Ricardo Munoz · Eduardo M. da Cruz
Carol G. Vetterly · David S. Cooper
Donald Berry *Editors*

Handbook of Pediatric Cardiovascular Drugs

Second Edition

Springer

Handbook of Pediatric Cardiovascular Drugs

Ricardo Munoz
Eduardo M. da Cruz
Carol G. Vetterly
David S. Cooper
Donald Berry
Editors

Handbook of Pediatric Cardiovascular Drugs

Second Edition

Springer

Editors
Ricardo Munoz
Cardiac Intensive Care Division
The Heart Institute
Children's Hospital of
Pittsburgh of UPMC
University of Pittsburgh
Pittsburgh, PA, USA

Eduardo M. da Cruz
Pediatric Cardiac Intensive Care
Department of Pediatrics
The Heart Institute
Children's Hospital Colorado
University of Colorado Denver
School of Medicine
Aurora, CO, USA

Carol G. Vetterly
Department of Pharmacy
Services, Children's Hospital
of Pittsburgh of UPMC
Pittsburgh, PA, USA

Department of Pharmacy
and Therapeutics
University of Pittsburgh
School of Pharmacy
Pittsburgh, PA, USA

David S. Cooper
Department of Pediatrics
Cardiac Intensive Care Unit
The Heart Institute
Cincinnati Children's Hospital
Medical Center
University of Cincinnati
College of Medicine
Cincinnati, OH, USA

Donald Berry
Department of Pharmacy
Children's Hospital of
Pittsburgh of UPMC
Pittsburgh, PA, USA

The views herein are those of the author(s) and do not reflect the official policy of the Department of the Army, Department of Defense, or the US Government

ISBN 978-1-4471-2463-4 ISBN 978-1-4471-2464-1 (eBook)
DOI 10.1007/978-1-4471-2464-1
Springer London Heidelberg New York Dordrecht

Library of Congress Control Number: 2014941733

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

My wife Lina, sons Rafael, Ricardo, and grandsons Julian and Daniel

Ricardo Munoz

To Suzanne, Esteban and Tomás
To my family
For their inspiring demeanor

Eduardo M. da Cruz

I would like to thank my wonderful and supportive family: my husband Tim, daughter Jasmine and my Mom, for their unconditional love and patience.

Carol G. Vetterly

To Mom, Lisa, Michael, Adam and Daniel
Thank you for your love, support and understanding

David S. Cooper

To Carolyn, Adrienne and Alysse
Thank you for your support and understanding

Donald E. Berry

Preface

In 2008, the first edition of the *Handbook of Pediatric Cardiovascular Drugs* was produced with the main purpose of providing health care practitioners with a tool to safely and consistently prescribe and administer cardiovascular drugs in children with cardiac disease. Half a decade later, this manual remains the only book of its nature, and the time has come to edit an updated version. As for the first edition, the editors have endeavored in this occasion to provide an overview of basic pediatric cardiovascular medications, in collaboration with highly reputed authors. This pocket reference handbook remains tailored to meet the daily challenges of practitioners who care for pediatric cardiac patients, from the newborn to the young adult. This book does not provide an extensive review of all cardiovascular medications, but does compile the basic information required to assist caregivers in their daily clinical practice.

We sincerely hope that this second edition of the *Handbook of Pediatric Cardiovascular Drugs* will be helpful to physicians, fellows, residents, mid levels, pharmacists, nurses and other practitioners within the multidisciplinary teams involved in the complex and high-risk care of pediatric and congenital patients with heart disease.

Pittsburgh, PA, USA — Ricardo Munoz
Aurora, CO, USA — Eduardo M. da Cruz
Pittsburgh, PA, USA — Carol G. Vetterly
Cincinnati, OH, USA — David S. Cooper
Pittsburgh, PA, USA — Donald Berry

About the Editors

Ricardo Munoz, MD, FAAP, FCCM, FACC, is Chief of the Cardiac Intensive Care Division, Director of the Cardiac Recovery Program, Medical Director for Global Business and Telemedicine at the Children's Hospital of Pittsburgh of UPMC. He is Director of International Affairs at the Children's Hospital of Pittsburgh of UPMC Heart Center, and Professor for Dr. Ricardo Munoz of Critical Care Medicine, Pediatrics and Surgery at the University of Pittsburgh, Pennsylvania, USA.

