Copyrighted Material

LANGE PHYSIOLOGY SERIES

Cardiovascular Physiology

LANGE

David E. Mohrman
Lois Jane Heller

fifth edition

Copyrighted Material

Preface

This text is intended to provide students with the core information and concepts necessary to develop a firm understanding of how the intact cardiovascular system operates. Specifically stated learning objectives, key concepts, and study questions for each chapter allow the student to test for mastery of the material presented. This format lends itself to independent study of the basics, which may be supplemented by additional material for individualized or specialized purposes.

We feel strongly that instruction in cardiovascular physiology should give the student not simply a collection of facts but also an understanding of how the intact cardiovascular system operates. Cardiovascular physiology is often a student's first exposure to the operation of a complete organ system, and the student therefore often finds it confusing to deal with the continual interactions that occur among the various system components. Consequently, we have tried to direct our presentation throughout toward the overall operation of the cardiovascular system rather than attempting to present all available facts.

The changes and additions to this sixth edition are the result of several factors, including new research findings, our own experience in using the previous editions, and helpful comments and criticisms from colleagues and students. For example, we have added a new section in Chapter 8 specifically dealing with overall system hemodynamics. This section is aimed at better explaining how the various components of the cardiovascular circuit interact in the operation of the intact system. As in previous revisions, we have tried to improve the usefulness of the text from the student's perspective. That is, we strive for an interesting, logically arranged text that makes the complex cardiovascular system understandable to the reader. To that end, we have done some rearranging and rewriting, improved and added figures, and updated study questions.

We wish to express our sincere thanks to all colleagues and students who have supplied us with suggestions for improving this text, and we will welcome your comments on and criticisms of this sixth edition.

David E. Mohrman, PhD
Lois Jane Heller, PhD

McGraw-Hill's ACCESSMedicine

Close Window

Copyright Information

Cardiovascular Physiology, Sixth Edition

Copyright © 2006, 2003, 1997, 1991, 1986, 1981 by The McGraw-Hill Companies, Inc. All rights reserved. Printed in the United States of America. Except as permitted under the United States Copyright Act of 1976, no part of this publication my be reproduced or distributed in any form or by any means, or stored in a data base or retrieval system, without prior written permission of the publisher.

Notice

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

McGraw-Hill's ACCESSMedicine

Close Window

Authors

David E. Mohrman, PhD
Associate Professor, Department of Medical and Molecular Physiology
School of Medicine
University of Minnesota, Duluth

Lois Jane Heller, PhD
Professor, Department of Medical and Molecular Physiology
School of Medicine
University of Minnesota, Duluth

McGraw-Hill's ACCESSMedicine

Print Close Window

Note: Large images and tables on this page may necessitate printing in landscape mode.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.

OBJECTIVES

The student understands the homeostatic role of the cardiovascular system, the basic principles of cardiovascular transport, and the basic structure and function of the components of the system.

- *Defines homeostasis.*
- *Identifies the major body fluid compartments and states the approximate volume of each.*
- *Lists two conditions, provided by the cardiovascular system that are essential for regulating the composition of interstitial fluid (ie, the internal environment).*
- *Diagrams the blood flow pathways between the heart and other major body organs.*
- *States the relationship among blood flow, blood pressure, and vascular resistance.*
- *Predicts the relative changes in flow through a tube caused by changes in tube length, tube radius, fluid viscosity, and pressure difference.*
- *Identifies the chambers and valves of the heart and describes the pathway of blood flow through the heart.*
- *Defines cardiac output.*
- *Describes the pathway of action potential propagation in the heart.*
- *Lists the five factors essential to proper ventricular pumping action.*
- *States the relationship between ventricular filling and cardiac output (Starling's Law of the Heart) and describes its importance in the control of cardiac output.*
- *Identifies the distribution of sympathetic and parasympathetic nerves in the heart and lists the basic effects of these nerves on the heart.*
- *Lists the major different types of vessels in a vascular bed and describes the morphological differences among them.*
- *Describes the basic anatomical features and function of the different vessel types.*
- *Identifies the major mechanisms in vascular control and blood flow distribution.*
- *Describes the basic composition of the fluid and cellular portions of blood.*

