arterial BP, stimulates venous constriction (which increases venous return and CO), and increases HR and contractility.

Arterial baroreceptors (pressor receptors), located in the carotid sinuses and in the aortic arch, are stimulated by stretch (**Figure 1.29**). They are especially important in the short-term regulation of systemic arterial BP. When stretched by a rise in BP, more afferent impulses are sent to the medulla (solitary tract nucleus) via the vagus nerve (from the aortic arch) or glossopharyngeal nerve (from the carotid sinuses). The solitary tract nucleus acts as a depressor control, which inhibits sympathetic output. Therefore, stimulation of vascular baroreceptors by increased BP inhibits the central sympathetic vasoconstrictor regions, which reduces efferent nerve traffic and allows peripheral vasodilation and BP reduction. Concurrent stimulation of vagal regions also slows HR. Baroreceptors operate over a limited range of BPs. Maximal receptor firing rates occur at a mean BP of 180–200 mm Hg, while afferent impulses cease at about 50–60 mm Hg. Reduced firing of baroreceptors allows more vasoconstrictor output to the peripheral circulation.

Cardiopulmonary baroreceptors located in the atria, ventricles, and pulmonary vessels also are tonically active and can alter peripheral resistance when stimulated by intracardiac and pulmonary pressures changes. For example, atrial

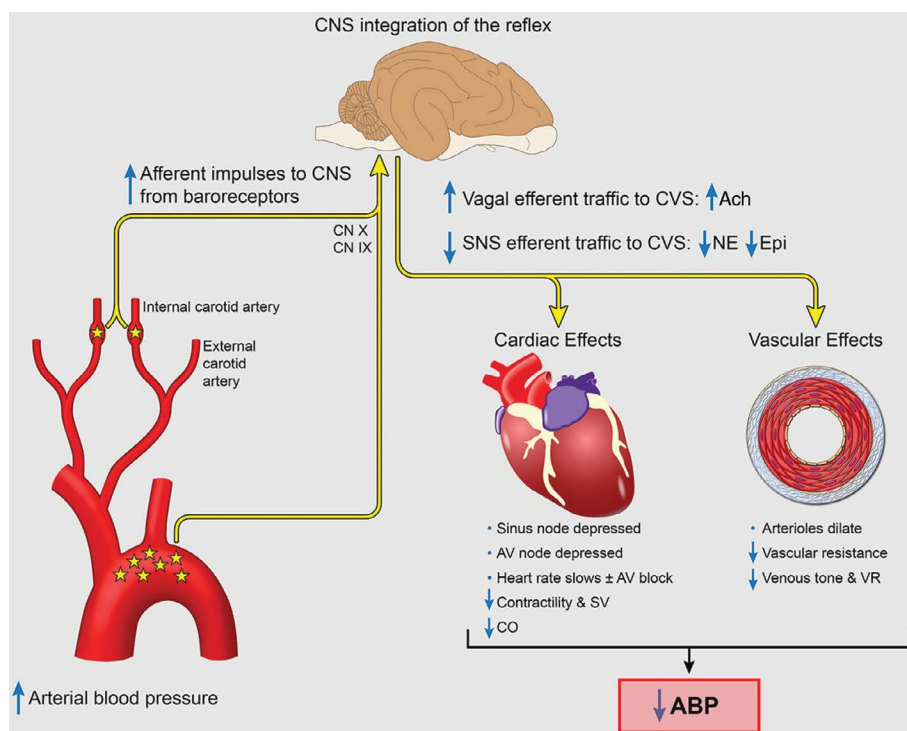


Figure 1.29 Arterial baroreceptor reflex schematic illustration. Stretch (baro-)receptors in the carotid sinuses and aortic arch respond to changes in arterial pressure. Increased arterial pressure (stretch) stimulates an increase in afferent nerve traffic to the brain, which ultimately inhibits efferent sympathetic nerve traffic and enhances vagal traffic to the CVS. The resulting decreases in heart rate, CO, and vasoconstriction lead to reduction in blood pressure. See section “Vascular Reflexes” for further details. ABP, arterial blood pressure; Ach, acetylcholine; AV, atrioventricular; CN, cranial nerve; CNS, central nervous system; CVS, cardiovascular system; Epi, epinephrine; NE, norepinephrine; CO, cardiac output; SNS, sympathetic nervous system; SV, stroke volume; VR, venous resistance.⁸