Eduardo M. da Cruz, MD, is Head of the Pediatric Cardiac Critical Care Program, the Pediatric Cardiology Inpatient Services, and Director of the Cardiac Intensive Care Unit and Cardiac Progressive Care Unit at the Children's Hospital of Colorado. He is Tenured Professor of Pediatrics, Pediatric Cardiology and Intensive Care at the University of Colorado Denver, School of Medicine, Aurora, Colorado, USA.

Carol G. Vetterly, PharmD, BCPS, is the Clinical Coordinator of Pharmacy Services and a Clinical Pharmacy Specialist in the Pediatric Intensive Care Unit at the Children's Hospital of Pittsburgh of UPMC. She is an Adjunct Assistant Professor of Pharmacy and Therapeutics at the University of Pittsburgh School of Pharmacy, Pennsylvania, USA.

David S. Cooper, MD, MPH, is Chief Safety Officer in the Heart Institute, Associate Medical Director of the Cardiovascular Intensive Care Unit and Medical Director of the Cardiac ECLS Program in the Heart Institute at Cincinnati Children's Hospital Medical Center. He is Co-Director of the

Center for Acute Care Nephrology. He is Associate Professor of Pediatrics at the University of Cincinnati College of Medicine, Ohio, USA.

Donald Berry, BSPharm, is a Clinical Pharmacy Specialist within the Cardiac Intensive Care Unit at the Children's Hospital of Pittsburgh of UPMC, Pennsylvania, USA.

Contents

Contributors

Cindy Barrett, MD Pediatric Cardiac Intensive Care, Department of Pediatrics, The Heart Institute, Children's Hospital Colorado, University of Colorado Denver, School of Medicine, Aurora, CO, USA

Allyson Berg, PharmD Department of Pharmacy, Children's Hospital Colorado, Aurora, CO, USA

Donald Berry, BSPharm Department of Pharmacy, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Grant Burton, MD Congenital Heart Surgery Unit (CHSU), Medical City Children's Hospital, Dallas, TX, USA

Andrea R. Chamberlain, PharmD, BCPS Division of Pharmacy, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

David S. Cooper, MD, MPH Department of Pediatrics, Cardiac Intensive Care Unit, The Heart Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Kelli L. Crowley, PharmD, BCPS Department of Pharmacy Services, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Department of Pharmacy and Therapeutics, University of Pittsburgh School of Pharmacy, Pittsburgh, PA, USA

Eduardo M. da Cruz Pediatric Cardiac Intensive Care, Department of Pediatrics, The Heart Institute, Children's Hospital Colorado, University of Colorado Denver, School of Medicine, Aurora, CO, USA

Sarah D. de Ferranti, MD, MPH Preventive Cardiology, Children's Hospital Boston, Harvard Medical School, Boston, MA, USA

Jamie A. Decker, MD Division of Pediatric Cardiology, Johns Hopkins All Children's Heart Institute, South Saint Petersburg, FL, USA

Amy Donnellan, CNP Department of Pediatrics, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Jennifer Eshelman, PharmD Department of Pharmacy, Children's Hospital Colorado, Aurora, CO, USA

Brian Feingold, MD, MS Department of Pediatric Cardiology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Ryan Flanagan, MD Division of Pediatric Cardiology, Department of Pediatrics, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Department of Pediatrics, Womack Army Medical Center, Fort Bragg, NC, USA

Stuart L. Goldstein, MD Department of Pediatrics, Center for Acute Care Nephrology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Sriya Gunawardena, MBBS Division of Hematology/Oncology, Department of Pediatrics, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Megan Horsley, RD, LD, CSP, CNSC Department of Pediatrics, Cardiac Intensive Care Unit, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Denise L. Howrie, PharmD University of Pittsburgh School of Pharmacy & Medicine, Pittsburgh, PA, USA

Department of Pharmacy, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

David Dunbar Ivy, MD Department of Pediatrics, Children's Hospital Colorado, Pediatric Cardiology, University of Colorado School of Medicine, Aurora, CO, USA