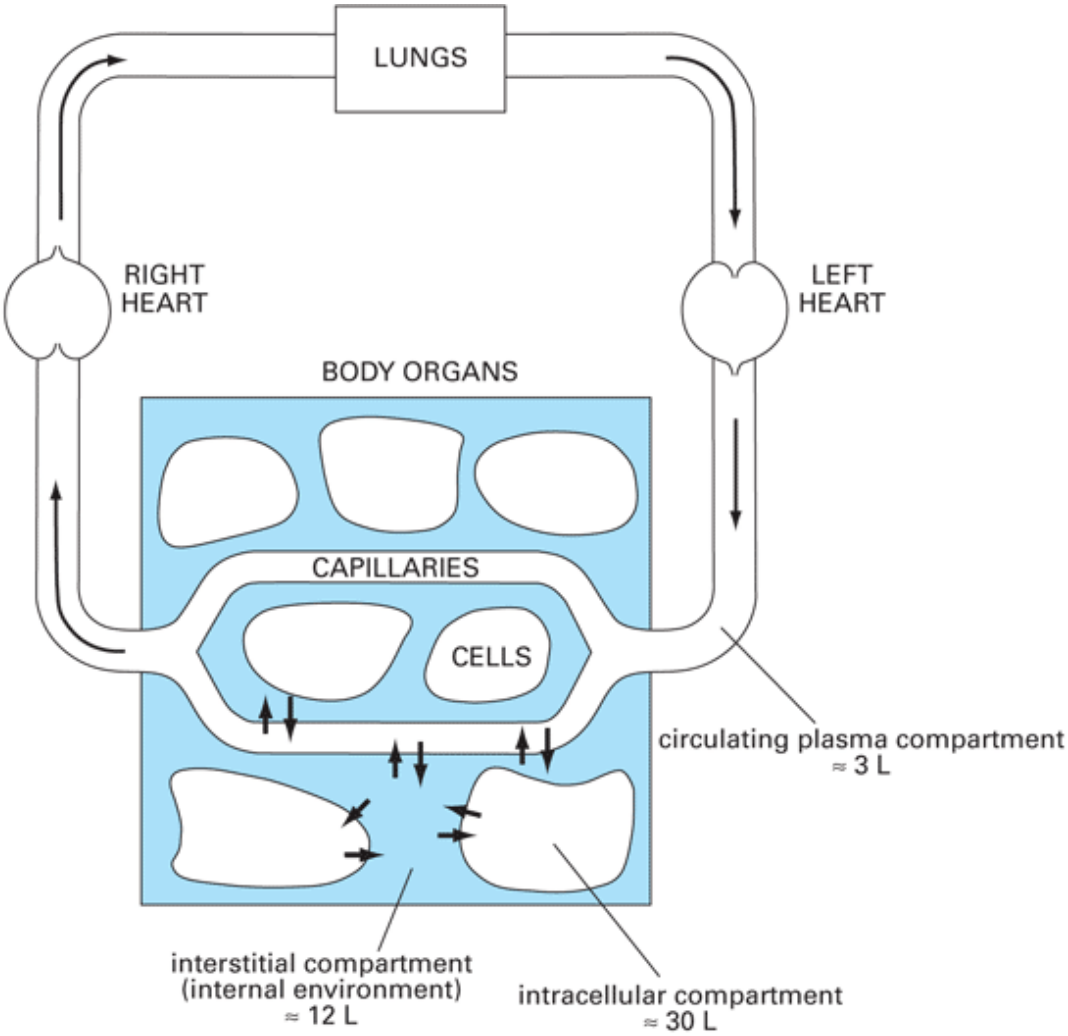
HOMEOSTATIC ROLE OF THE CARDIOVASCULAR SYSTEM

A nineteenth-century French physiologist, Claude Bernard (1813–1878), first recognized that all higher organisms actively and constantly strive to prevent the external environment from upsetting the conditions necessary for life within the organism. Thus the temperature, oxygen concentration, pH, ionic composition, osmolarity, and many other important variables of our *internal environment* are closely controlled. This process of maintaining the "constancy" of our internal environment has come to be known as *homeostasis.* To accomplish this task, an elaborate material transport network, the

cardiovascular system, has evolved.

Three compartments of watery fluids, known collectively as the *total body water,* account for about 60% of body weight. This water is distributed among the *intracellular, interstitial,* and *plasma* compartments, as indicated in Figure 1–1. Note that about two thirds of our body water is contained within cells and communicates with the interstitial fluid across the plasma membranes of cells. Of the fluid that is outside cells (ie, extracellular fluid), only a small amount, the *plasma volume,* circulates within the cardiovascular system. Blood is composed of plasma and roughly an equal volume of formed elements (primarily red cells). The circulating plasma fluid communicates with the interstitial fluid across the walls of small capillary vessels within organs.

Figure 1–1.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Major body fluid compartments with average volumes indicated for a 70-kg human. Total body water is about 60% of body weight.

The interstitial fluid is the immediate environment of individual cells. (It is the "internal environment"

referred to by Bernard.) These cells must draw their nutrients from and release their products into the interstitial fluid. The interstitial fluid cannot, however, be considered a large reservoir for nutrients or a large sink for metabolic products since its volume is less than half that of the cells that it serves.

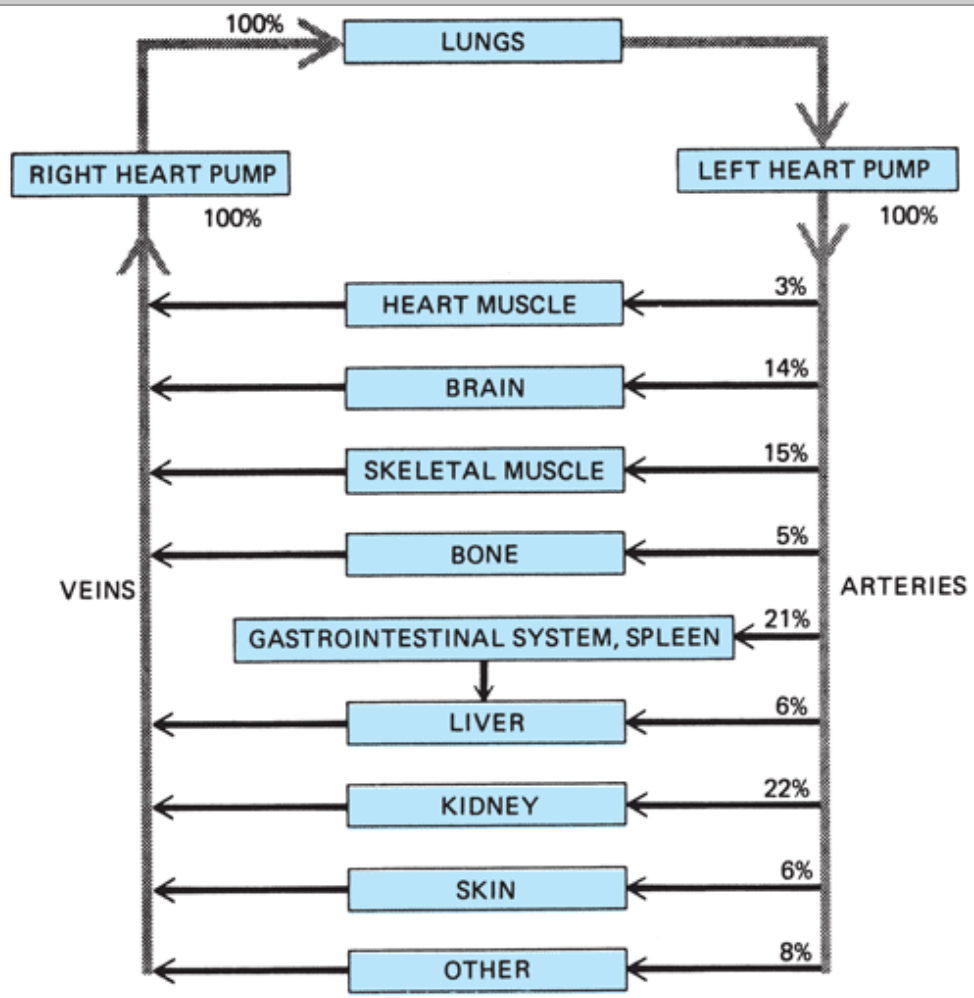
The well-being of individual cells therefore depends heavily on the homeostatic mechanisms that regulate the composition of the interstitial fluid. This task is accomplished by continuously exposing the interstitial fluid to "fresh" circulating plasma fluid.

