Physiopathology of the Cardiovascular System

Joseph S. Alpert, M.D.

Physiopathology of the Cardiovascular System

Joseph S. Alpert, M.D.
Professor of Medicine and Director,
Division of Cardiovascular Medicine,
University of Massachusetts Medical School,
Worcester, Massachusetts

Foreword by
DeWitt S. Goodman, M.D., Series Editor
Professor of Medicine and Chief,
Division of Metabolism and Nutrition,
Columbia University College of Physicians
and Surgeons, New York

Little, Brown and Company Boston/Toronto

First Edition

Library of Congress Catalog Card No. 83-81378

ISBN 0-316-03504-1

Printed in the United States of America

HAL

Notice

The indications and dosages of all drugs in this book have been recommended in the medical literature to conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the Food and Drug Administration for use in the diseases and dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

Contributors

Andrew J. Cohen, M.D.
Assistant Professor of Medicine and Physiology, Division of Renal Medicine, University of Massachusetts Medical School; Acting Chief, Division of Renal Medicine, University of Massachusetts Medical Center, Worcester, Massachusetts
Chapter 9

Robert J. Goldberg, Ph.D.
Assistant Professor of Medicine and Epidemiology, Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts
Chapter 4

Joel M. Gore, M.D.
Assistant Professor of Medicine, University of Massachusetts Medical School; Associate Director, Coronary Care Unit, University of Massachusetts Medical Center, Worcester, Massachusetts
Chapter 4

Roger B. Hickler, M.D.
Lamar Soutter Distinguished Professor of Medicine and Director, Division of Geriatric Medicine, University of Massachusetts Medical School; Director, Division of Geriatric Medicine, University of Massachusetts Hospital, Worcester, Massachusetts
Chapter 10

Richard S. Irwin, M.D.
Associate Professor of Medicine, University of Massachusetts Medical School; Director, Division of Pulmonary Medicine, University of Massachusetts Medical Center, Worcester, Massachusetts
Chapter 8

Emil R. Smith, Ph.D
Associate Professor of Pharmacology, University of Massachusetts Medical School, Worcester, Massachusetts
Chapter 14

Carl Teplitz, M.D.
Professor of Medical Sciences, Division of Biology and Medicine, Brown University Program in Medicine; Director, Division of Surgical Pathology, Rhode Island Hospital, Providence, Rhode Island
Chapter 8

Foreword by the Series Editor

The goal of the Little, Brown Physiopathology Series is to provide textbooks that describe and illustrate the scientific foundations underlying the current practice of clinical medicine. The concept of this series developed from curricular changes that occurred in American medical schools during the early 1970s. These changes resulted in increased emphasis in the teaching of normal and abnormal human biology, usually to second-year medical students, as the bridge between the traditional basic science courses and the clinical clerkships. A need existed for textbooks in this "bridge" area; this series was designed to address this need.

Each book in this series deals with a different medical subspecialty. Each book aims to provide a clear and solid discussion of the basic scientific concepts and principles on which the clinical subspecialty is built. This discussion includes selected aspects of normal and abnormal physiology, biochemistry, morphology, cell biology, and so on, as appropriate. The discussion of the basic science material is usually presented in the context of the approach to the study of clinical material. Major clinical phenomena and disease processes are, in turn, analyzed in terms of normal and abnormal human biology. Thus, the books show how the art of modern clinical medicine involves firm scientific knowledge and the scientific approach in order to be effective.

Although designed for second-year medical students, this series will, we hope, be useful as well to more advanced students and practitioners as a readable and up-to-date review of the scientific basis for clinical practice in a given area.

DeWitt S. Goodman

Preface

Nothing in clinical medicine is as exciting as that moment when one understands the pathophysiology of the patient's condition and knows specific therapy that will reverse or impede the progress of that pathophysiologic process. Based on a solid understanding of both normal physiology and pathology, the pathophysiologic sequence of a particular disease is the key to understanding its natural history, its method of presentation, and the therapeutic approaches to its management.