Pediatric Cardiology, Children's Hospital Colorado, Aurora, CO, USA

Lindsey Justice, MSN, CPNP-AP Department of Pediatrics, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Jonathan Kaufman, MD Pediatric Cardiac Intensive Care, Department of Pediatrics, The Heart Institute, Children's

Hospital Colorado, University of Colorado Denver, School of Medicine, Aurora, CO, USA

Traci Kazmerski, MD Division of Pulmonology, Department of Pediatrics, Allergy and Immunology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Timothy K. Knilans, MD Division of Pediatrics and Pediatric Cardiology, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

David M. Kwiatkowski, MD Department of Pediatrics, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Erica P. Lin, MD Cardiovascular Anesthesia, The Heart Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Angela Lorts, MD Department of Pediatrics, Advanced Heart Failure, The Heart Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Ryan Moore, MD Pediatric Cardiology, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Ricardo Munoz, MD, FAAP, FCCM, FACC Cardiac Intensive Care Division, The Heart Institute, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh, Pittsburgh, PA, USA

Phuong-Tan Nguyen-Ha, PharmD Department of Pharmacy, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Jaclyn E. Sawyer, PharmD Division of Pharmacy, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Robert L. Poole, PharmD, FPPAG, FCSHP, FASHP Department of Pharmacy, Lucile Packard Children's Hospital Stanford, Clinical Professor of Pharmacy, University of California, San Francisco, USA

James P. Spaeth, MD Cardiovascular Anesthesia, The Heart Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Shinichi Takatsuki, MD Department of Pediatrics, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA

Cécile Tissot, MD Division of Pediatrics-Cardiology, Department of Pediatrics, Geneva University Children's Hospital, Geneva, Switzerland

Carol G. Vetterly, PharmD, BCPS Department of Pharmacy Services, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Department of Pharmacy and Therapeutics, University of Pittsburgh School of Pharmacy, Pittsburgh, PA, USA

Steven Webber, MBChB, MRCP Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN, USA

Chapter 1
Cardiac Physiology

Brian Feingold, Ricardo Munoz, and Ryan Flanagan

Abstract A basic understanding of cardiovascular physiology is fundamental to the comprehension of the conditions and pharmacologic mechanisms described throughout this Handbook. This chapter will provide an overview of cardiovascular physiology while highlighting the unique aspects of the neonatal and pediatric heart. While not intended to be an exhaustive review, the chapter should serve to familiarize the reader with concepts, such as cardiac structure and function, electrophysiology, shunt lesions, contractility, preload and afterload, and clinical measures of cardiac function, to be discussed in greater detail in other chapters.

B. Feingold, MD, MS
Department of Pediatric Cardiology,
Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

R. Munoz, MD, FAAP, FCCM, FACC
Cardiac Intensive Care Division, The Heart Institute,
Children's Hospital of Pittsburgh of UPMC,
University of Pittsburgh, Pittsburgh, PA, USA

R. Flanagan, MD (✉)
Division of Pediatric Cardiology, Department of Pediatrics,
Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Department of Pediatrics, Womack Army Medical Center,
2817 Reilly Road, Fort Bragg, NC, USA
e-mail: ryanflanagan1@yahoo.com

R. Munoz et al. (eds.), *Handbook of Pediatric Cardiovascular Drugs*, DOI 10.1007/978-1-4471-2464-1_1,

Keywords Cardiac physiology • Dysrhythmias • Shunt lesions • Preload • Afterload • Contractility

A basic understanding of cardiovascular physiology is fundamental to the comprehension of the conditions and pharmacologic mechanisms described throughout this Handbook. With that goal in mind, this chapter will provide an overview of cardiovascular physiology while highlighting the unique aspects of the neonatal and pediatric heart. While not intended to be an exhaustive review, the chapter should serve to familiarize the reader with concepts to be discussed in greater detail in other chapters. For those seeking further knowledge, a list of more comprehensive sources is provided at the conclusion of this chapter.