As blood passes through capillaries, solutes exchange between plasma and interstitial fluid by the process of diffusion. The net result of transcapillary diffusion is always that interstitial fluid tends to take on the composition of the incoming blood. If, for example, potassium ion concentration in the interstitium of a particular skeletal muscle were higher than that in the plasma entering the muscle, potassium would diffuse into the blood as it passed through the muscle's capillaries. Since this removes potassium from the interstitial fluid, interstitial potassium ion concentration would decrease. It would stop decreasing when net movement of potassium into capillaries no longer occurred, ie, when interstitial concentration reached that of incoming plasma.

Two conditions are essential for this circulatory mechanism to effectively control the composition of interstitial fluid: (1) there must be adequate blood flow through the tissue capillaries, and (2) the chemical composition of the incoming (or arterial) blood must be controlled to be that which is optimal in the interstitial fluid. Figure 1–1 shows how the cardiovascular transport system operates to accomplish these tasks. As discussed above, substances are transported between cells and plasma in capillary vessels within organs by the process of diffusion. This transport occurs over extremely small distances because no cell in the body is located farther than about 10 μm from a capillary. Over such microscopic distances, *diffusion* is a very rapid process that can move huge quantities of material. Diffusion, however, is a very poor mechanism by which to move substances from the capillaries of one organ, such as the lungs, to the capillaries of another organ that may be 1 meter or more distant. Consequently, substances are transported between organs by the process of *convection,* by which the substances move along with blood flow simply because they are dissolved or otherwise contained within blood. The relative distances involved in cardiovascular transport are not well illustrated in Figure 1–1. If the figure were drawn to scale with 1 inch representing the distance from capillaries to cells within a calf muscle, the capillaries in the lungs would have to be located about 15 miles away!

The overall functional arrangement of the cardiovascular system is illustrated in Figure 1–2. Since a functional rather than an anatomical viewpoint is expressed in this figure, the heart appears in three places: as the right heart pump, as the left heart pump, and as the heart muscle tissue. It is common practice to view the cardiovascular system as (1) the *pulmonary circulation,* composed of the right heart pump and the lungs, and (2) the *systemic circulation,* in which the left heart pump supplies blood to the systemic organs (all structures except the gas exchange portion of the lungs). The pulmonary and systemic circulations are arranged in series, ie, one after the other. Consequently, the right and left hearts must each pump an identical volume of blood each minute. This amount is called the*cardiac output.* A cardiac output of 5 to 6 L/min is normal for a resting individual.

Figure 1–2.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Cardiovascular circuitry indicating the percentage distribution of cardiac output to various organ systems in a resting individual.

As indicated in Figure 1–2, the systemic organs are functionally arranged in parallel (ie, side by side) within the cardiovascular system. There are two important consequences of this parallel arrangement. First, nearly all systemic organs receive blood of identical composition—that which has just left the lungs and is known as *arterial blood.* Second, the flow through any one of the systemic organs can be controlled independently of the flow through the other organs. Thus, for example, the cardiovascular response to whole body exercise can involve increased blood flow through some organs, decreased blood flow through others, and unchanged blood flow through yet others.

Many of the organs in the body help perform the task of continually reconditioning the blood circulating in the cardiovascular system. Key roles are played by organs, such as the lungs, that communicate with the external environment. As is evident from the arrangement shown in Figure 1–2, any blood that has just passed through a systemic organ returns to the right heart and is pumped through the lungs, where oxygen and carbon dioxide are exchanged. Thus the blood's gas composition is always reconditioned immediately after leaving a systemic organ.

Like the lungs, many of the systemic organs also serve to recondition the composition of blood, although the flow circuitry precludes their doing so each time the blood completes one circuit. The kidneys, for example, continually adjust the electrolyte composition of the blood passing through them. Because the blood conditioned by the kidneys mixes freely with all the circulating blood and because electrolytes and water freely pass through most capillary walls, the kidneys control the electrolyte balance of the entire internal environment. To achieve this, it is necessary that a given unit of blood pass often through the kidneys. In fact, the kidneys (under resting conditions) normally receive about one fifth of the cardiac output. This greatly exceeds the amount of flow that is necessary to supply the nutrient needs of the renal tissue. This situation is common to organs that have a blood-conditioning function.