I have tried to present in this short text a clear and concise overview of the pathophysiology of most of the common cardiovascular diseases. The myocardium is limited in the number of responses that it can make to a variety of pathological conditions: mechanical difficulties may arise resulting in heart failure, or electrical abnormalities may appear resulting in arrhythmias. The first thirteen chapters deal with heart failure and those conditions that commonly produce heart failure. Underlying renal and respiratory mechanisms in cardiac failure are discussed along with myocardial aspects. Chapter 14 is a discussion of cardiac electrical disturbances, the resultant arrhythmias, and their therapy. The last two chapters deal with peripheral cardiovascular disease and pulmonary embolism. There are three appendixes, the first of which briefly details clinical invasive and noninvasive techniques for quantitating myocardial contractile function. The second appendix is a series of questions, typical of the sort commonly given on national board examinations, dealing with the material presented in the text; the third appendix provides the answers to these questions. I believe that any student who reads this text carefully will come away with a firm understanding of the basic principles of cardiovascular pathophysiology so essential in the appropriate management of patients with these disorders.

Many individuals have aided me immeasurably in the preparation of this text. I would particularly like to acknowledge the secretarial assistance of Mrs. Marilyn Parks and Word Processing of Worcester. A number of the ideas and concepts expressed in this text were arrived at following discussions with my colleagues here at the University of Massachusetts Medical Center. The constant intelligent and incisive criticism of Lin Richter Paterson, former Medical Editor of Little,

Brown and Company, is appreciated with this present text as with previous work. Finally, I would like to acknowledge the constant and vital psychological and physical support of my family: my wife Helle, my daughter Eva, and my son Niel.

J. S. A.

Contents

1 : The Failing Myocardium

All patients with symptomatic cardiovascular disease have in one sense or another developed "heart failure." That is, one of the myriad functions of the cardiovascular system has failed. However, this broad definition does not capture the way in which the term *heart failure* is generally used by clinicians. Rather, physicians who use the term *heart failure* are actually referring to a set of clinical signs and symptoms that usually occur as a result of inadequate cardiac function. Abnormal function of a number of different cardiac processes can result in the clinical syndrome of heart failure. Most of these processes have a single common theme—inadequate myocardial function. This chapter will briefly review normal myocardial function as it relates to disordered myocardial performance in heart failure. Experimental and clinical cardiac dysfunction in heart failure as well as a variety of compensatory mechanisms will be discussed.

Regulation of Cardiac Performance

The physiology of cardiac muscular performance has been extensively studied in recent years. The reader should review previously studied materials regarding the regulation of the normal circulation. A number of excellent references dealing with normal circulatory physiology are provided in the Suggested Readings for this chapter.* A brief and simplified review of normal cardiovascular function follows.

Cardiac performance depends on three variables: preload, afterload, and intrinsic myocardial contractility (Fig. 1-1). *Preload* is defined as the tension or stretch of the myocardial fibers before contraction begins. The well-known Starling, or length-tension, relationship for myocardial fibers states that increased stretch or preload on these fibers results in increased shortening of performance (Fig. 1-2). It is helpful to think of this relationship as the "rubber band law" of cardiac performance: the more you stretch the rubber band (up to the point of overstretching or breakage), the more vigorously it snaps back. In the intact heart, preload is determined by the extent of filling of the ventricles. Preload measurements commonly used in the clinical setting include the pressure and volume of the ventricle at end-diastole.

*Particularly excellent is Chapter 9 in E. Braunwald et al (1976).