receptor stretch mediates reduced sympathetic output to the kidneys (increasing renal blood flow and urine output), although it enhances sympathetic output to the sinus node (increasing HR). Cardiopulmonary baroreceptor activation can alter BP reflexively by inhibiting the vasoconstrictor center in the medulla, as well as inhibiting renin (and thus Ang), aldosterone, and antidiuretic hormone release. Changes in the rate of urine output resulting from cardiopulmonary baroreceptor effects are important in blood volume regulation, too. Peripheral chemoreceptors in the area of the aortic arch (aortic bodies) and carotid sinuses (carotid bodies) react to changes in PO_2 , PCO_2 , and pH of the blood. They mainly are involved with regulating respiration but can influence the medullary vasomotor regions to some degree.

Hormonal (Humoral) Factors Epinephrine and NE also can function as hormones, when released into the circulation by the adrenal gland. This normally is less important in BP control than NE release from sympathetic nerve terminals. Epinephrine in low concentrations dilates resistance vessels (a beta-adrenergic effect) in some tissues (such as skeletal muscle). However, high concentrations of epinephrine induce vasoconstriction (alpha-adrenergic effect). NE mediates vasoconstriction (alpha-adrenergic effect).

The renin-angiotensin-aldosterone system (RAAS) influences vascular smooth muscle tone and blood volume through a complex interplay of effects. The traditional description of the RAAS cascade focuses on the production of AngII via a two-step process (**Figure 1.30**). First, the inactive precursor

protein, angiotensinogen, is cleaved by renin into the 10-amino acid peptide AngI, also called AngI(1-10); renin release from the kidney occurs in response to increased sympathetic activation, reduced renal perfusion pressure, hypovolemia, and decreased distal tubular sodium load. Angiotensin converting enzyme (ACE) converts AngI into the active, 8-amino acid peptide, AngII or AngII(1-8). AngII's effects include potent vasoconstriction and reduced sodium and water secretion, through stimulation of aldosterone release from the adrenal cortex and direct renal effects. AngII stimulates thirst and promotes vasopressin release from the pituitary gland, too. Angiotensin type 1 receptors (AngIRs) mediate all these AngII effects. Synthesis of RAAS components also can occur at the local tissue level, where the effects of AngII and aldosterone promote myocardial and vascular wall hypertrophy and fibrosis. The entire RAAS cascade does not end with AngII, however. Multiple other enzyme pathways and Ang metabolites have been identified, some of which have counterbalancing vasodilatory and natriuretic effects. **Chapter 20** (p. 305) provides some additional information about this "expanded" RAAS in the context of heart failure. Vasopressin (also called antidiuretic hormone) is released from the pituitary gland in response to low arterial BP as well as osmotic stimuli. It has a direct vasoconstrictor effect. It also plays an indirect role in BP regulation by stimulating renal volume retention and thirst.

The natriuretic peptides, atrial or A-type (ANP) and brain or B-type (BNP) natriuretic peptides, are hormones released from the myocardium in response to stretch and, in the case