Blood-conditioning organs can also withstand, at least temporarily, severe reductions of blood flow. Skin, for example, can easily tolerate a large reduction in blood flow when it is necessary to conserve body heat. Most of the large abdominal organs also fall into this category. The reason is simply that because of their blood-conditioning functions, their normal blood flow is far in excess of that necessary to maintain their basal metabolic needs.

The brain, heart muscle, and skeletal muscles typify organs in which blood flows solely to supply the metabolic needs of the tissue. They do not recondition blood for the benefit of any other organ. Flow to brain and heart muscle is normally only slightly greater than that required for their metabolism, and they do not tolerate blood flow interruptions well. Unconsciousness can occur within a few seconds after stoppage of cerebral flow, and permanent brain damage can occur in as little as 4 minutes without flow. Similarly, the heart muscle (myocardium) normally consumes about 75% of the oxygen supplied to it, and the heart's pumping ability begins to deteriorate within beats of a coronary flow interruption. As we shall see later, the task of providing adequate blood flow to the brain and the heart muscle receives a high priority in the overall operation of the cardiovascular system.

THE BASIC PHYSICS OF BLOOD FLOW

As outlined above, the task of maintaining interstitial homeostasis requires that an adequate quantity of blood flow continuously through each of the millions of capillaries in the body. In a resting individual, this adds up to a cardiac output of about 5 L/min (about 80 gallons/h). As people go about their daily lives, the metabolic rates and therefore the blood flow requirements in different organs and regions throughout the body change from moment to moment. Thus, the cardiovascular system must continuously adjust both the magnitude of cardiac output and how that cardiac output is distributed to different parts of the body. One of the most important keys to comprehending how the cardiovascular system operates is a thorough understanding of the relationship among the physical factors that determine the rate of fluid flow through a tube.



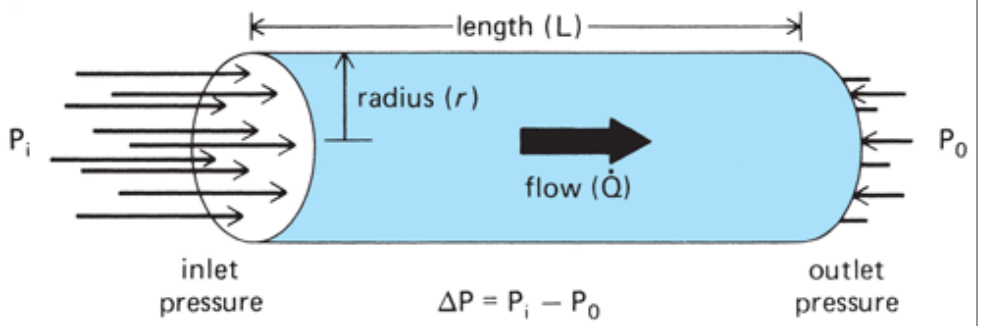
The tube depicted in Figure 1–3 might represent a segment of any vessel in the body. It has a certain length (L) and a certain internal radius (r) through which blood flows. Fluid flows through the tube only when the pressures in the fluid at the inlet and outlet ends (P_i and P_o) are unequal, ie, when there is a pressure difference (ΔP) between the ends. Pressure differences supply the driving force for flow. Because friction develops between moving fluid and the stationary walls of a tube, vessels tend to resist fluid movement through them. This *vascular resistance* is a measure of how difficult it is to make fluid flow through the tube, ie, how much of a pressure difference it takes to cause a certain flow. The all-important relation among flow, pressure difference, and resistance is described by the *basic flow equation* as follows:

$$\text{Flow} = \frac{\text{pressure difference}}{\text{resistance}}$$

$$\dot{Q} = \frac{\Delta P}{R}$$

where $\dot{Q}$ = flow rate (volume/time)
ΔP = pressure difference (mmHg[1])
R = resistance to flow (mmHg × time/volume)

Figure 1–3.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Factors influencing fluid flow through a tube.

The basic flow equation may be applied not only to a single tube but to complex networks of tubes, eg, to the vascular bed of an organ or to the entire systemic system. The flow through the brain, for example, is determined by the difference in pressure between cerebral arteries and veins divided by the overall resistance to flow through the vessels in the cerebral vascular bed. It should be evident from the basic flow equation that there are only two ways in which blood flow through any organ can be changed: (1) by changing the pressure difference across its vascular bed, or (2) by changing its vascular resistance. Most often, it is changes in an organ's vascular resistance that cause the flow through the organ to change.

From the work of the French physician Jean Leonard Marie Poiseuille (1799–1869), who performed experiments on fluid flow through small glass capillary tubes, it is known that the resistance to flow through a cylindrical tube depends on several factors, including the radius and length of the tube and the viscosity of the fluid flowing through it. These factors influence resistance to flow as follows:

$$R = \frac{8L\eta}{\pi r^4}$$

where r = inside radius of the tube
L = tube length
η = fluid viscosity

Note that the internal radius of the tube is raised to the fourth power in this equation. Thus even small changes in the internal radius of a tube have a very large influence on its resistance to flow. For example, halving the inside radius of a tube will increase its resistance to flow by 16-fold.

The preceding equations may be combined into one expression known as the *Poiseuille equation,* which includes all the terms that influence flow through a cylindrical vessel.[2]

$$\dot{Q} = \Delta P \frac{\pi r^4}{8L\eta}$$

Again note that flow occurs only when a pressure difference exists. It is not surprising then that arterial blood pressure is an extremely important and carefully regulated cardiovascular variable. Also note once again that, for any given pressure difference, tube radius has a very large influence on the flow through a tube. It is logical, therefore, that organ blood flows are regulated primarily through changes in the radius of vessels within organs. Whereas vessel length and blood viscosity are factors that influence vascular resistance, they are not variables that can be easily manipulated for the purpose of moment-to-moment control of blood flow.