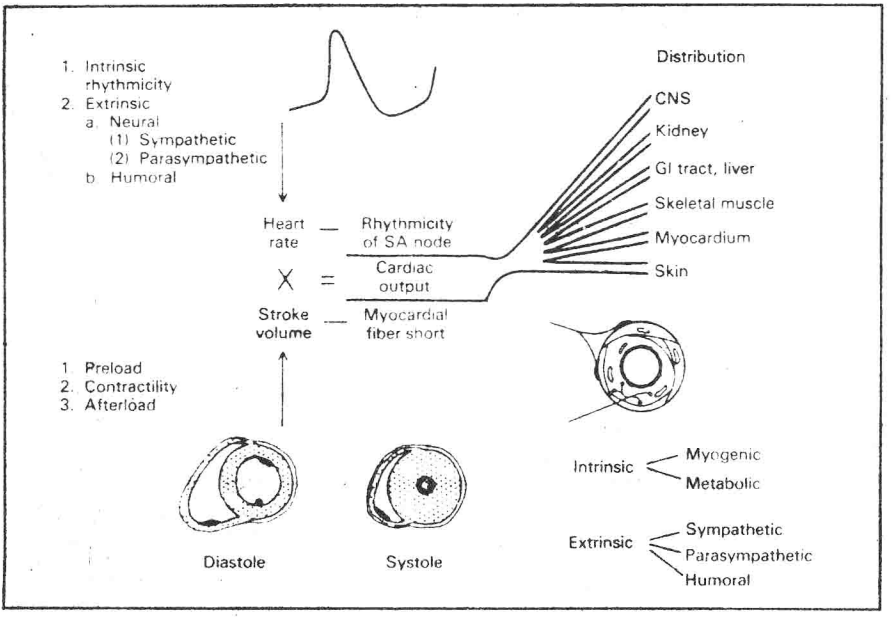

Fig. 1-1 : Schematic representation of the circulation. Cardiac output and its two determinants, heart rate and stroke volume, are central to circulatory control. Stroke volume is determined by preload, contractility, and afterload; heart rate is determined by intrinsic rhythmicity and extrinsic factors both neural and humoral. The cardiac output is distributed to a number of vascular beds. Regulation of the distribution of cardiac output depends on intrinsic and extrinsic influences on the arterioles. (From Braunwald E: Regulation of the circulation. *N Engl J Med* 290:1124–1129, 1420–1425, 1974, with permission of the author and publisher.)

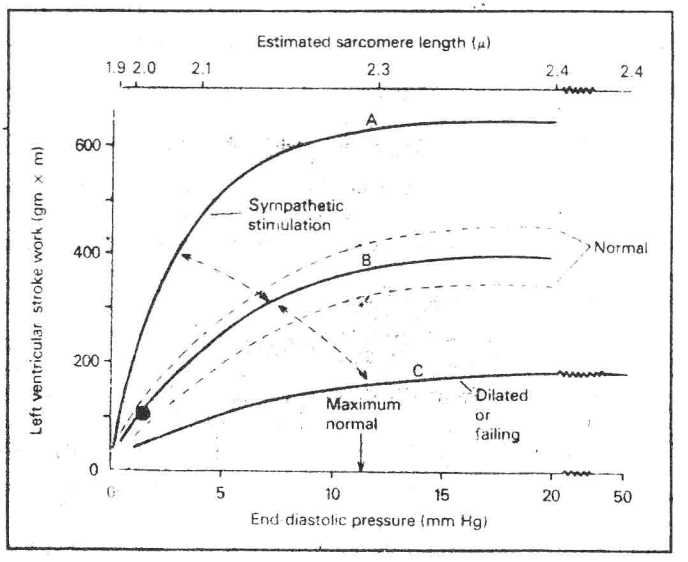

Fig. 1-2 : The cardiac length-tension or Starling relationship. Any increase in preload or resting tension (up to a point) results in an increase in cardiac performance. Thus, increasing ventricular volume results in increasing stroke volume. Curve B is a Starling curve from a normal ventricle. Curve A is from a ventricle with increased myocardial contractility and Curve C is from a ventricle with depressed myocardial contractility.

Afterload is defined as the tension in the myocardium during active contraction. This tension is determined by the resistance against which the myocardium is contracting. Thus, afterload is the work load facing the contracting myocardium. In the intact heart, afterload measurements commonly employed include ventricular systolic wall tension and ventricular systolic pressure.

Intrinsic myocardial contractility is the most difficult property of cardiac function to define. This feature of myocardial function relates to the intrinsic vigor or "oomph" of contraction of the myocardial fibers. Despite long-standing (and continuing) efforts to arrive at an ideal characterization of intrinsic myocardial contractility, no agreement has been reached on this entity. A number of variables have been suggested as truly reflecting intrinsic myocardial contractility (see Appendix A), and have been measured in clinical settings. For example, a number of measurements have been derived from recordings of the isovolumic phase of ventricular systole (rate of rise of isovolumic systolic pressure or dp/dt; maximum velocity of contraction or rate of pressure rise [V_{max}]). Unfortunately, these variables are not determined by intrinsic myocardial contractility alone, as preload and afterload exert some influence on them. Other contractility indices have been determined from analyses of ventricular wall motion obtained at the time of cardiac catheterization (see Appendix A). Variables such as ejection fraction (stroke volume/end-diastolic volume) and velocity of circumferential fiber shortening (V_{cf}) are derived in this manner. As with the indices derived from isovolumic systolic pressure recordings, ejection fraction and V_{cf} (so-called ejection phase indices) are also influenced by preload and afterload. Changes in myocardial contractility can also be demonstrated by constructing serial Starling curves. Thus, an increased myocardial inotropic state results in a movement of the Starling curve upward and to the left (Fig. 1-2). Depressed myocardial contractility results in movement of the Starling curve downward and to the right (Fig. 1-2).