1.1 Basic Cardiac Structure and Function

The human heart is in essence two pumps connected in series, delivering blood to the pulmonary and systemic circulations. It is comprised of two atria which receive venous blood, two ventricles which pump blood, valves which prevent the backflow of blood, and a conduction system which transmits the electrical impulses that drive cardiac activity. The electrical signal is propagated and converted to mechanical activity through a series of biochemical interactions which involve stereotyped ion fluxes (mainly Na^+, Ca^{++}, K^+) through voltage-gated ion 'pores' and downstream protein interactions. While inherited or acquired defects in these components may result in cardiac disease, these same mechanisms form the basis of pharmacologic therapies.

1.2 Electrophysiology

Rhythmic and coordinated contraction of the heart is accomplished by the propagation of an electrical impulse (action potential) in a precise manner (Fig. 1.1). Each action potential

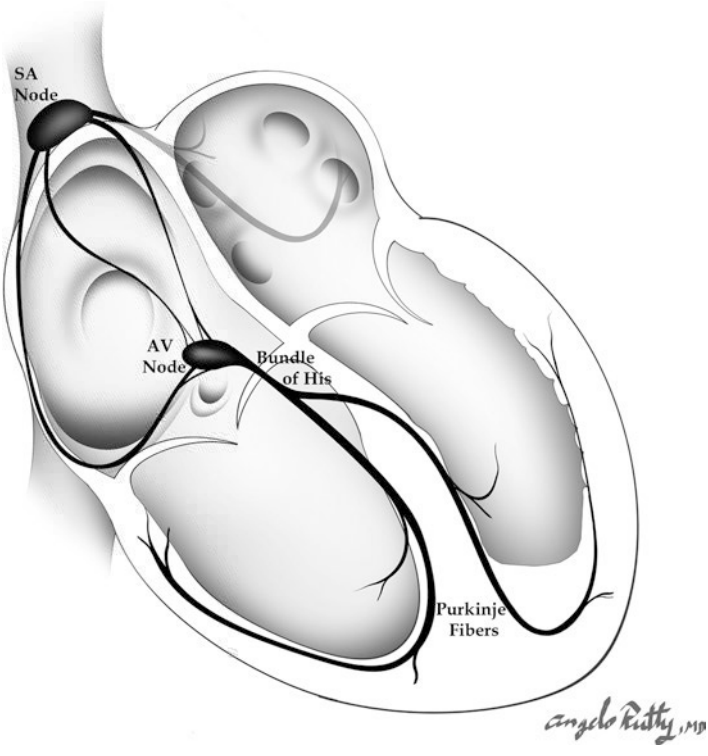

FIGURE 1.1 Diagrammatic representation of structures involved in normal cardiac conduction. *SA* sino-atrial, *AV* atrio-ventricular

is normally initiated by the sino-atrial (SA) node, a specialized group of myocardial cells in the high right atrium. These cells exhibit automaticity, meaning they spontaneously become electrically active (depolarize). The impulse then spreads to adjacent atrial myocytes via cell-to-cell connections termed gap junctions. Ultimately, the wave of depolarization reaches a second group of specialized cells at the bottom of the right atrium, near the crux of the heart, called the atrio-ventricular (AV) node. Because the atria and ventricles are electrically isolated from one another by a circumferential band of fibrous tissue at the level of the tricuspid and mitral valves, the

only path for impulse propagation is via the AV node. After a brief (approximately 0.1 s), intrinsic delay at the AV node, the action potential is propagated quickly down the bundle of His and Purkinje fibers within the ventricular myocardium. This rapidly conducting network acts as 'wiring' to convey the impulse to the apex of the heart, allowing for a coordinated, mechanically efficient contraction of the ventricles.

1.2.1 Action and Resting Potentials

At rest, cardiac myocytes maintain a net negative electrical gradient with respect to the extracellular environment (resting potential). The gradient results from the activities of ion channels and transporters within the cell membrane and is essential to the myocyte's (and heart's) ability to propagate electrical impulse. With sufficient stimulus, alterations in the myocyte's permeability to Na^+ result in a net positive electrical gradient with respect to the extracellular environment (depolarization). Further, changes in the myocyte's ion permeability to K^+, Cl^-, and Ca^{++}, result in the eventual restoration of the negative intracellular environment. When plotted against time, the changes in electrical potential are conventionally described as having five distinct phases (Fig. 1.2) which correspond to the stereotyped alterations in membrane permeability of the cardiac myocyte. Anti-arrhythmic medications exert their influence by altering membrane permeability, affecting the characteristics of the action potential. For example, class Ia agents (procainamide, disopyramide, and quinidine) affect Na^+ influx, resulting in a decreased rate of phase 0 depolarization and mild prolongation of repolarization [1].