In regard to the overall cardiovascular system as depicted in Figures 1–1 and 1–2, one can conclude that blood flows through the vessels within an organ only because a pressure difference exists between the blood in the arteries supplying the organ and the veins draining it. The primary job of the heart pump is to keep the pressure within arteries higher than that within veins. Normally, the average pressure in systemic arteries is near 100 mmHg, and the average pressure in systemic veins is near 0 mmHg.

Therefore, because the pressure difference (∆*P*) is identical across all systemic organs, cardiac output is distributed among the various systemic organs solely on the basis of their individual resistances to flow. Because blood flows along the path of least resistance, organs with relatively low resistance receive relatively high flow.

[1] Although pressure is most correctly expressed in units of force per unit area, it is customary to express pressures within the cardiovascular system in millimeters of mercury. For example, mean arterial pressure may be said to be 100 mmHg because it is the same as the pressure existing at the bottom of a mercury column 100 mm high. All cardiovascular pressures are expressed relative to atmospheric pressure, which is approximately 760 mmHg.

[2] Poiseuille's equation properly applies only to a homogeneous fluid flowing through rigid nontapered tubes with a certain flow pattern called laminar flow. Although not all these conditions are rigidly met for any vessel within the body, the approximation is close enough to permit general conclusions to be drawn from Poiseuille's equation.

THE HEART

Pumping Action

The heart lies in the center of the thoracic cavity suspended by its attachments to the great vessels within a thin fibrous sac called the *pericardium.* A small amount of fluid in the sac lubricates the surface of the heart and allows it to move freely during contraction and relaxation. Blood flow through all organs is passive and occurs only because arterial pressure is kept higher than venous pressure by the pumping action of the heart. The right heart pump provides the energy necessary to move blood through the pulmonary vessels, and the left heart pump provides the energy to move blood through the systemic organs.

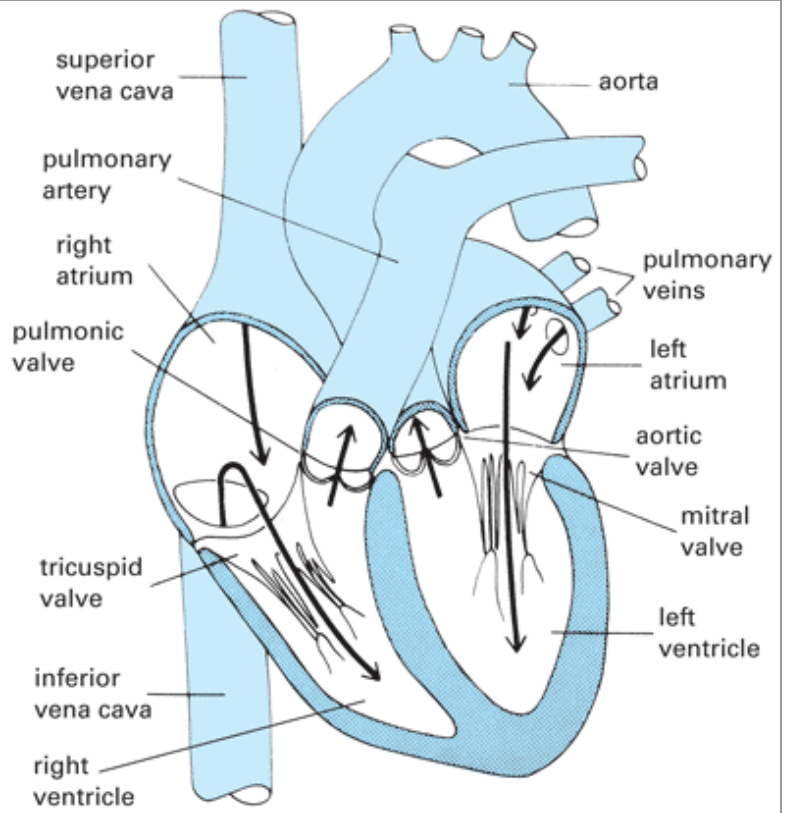
The amount of blood from each ventricle pumped/minute (the *cardiac output,* CO) depends on the volume of blood ejected per beat (the *stroke volume,* SV) and the number of heart beats per minute (the*heart rate,* HR) as follows:

$$CO = SV \times HR$$
$$\text{volume/minute} = \text{volume/beat} \times \text{beats/minute}$$

It should be evident from this relationship that all influences on cardiac output must act by changing either the heart rate or the stroke volume. These influences will be described in detail in subsequent chapters.

The pathway of blood flow through the chambers of the heart is indicated in Figure 1–4. Venous blood returns from the systemic organs to the right atrium via the superior and inferior venae cavae. It passes through the *tricuspid valve* into the right ventricle and from there is pumped through the *pulmonic valve* into the pulmonary circulation via the pulmonary arteries. Oxygenated pulmonary venous blood flows in pulmonary veins to the left atrium and passes through the *mitral valve* into the left ventricle. From there it is pumped through the *aortic valve* into the aorta to be distributed to the systemic organs.

Figure 1–4.