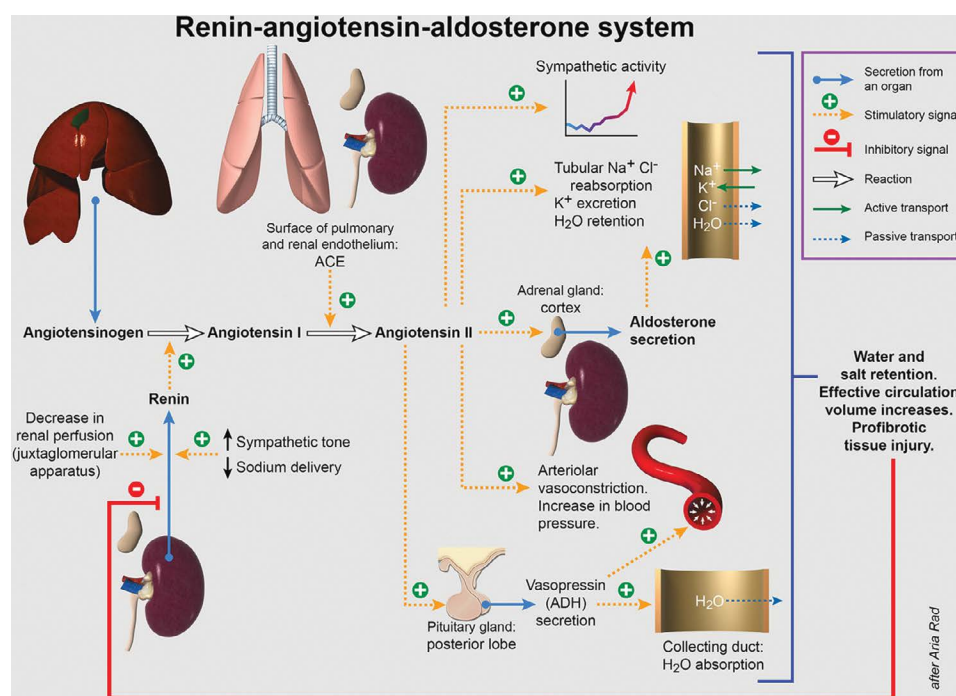


Figure 1.30 Schematic diagram illustrating components and effects of the renin-angiotensin-aldosterone system. ACE, angiotensin converting enzyme; ADH, antidiuretic hormone.⁸

of BNP, potentially from cardiomyocyte hypertrophy and ischemia. These hormones induce diuresis and vasodilation. In essence, they antagonize the effects of AngII at the vascular, renal and tissue levels. See [Chapter 20](#) (p. 308) for more information about natriuretic peptides.

Cardiovascular Responses to Stress and Exercise

The CV system can respond to a variety of stressors. Some of these are physiological, such as exercise and the need for increased gastrointestinal blood flow after eating. Others relate to a sudden fall in arterial pressure and involve acute activation of BP control mechanisms (see section “Control of the Circulation”). Various forms of shock are relevant here, too. Heart failure sometimes disrupts CV homeostasis acutely; however, progressive and chronic neurohormonal compensatory mechanism activation is more common in companion animals ([Chapter 20](#)).

Certain structural and functional adaptations are associated with athletic activity and training. This is an expansive subject and CV responses to athletic training can vary with the species, intensity and duration of exercise, environment (temperature and humidity), and past training. Issues related to the equine athlete are discussed more fully in other sources (see section “Suggested Additional Readings and References”). Some general principles of exercise physiology are reviewed here briefly.

Aerobic capacity, or maximal rate of O₂ uptake (VO_{2 max}), is considered an important indicator of athletic ability. The ability to greatly increase CO during exercise is the most important factor in determining aerobic capacity. Horses have the ability to produce a high maximal CO. Heart size (which is a major determinant of SV) and HR determine CO (as CO = SV × HR). Heart size is proportionately larger in racing breeds, and especially in individual elite athletes. Exercise training can increase heart size and a larger ventricle produces a larger SV. HR increases markedly during maximal exercise, for example, up to approximately 240 beats/min in the galloping horse. While SV can increase to a small degree during exercise, it is the great increase in HR that allows CO in the elite equine athlete to increase from ~30 L/min at rest to over 350 L/min during racing. Sympathetic activation also increases myocardial contractility as well as HR, further enhancing CO. Systemic arterial pressure also increases and MAP can reach around 200 mm Hg.