None of the available measurements of myocardial contractility reflect perfectly the intrinsic state of myocardial contractility free from the influences of preload and afterload. On the other hand, each of the suggested indices reflects myocardial contractility at least in part, and most studies dealing with the state of myocardial contractility in the failing myocardium employ a number of different variables in the hope that abnormality in several of these measurements will be more meaningful than abnormality in a solitary index.

A large number of factors are capable of increasing (positively inotropic) or decreasing (negatively inotropic) myocardial contractility. As noted in Fig. 1-3, autonomic nervous stimulation, circulating catecholamines, acid-base disturbances, hypoxia, and a variety of other conditions and substances can alter myocardial contractile states.

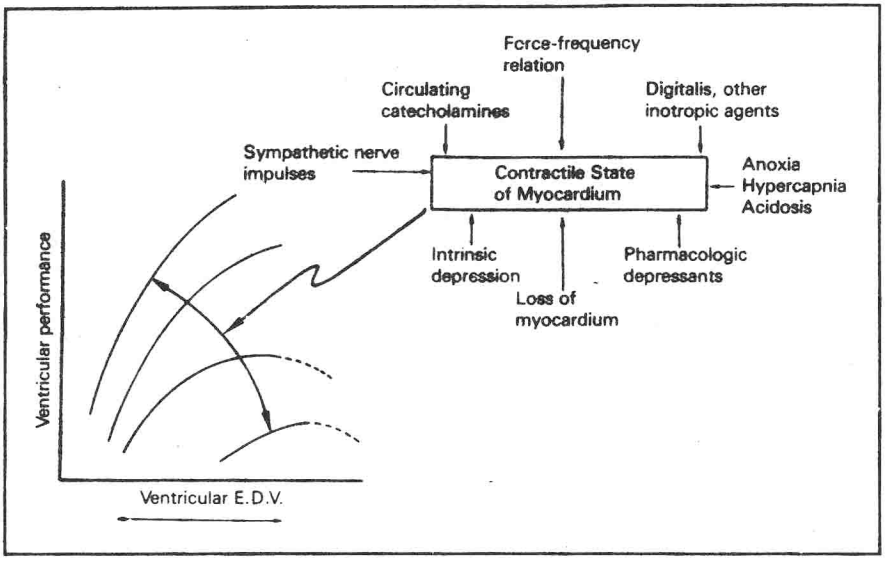

Fig. 1-3 : Factors that influence myocardial contractility. At the upper right are depicted a number of common factors that increase or decrease myocardial contractility. At the lower left are depicted the family of Starling curves that result from various levels of myocardial contractility. E.D.V. = ventricular end-diastolic volume, a measure of ventricular preload. (From Braunwald E, Ross J Jr, Sonnenblick, EH: *Mechanisms of Contraction of the Normal and Failing Heart.* Boston, Little, Brown, 1976, with permission of the authors and publisher.)

Cardiac output is determined by the product of heart rate times stroke volume. The three major variables just discussed (preload, afterload, and contractility) determine stroke volume. Heart rate is determined by properties of the cardiac cells themselves as well as by extrinsically acting influences, e.g., sympathetic and parasympathetic nerve stimulation and circulating catecholamine stimulation (Fig. 1-1). Cardiac output, systemic arterial pressure, and peripheral vascular resistance are related by the circulatory version of Ohm's law ($E = IR$), pressure = cardiac output $\times$ resistance. A number of factors affect peripheral vascular resistance. Metabolic by-products, or metabolites, relax vascular smooth muscle thereby producing vasodilation (Fig. 1-4). Intrinsic properties of vascular smooth muscle (myogenic factors) as well as extrinsic influences such as autonomic nerve stimulation and circulating catecholamines dilate or constrict arterioles, the major site of peripheral vascular resistance. Autonomic nerve stimulation and circulating catecholamines determine the extent to which the capacitance or storage section of the cardiovascular system, the veins, are dilated or constricted. Changes in venous capacity, in turn, result in alterations in venous return to the heart. Venous return, of course, determines preload, thereby effecting changes in stroke volume (Fig. 1-4). A number of other factors also