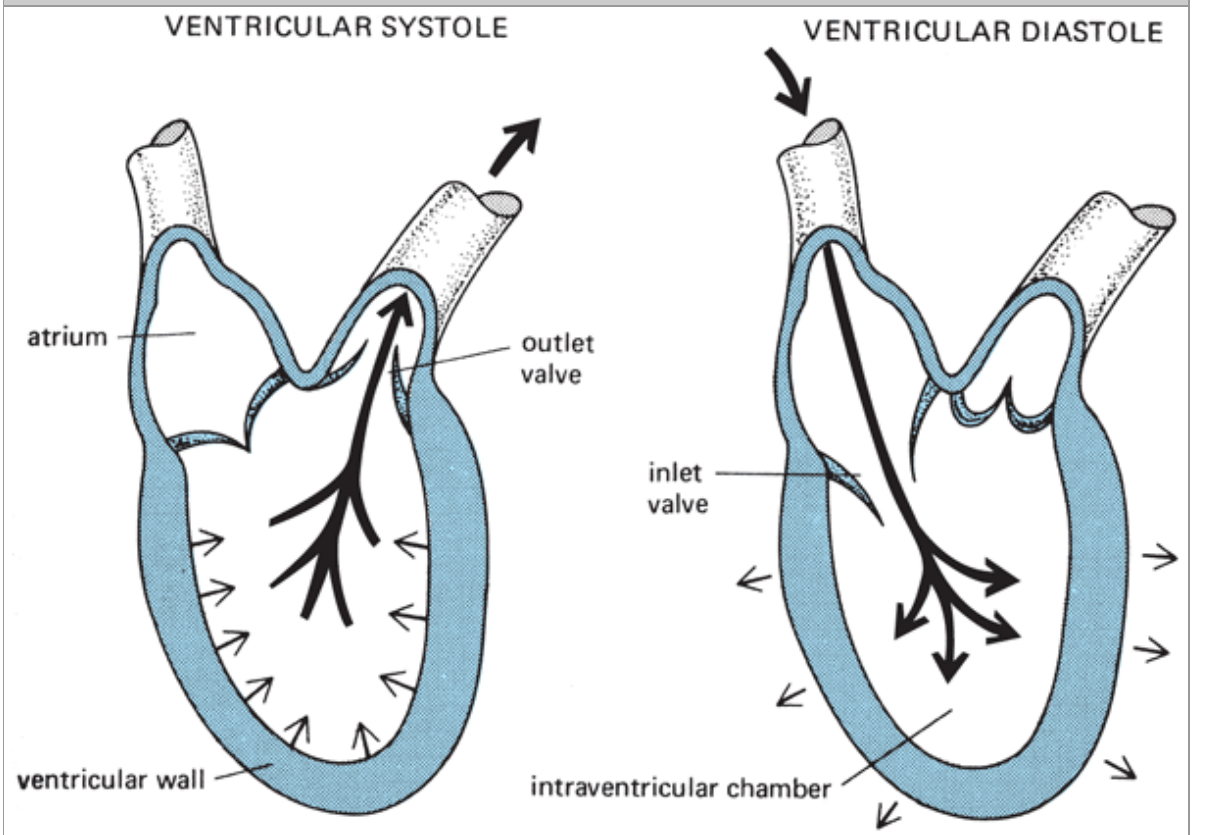
Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Pathway of blood flow through the heart.

Although the gross anatomy of the right heart pump is somewhat different from that of the left heart pump, the pumping principles are identical. Each pump consists of a ventricle, which is a closed chamber surrounded by a muscular wall, as illustrated in Figure 1–5. The valves are structurally designed to allow flow in only one direction and passively open and close in response to the direction

of the pressure differences across them. Ventricular pumping action occurs because the volume of the intraventricular chamber is cyclically changed by rhythmic and synchronized contraction and relaxation of the individual cardiac muscle cells that lie in a circumferential orientation within the ventricular wall.

Figure 1–5.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Ventricular pumping action.

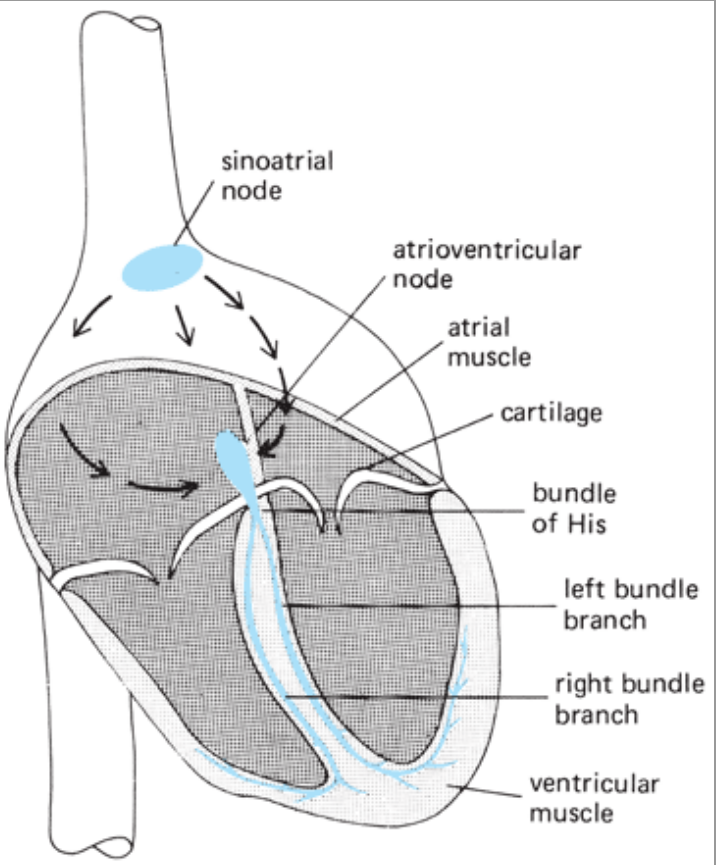
When the ventricular muscle cells are contracting, they generate a circumferential tension in the ventricular walls that causes the pressure within the chamber to increase. As soon as the ventricular pressure exceeds the pressure in the pulmonary artery (right pump) or aorta (left pump), blood is forced out of the chamber through the outlet valve as shown in Figure 1–5. This phase of the cardiac cycle during which the ventricular muscle cells are contracting is called *systole.* Because the pressure is higher in the ventricle than in the atrium during systole, the inlet or atrioventricular (AV) valve is closed. When the ventricular muscle cells relax, the pressure in the ventricle falls below that in the atrium, the AV valve opens, and the ventricle refills with blood as shown on the right of Figure 1–5. This portion of the cardiac cycle is called *diastole.* The outlet valve is closed during diastole because arterial pressure is greater than intraventricular pressure. After the period of diastolic filling, the systolic phase of a new cardiac cycle is initiated.