1.2.2 Automaticity

Automaticity refers to the intrinsic ability of a cardiomyocyte or cluster of cells to spontaneously depolarize and thus initiate propagation of an action potential. Such cells are termed "pacemaker cells" and include those of the SA and AV nodes.

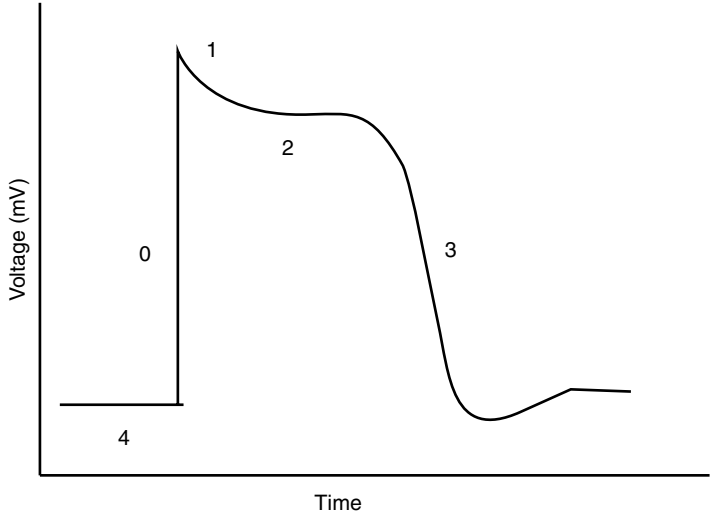

FIGURE 1.2 The action potential of a Purkinje fiber. Phase *4* is the resting state prior to electrical stimulation. Phase *0* is the rapid depolarization as a result of Na^+ influx. Phase *1* is the initial stage of repolarization due to closure of Na^+ channels and efflux of Cl^-. Phase *2*, or the plateau phase, is mediated primarily by Ca^{++} influx. Phase *3* is the rapid repolarization and is facilitated primarily by K^+ efflux. *mV* millivolts

Cells of the His-Purkinje system and even the ventricular myocardium may also spontaneously depolarize under circumstances of particularly slow cardiac rhythms (e.g., sinus node arrest, complete heart block). Because of the more rapid depolarization of the usual pacemakers, the automaticity of these cells is often not manifested during normal cardiac rhythm. Furthermore, after injury, cells which typically do not possess automaticity may acquire altered membrane conductance with resultant current leakage and spontaneous depolarization resulting in automatic tachycardias. Figure 1.3 depicts the action potential for cells of the SA and AV nodes. Notice the positively sloped phase 4, progressing toward threshold potential at which point phase 0 occurs. The slope of the phase 4 depolarization is a key determinant in the rate

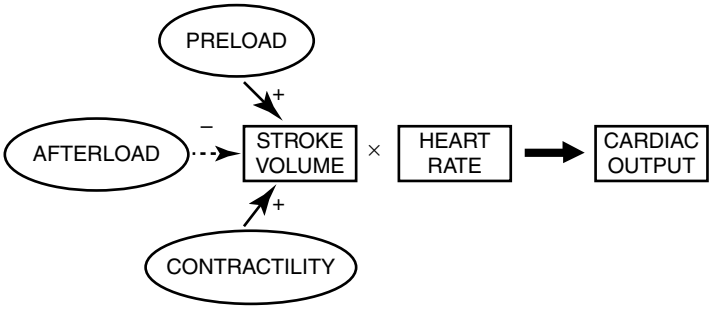

FIGURE 1.3 Preload, contractility, and afterload each impact cardiac output via their effects on stroke volume

of initiation of an action potential and thus overall heart rate. Modulation of automaticity occurs via the autonomic nervous system and may thus be affected by pharmacologic agents acting centrally (dexmedetomidine, clonidine) or those affecting the action potential initiation and propagation at the level of the myocytes (digoxin, beta-blockers). In clinical practice there is often an overlap of direct and autonomic effects with many pharmacologic agents.