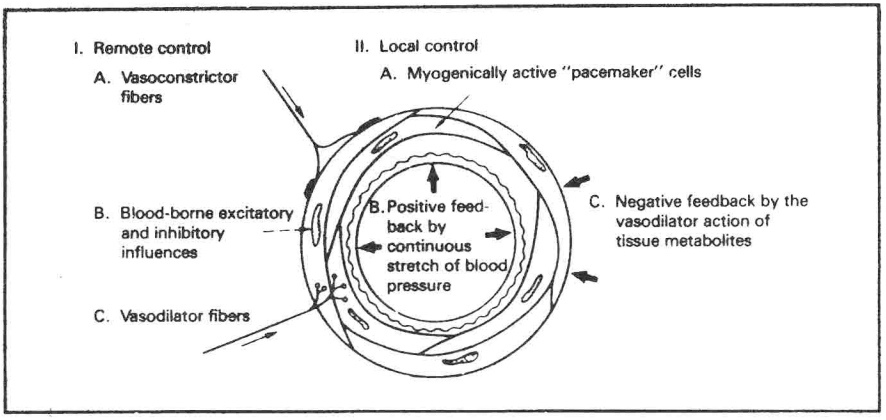

Fig. 1-4 : Factors that determine resistance of arterioles. Three local factors affect vascular smooth muscle tone (and hence vasoconstriction or vasodilatation): (1) smooth muscle pacemaker cells, (2) stretch on vascular smooth muscle from the level of the blood pressure, and (3) vasodilator metabolites. Distant factors may also affect vascular smooth muscle, e.g., sympathetic neural activity (vasoconstrictor and vasodilator fibers) and humoral influences such as catecholamines and hormones. (From Folkow B, Neil E: Principles of vascular control, in Folkow B, Neil E: *Circulation*. New York, Oxford University Press, 1971, chap. 16, pp 285–306, with permission of the authors and publisher.)

contribute to preload or the precontractile stretch of the myocardium (Fig. 1-5).

An understanding of the operation and integration of all of the controlling influences of the cardiovascular system can best be gained by observing what happens to the cardiovascular system during exercise. When exercise commences, local metabolites and sympathetic nerve stimulation (via beta-adrenergic vasodilator fibers) produce arteriolar vasodilatation in exercising skeletal muscles. Consequently, blood flow *increases* remarkably in these exercising muscles. At the same time that vasodilatation is occurring in exercising muscles, sympathetic nervous stimulation (via alpha-adrenergic vasoconstrictor fibers) produces vasoconstriction with resultant *decreases* in blood flow in a variety of other organ systems (skin, nonexercising muscle, kidneys, splanchnic bed). Beta-adrenergic stimulation of the heart results in increases in heart rate and myocardial contractility. The exercising muscles milk venous blood back towards the heart (the so-called muscle pump) thereby increasing venous return and preload. All of these influences on the heart cause an increase in cardiac output, an essential part of the circulatory system's response to exercise. The end result of these regulatory changes in cardiovascular function is a graded increase in cardiac output with increasing levels of exertion. The increased blood flow emanating from the left ventricle is distributed to the exercising muscles in order to satisfy