Excitation

Efficient pumping action of the heart requires a precise coordination of the contraction of millions of individual cardiac muscle cells. Contraction of each cell is triggered when an electrical excitatory

impulse (*action potential*) sweeps over its membrane. Proper coordination of the contractile activity of the individual cardiac muscle cells is achieved primarily by the conduction of action potentials from one cell to the next via gap junctions that connect all cells of the heart into a functional syncytium (ie, acting as one synchronous unit). In addition, muscle cells in certain areas of the heart are specifically adapted to control the frequency of cardiac excitation, the pathway of conduction, and the rate of the impulse propagation through various regions of the heart. The major components of this specialized excitation and conduction system are shown in Figure 1–6. They include the *sino-atrial node* (SA node), the *atrioventricular node* (AV node), the *bundle of His,* and the right and left *bundle branches* made up of specialized cells called *Purkinje* fibers.

Figure 1–6.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Electrical conduction system of the heart.

The SA node contains specialized cells that normally function as the heart's pacemaker and initiate the action potential that is conducted through the heart. The AV node contains slowly conducting cells that normally function to create a slight delay between atrial contraction and ventricular contraction. The Purkinje fibers are specialized for rapid conduction and assure that all ventricular cells contract at nearly the same instant.

Requirements for Effective Operation

For effective efficient ventricular pumping action, the heart must be functioning properly in five basic

respects:

1. The contractions of individual cardiac muscle cells must occur at regular intervals and be synchronized (not *arrhythmic*).

2. The valves must open fully (not *stenotic*).

3. The valves must not leak (not *insufficient* or *regurgitant*).

4. The muscle contractions must be forceful (not *failing*).

5. The ventricles must fill adequately during diastole.

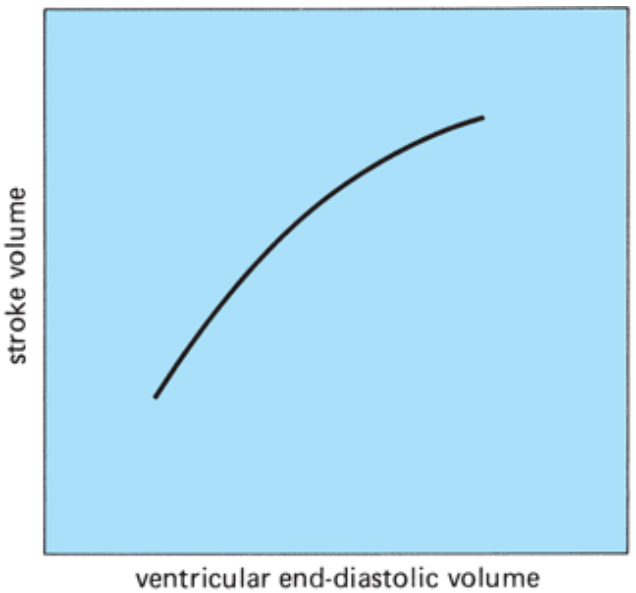
In the subsequent chapters, we will study in detail how these requirements are met in the normal heart.

Control of the Heart & Cardiac Output

Diastolic Filling

One of the most fundamental causes of variations in stroke volume was described by William Howell in 1884 and by Otto Frank in 1894 and formally stated by E. H. Starling in 1918. These investigators demonstrated that as cardiac filling increases during diastole, the volume ejected during systole also increases. As a consequence, and as illustrated in Figure 1–7, with other factors equal, stroke volume increases as cardiac end-diastolic volume increases. This phenomenon (commonly referred to as Starling's law of the heart) is an intrinsic property of the cardiac muscle and is one of the primary regulators of cardiac output. The mechanisms responsible for this phenomenon will be described in detail in subsequent chapters.

Figure 1–7.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Starling's law of the heart.

Autonomic Neural Influences

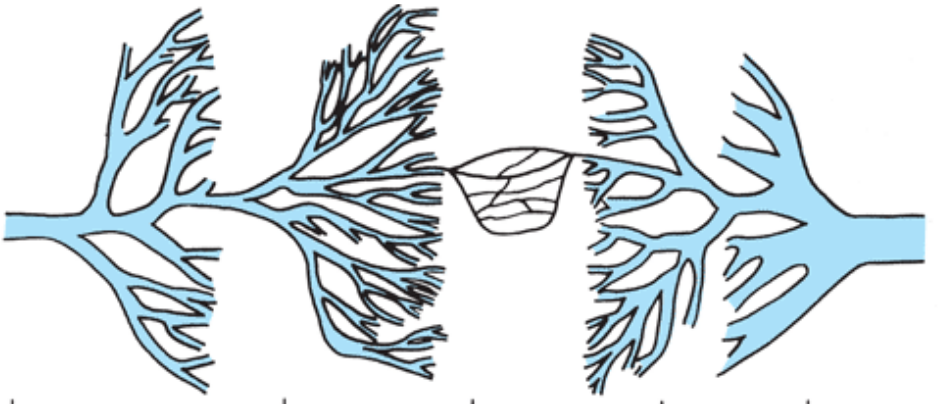
While the heart can inherently beat on its own, cardiac function can be influenced profoundly by neural inputs from both the sympathetic and parasympathetic divisions of the autonomic nervous system. These inputs allow us to modify cardiac pumping as is appropriate to meet changing homeostatic needs of the body. All portions of the heart are richly innervated by *adrenergic sympathetic fibers.* When active, these sympathetic nerves release *norepinephrine* (noradrenaline) on cardiac cells. Norepinephrine interacts with β_1-adrenergic receptors on cardiac muscle cells to increase heart rate, increase action potential conduction velocity, and increase force of contraction and rates of contraction and relaxation. Overall, sympathetic activation acts to increase cardiac pumping.