1.2.3 Electromechanical Coupling

On a macroscopic level, propagation of the action potential from the high right atrium to the AV node, His-Purkinje system, and finally the ventricular myocardium allows for ordered, coordinated myocardial contraction and relaxation. On a cellular level, this is accomplished by coupling the changes in electrical environment to changes in mechanical activity (myocardial contraction and relaxation) via fluctuations of cytosolic Ca^{++} concentration. As a consequence of depolarization, cytosolic Ca^{++} concentration markedly increases via influx from the cell membrane as well as release of intracellular calcium stores within the sarcoplasmic reticulum. Ca^{++} directly enables the interaction of the contractile elements actin and myosin, the result of which is myofiber

shortening. Just as the process of myocyte contraction is reliant upon Ca^{++}, myocardial relaxation is an *active* process, requiring the expenditure of energy in the form of adenosine triphosphate (ATP) to scavenge Ca^{++} from the cytosol quickly and inhibit continued contraction [2]. The neonatal myocardium has a poorly developed calcium transport process which results in an exaggerated dependence upon extra-cellular calcium concentration to maintain cardiac contractility in neonates. For further detail on the downstream interactions between contractile elements and the process of electromechanical coupling, the reader is referred to selections referenced at the conclusion of this chapter.

1.2.4 Dysrhythmias

While an extensive review of all dysrhythmias is outside the scope of this chapter, a brief overview of the mechanisms of the basic categories of dysrhythmias is provided. On the simplest level, heart rhythm abnormalities can be divided into those that are 'too slow' (bradyarrhythmias) and those that are 'too fast' (tachyarrhythmias). Bradyarrhythmias primarily result from delay or block in conduction of the impulse from the high right atrium to AV node and His-Purkinje system, and most involve disease of the AV nodal tissue [first degree and second degree type I (Wenckebach) heart block] or of the His-Purkinje system [second degree type II (Mobitz) and third degree (complete) heart block]. Bradyarrhythmias may also result from disease of the sinus node (ineffective automaticity), such that no appropriate pacemaker is available to establish a physiologic heart rate. Tachyarrhythmias are more varied in terms of etiologies and can originate from the atria, ventricles, or AV node. However, the mechanism which underlies each can often be categorized as automatic or re-entrant. An automatic tachycardia results from a cell or cluster of cells acquiring abnormal automaticity, such that this region of the heart spontaneously depolarizes more rapidly than the sinus node, establishing the heart rate at greater than physiologic rates. The most common examples of automatic

tachycardias include ectopic atrial tachycardia, multifocal atrial tachycardia, and junctional ectopic tachycardia. Automatic tachycardias tend to exhibit a gradual 'warm-up' and/or 'cool-down' phases at onset and termination, and despite the overall rapid rate, there is subtle variability in heart rate over time. In contrast, re-entrant tachycardias result from additional, non-physiologic electrical pathways that allow conduction of an impulse to back to a region of the heart that has repolarized following the earlier conduction of the *same* impulse. Such 'short-circuits' essentially allow the same impulse to recycle itself and lead to successive depolarizations. Re-entrant tachyarrhythmias characteristically have an abrupt onset and termination and a non-varying rate during the tachycardia. The re-entrant circuit may exist exclusively within the atria (atrial flutter), ventricles (ventricular tachycardia), or AV node (AV node re-entrant tachycardia), or may be comprised of tissue that connects the atria, AV node, and/or ventricles (accessory pathway tachycardia).

1.3 Cardiovascular Physiology

Care of the patient with hemodynamic derangements remains rooted in basic physiologic concepts – preload, contractility, and afterload – first described in the late 19th century. These factors directly impact stroke volume, which along with heart rate are the key determinants of cardiac output (Fig. 1.4).

1.3.1 Preload

Preload refers to the ventricle's intrinsic ability, within a physiologic range, to alter the force of contraction based on the degree of ventricular filling just prior to contraction (end-diastolic volume/fiber length). The greater the end-diastolic volume, and thus ventricular myofiber stretch, the greater the force of contraction. This relationship of increasingly forceful contraction with increasing preload continues to correlate until the myocardial fibers are stretched to a point