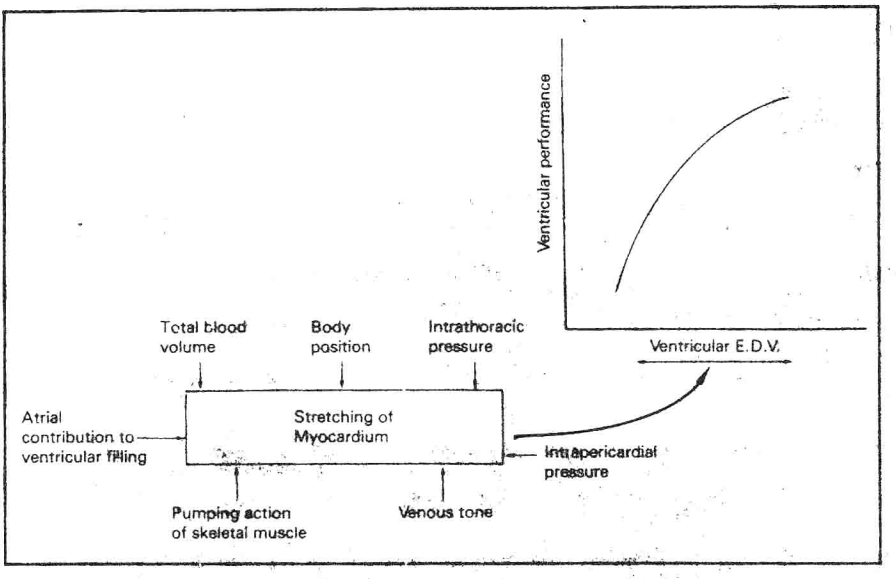

Fig. 1-5 : Factors that influence myocardial preload or stretching. At the lower left are depicted a number of common factors that increase or decrease preload. At the upper right is depicted a Starling curve that results from various levels of ventricular preload. E.D.V. = ventricular end-diastolic volume, a measure of ventricular preload. (From Braunwald E, Ross J Jr, Sonnenblick, EH: *Mechanisms of Contraction of the Normal and Failing Heart*. Boston, Little, Brown, 1976, with permission of the authors and publisher.)

increased demand for oxygen and nutrients in these skeletal muscles.

Diastolic Cardiac Function

So far we have discussed only systolic function of the heart. A variety of factors influence the diastolic behavior of the myocardium, also known as *compliance*. The compliance of myocardial tissue is inversely related to its stiffness. Thus, stiff, inelastic myocardium is said to be noncompliant or reduced in compliance. Pressure and volume in the ventricles are exponentially related during diastole (Fig. 1-6). Thus, as diastolic volume increases there is initially only a modest increase in diastolic ventricular pressure. At higher levels of ventricular distension, however, the rate of rise of diastolic pressure increases. In this manner, small increases in volume in a distended ventricle can result in larger increases in pressure (Fig. 1-6). A number of conditions can alter ventricular compliance (Fig. 1-1, Table 1-1). Most pathologic states decrease ventricular compliance; a minority of conditions increase compliance (Table 1-1). Just as with Starling performance curves, an individual ventricle may demonstrate a whole family of differing diastolic pressure-volume curves under a variety of influences (hypoxia, hypothermia, infarction).

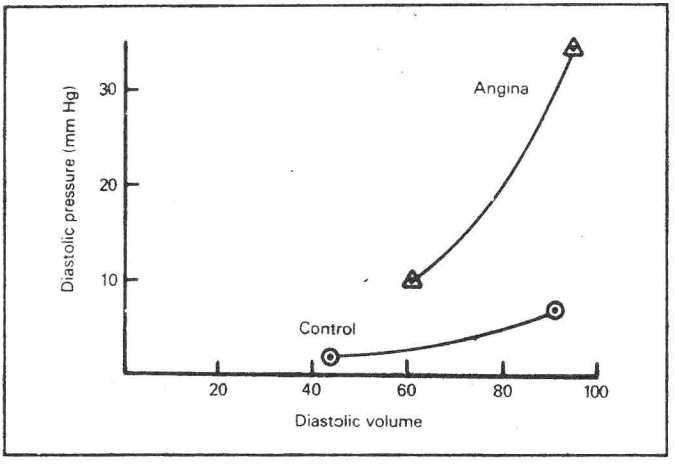

Fig. 1-6 : Effect of ischemia on ventricular compliance. Left ventricular diastolic pressure-volume curves are shown for the same patient during a control period and during an episode of myocardial ischemia. During ischemia, there are remarkable increases in end-diastolic pressure but only minimal increases in end-diastolic volume demonstrating a large decrease in ventricular diastolic compliance (increased myocardial stiffness) during ischemia. (From Gaasch WH et al: Left ventricular compliance: Mechanisms and clinical implications. *Am J Cardiol* 38:645–653, 1976, with permission of the authors and publisher.)