Besides a high CO, the ability to increase arterial O₂ content also is an important factor in supporting maximal aerobic capacity. Arterial O₂ content is a function of blood hemoglobin concentration and O₂ saturation. In the horse, splenic contraction can almost double circulating hemoglobin concentration, compared to resting level. Proportionately, equine spleen size is larger than other species, and racing breeds have larger spleens than nonracing breeds.

Distribution of the CO among various tissues is markedly altered during exercise. For example, blood flow to skeletal muscle at rest is about 10–20% of the total CO; however, it can increase to 80–90% of CO during maximal exercise. Simultaneously, the percentage of CO to the splanchnic and renal circulations might drop from ~50% to ~5%. These shifts result from regional changes in arteriolar resistance and capillary recruitment.

The marked increase in CO during exercise distends the pulmonary vasculature and, although this is a relatively low-resistance and low-pressure system, pulmonary arterial pressure does greatly increase during strenuous exercise. Mean pulmonary arterial pressures of 90–140 mm Hg have been documented in horses during exercise. This likely relates in part to LA pressure elevation during high intensity exercise, which promotes high pulmonary capillary pressure. Combined with marked alveolar pressure fluctuations and other factors, this exercise-induced pulmonary hypertension can lead to alveolar capillary rupture (exercise-induced pulmonary hemorrhage). Besides these CV factors, VO_{2 max} also depends on the respiratory system's ability to take up O₂ (which can be a limiting factor at maximal exercise), as well as the diffusion of O₂ into skeletal muscle mitochondria and muscle oxidative enzyme capacity.

Notes

1. Nernst equation:

$$E_K = -61.5 \log([K^+]_i/[K^+]_o)$$
 E_K , potassium equilibrium potential; $[K^+]_i$, intracellular K⁺ concentration; $[K^+]_o$, extracellular K⁺ concentration.
2. Fick principle:
 The amount of a substance taken up (or released) by an organ per unit time is equal to the arterial-venous concentration difference of that substance × blood flow.
3. Laplace relationship:

$$\tau = Pr/w$$
 τ , wall stress; P, transmural pressure; r, chamber radius; w, wall thickness.
4. Amount of flow in a vessel over a given time:
 $Q = \text{velocity of flow } ([\Delta Pr^2]/8\eta l) \times \text{cross-sectional area } (\pi r^2)$
 r , vessel radius; η , viscosity; l , vessel length.
 Rewritten, this is Poiseuille's law: $Q = (\Delta Pr^4)/8\eta l$
 Since $Q = \text{flow}$ and $\Delta P = \text{pressure difference}$, the rest equals conductance. Because resistance is the reciprocal of conductance: $R = 8\eta l/\pi r^4$.
5. Reynold's number = $(\sigma/\eta)VD$
 σ , fluid density; η , viscosity; V, average velocity; D, vessel diameter.
6. Fick's Law of Diffusion:
 Diffusion of a substance = $DA([Sc] - [Si])/\Delta x$
 D , diffusion coefficient for that substance; A, area available for diffusion (this increases when more capillaries are open); $[Sc]$, concentration of the substance within the capillary; $[Si]$, concentration of the substance within the interstitium; Δx , distance over which the substance must travel (this decreases when more capillaries are open).

7. Starling's forces:

$$Q_f = k[(P_c + \pi_i) - (P_i + \pi_p)]$$

Q_f , fluid movement; P_c , capillary hydrostatic pressure; P_i , interstitial fluid hydrostatic pressure; π_i , interstitial fluid oncotic pressure; π_p , plasma oncotic pressure; k , filtration constant for capillary membrane.

8. Computer graphic artwork by **Tim Vojt** BFA, Senior Medical Illustrator, The Ohio State University College of Veterinary Medicine.

Suggested Additional Reading and References

Also See Online Comprehensive Bibliography at: <https://www.routledge.com/9781482246223>.

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