Alterations in Cardiac Function in Heart Failure

The term *heart failure*, or more often, *congestive heart failure*, is often loosely used in clinical settings. Clinical practice would benefit from more precise usage of such terms. In short, heart failure is a state in which abnormal cardiac function results in inadequate pumping of blood to metabolizing tissues. Note that this definition does not imply that any particular aspect of cardiac function is more abnormal than any other. Indeed, a variety of cardiac conditions can and do produce this abnormality in cardiac function. In addition, this definition of the term *heart failure* emphasizes the imbalance between cardiac pumping action and peripheral *demand*.

Contractility in the Failing Myocardium

There can be little doubt that myocardial contractility is abnormally depressed in the presence of heart failure. A number of experimental animal models of heart failure have been carefully studied. One of

Table 1-1 : Causes of alterations in ventricular compliance

Decreased compliance	Increased compliance
Ischemia	Earliest phase of myocardial infarction
Healing or healed myocardial infarction	Chronic aortic regurgitation
Hypertrophy	
Fibrosis	
Amyloid heart disease	
Constrictive pericarditis	
Hypothermia	

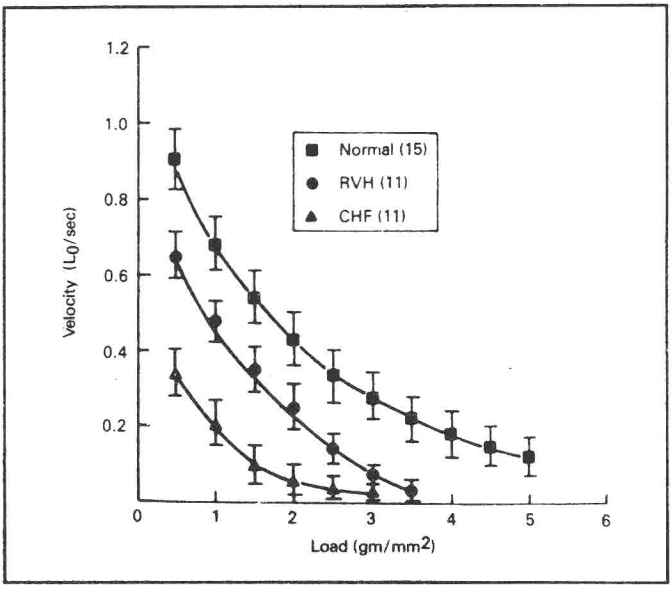

Fig. 1-7 : Effect of hypertrophy and heart failure on myocardial contractility. Force-velocity curves from three groups of cat papillary muscles. Force-velocity curves are one measure of myocardial contractility. Papillary muscles were obtained from cats with experimental right ventricular hypertrophy (RVH) and heart failure (CHF). Average values ± 1 standard error of the mean are given for each point. Note depressed myocardial function in hypertrophied and failing myocardium. (From Spann JF Jr et al: Contractile state of cardiac muscle obtained from cats with experimentally produced ventricular hypertrophy and heart failure. *Circ Res* 21:341, 1967, with permission of the authors and publisher.)

the most popular animal models of heart failure is that of pulmonary stenosis with or without tricuspid regurgitation. In such animals, the pulmonary artery is constricted by a surgical ligature. The tricuspid valve can be surgically damaged at the same time, thereby producing a regurgitant valve. These animals develop right ventricular failure. Examination of the contractile function of isolated pieces of right ventricular muscle from such animals demonstrates markedly reduced values for a variety of contractility indices (Fig. 1-7). Increments in contractility indices secondary to positive inotropic agents (for example, epinephrine) are also reduced in myocardial samples from animals with experimentally induced heart failure. Electron microscopic studies of myocardial samples from heart failure animals reveal no abnormality in structure, implying that derangements such as overstretching are not the cause of depressed myocardial contractility. Similar results, i.e., depressed myocardial contractility despite normal ultrastructural appearance, have been demonstrated in a variety of animal models of heart failure as well as in myocardial samples taken at the time of surgery from patients with heart failure. It is of