Cholinergic parasympathetic nerve fibers travel to the heart via the vagus nerve and innervate the SA node, the AV node, and atrial muscle. When active, these parasympathetic nerves release *acetylcholine* on cardiac muscle cells. Acetylcholine interacts with *muscarinic* receptors on cardiac muscle cells to decrease heart rate (SA node) and decrease action potential conduction velocity (AV node). Parasympathetic nerves may also act to decrease the force of contraction of atrial (not ventricular) muscle cells. Overall, parasympathetic activation acts to decrease cardiac pumping. Usually an increase in parasympathetic nerve activity is accompanied by a decrease in sympathetic nerve activity, and vice versa.

THE VASCULATURE

Blood that is ejected into the aorta by the left heart passes consecutively through many different types of vessels before it returns to the right heart. As diagrammed in Figure 1–8, the major vessel classifications are *arteries, arterioles, capillaries, venules,* and *veins.* These consecutive vascular segments are distinguished from one another by differences in physical dimensions, morphological characteristics, and function. One thing that all vessels have in common is that they are lined with a contiguous single layer of endothelial cells. In fact, this is true for the entire circulatory system including the heart chambers and even the valve leaflets.

Figure 1–8.



	ARTERIES		ARTERIOLES	CAPILLARIES	VENULES		VEINS
	Aorta				one-way valves		Venae cavae
internal diameter	2.5 cm	0.4 cm	30 μm	5μm	70 μm	0.5 cm	3 cm
wall thickness	2 mm	1 mm	20 μm	1 μm	7μm	0.5 mm	1.5 mm
number	1	160	5×10^7	10^{10}	10^8	200	2
total cross-sectional area	4.5 cm^2	20 cm^2	400 cm^2	4500 cm^2	4000 cm^2	40 cm^2	18 cm^2

Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Structural characteristics of the peripheral vascular system.

Some representative physical characteristics are shown in Figure 1–8 for each of the major vessel types. It should be realized, however, that the vascular bed is a continuum and that the transition from one type of vascular segment to another does not occur abruptly. The total cross-sectional area through which blood flows at any particular level in the vascular system is equal to the sum of the cross-sectional areas of all the individual vessels arranged in parallel at that level. The number and total cross-sectional area values presented in Figure 1–8 are estimates for the entire systemic circulation.

Arteries are thick-walled vessels that contain, in addition to some smooth muscle, a large component of elastin and collagen fibers. Primarily because of the elastin fibers, which can stretch to twice their unloaded length, arteries can expand to accept and temporarily store some of the blood ejected by the heart during systole and then, by passive recoil, supply this blood to the organs downstream during diastole. The aorta is the largest artery and has an inside diameter of about 25 mm. Arterial diameter decreases with each consecutive branching, and the smallest arteries have diameters of approximately 0.1 mm. The consecutive arterial branching pattern causes an exponential increase in arterial

numbers. Thus, while individual vessels get progressively smaller, the total cross-sectional area available for blood flow within the arterial system increases to severalfold that in the aorta. Arteries are often referred to as *conduit* vessels because they have relatively low and unchanging resistance to flow.


Arterioles are smaller and structured differently than arteries. In proportion to lumen size, arterioles have much thicker walls with more smooth muscle and less elastic material than arteries. Because arterioles are so muscular, their diameters can be actively changed to regulate the blood flow through peripheral organs. Despite their minute size, arterioles are so numerous that in parallel their collective cross-sectional area is much larger than that at any level in arteries. Arterioles are often referred to as *resistance* vessels because of their high and changeable resistance, which regulates peripheral blood flow through individual organs.

Capillaries are the smallest vessels in the vasculature. In fact, red blood cells with diameters of 7 μm must deform to pass through them. The capillary wall consists of a single layer of endothelial cells, which separate the blood from the interstitial fluid by only about 1 μm. Capillaries contain no smooth muscle and thus lack the ability to change their diameters actively. They are so numerous that the total collective cross-sectional area of all the capillaries in systemic organs is more than 1000 times that of the root of the aorta. Given that capillaries are about 0.5 mm in length, the total surface area available for exchange of material between blood and interstitial fluid can be calculated; it exceeds 100 m^2. For obvious reasons, capillaries are viewed as the *exchange* vessels of the cardiovascular system. In addition to the transcapillary diffusion of solutes that occurs across these vessel walls, there can sometimes be net movements of fluid (volume) into and/or out of capillaries. For example, tissue swelling (*edema*) is a result of net fluid movement from plasma into the interstitial space.

After leaving capillaries, blood is collected in venules and veins and returned to the heart. Venous vessels have very thin walls in proportion to their diameters. Their walls contain smooth muscle and the diameters of venous vessels can actively change. Because of their thin walls, venous vessels are quite distensible. Therefore, their diameters change passively in response to small changes in transmural distending pressure (ie, the difference between the internal and external pressures across the vessel wall). Venous vessels, especially the larger ones, also have one-way valves that prevent reverse flow. As will be discussed later, these valves are especially important in the cardiovascular system's operation during standing and during exercise. It turns out that peripheral venules and veins normally contain more than 50% of the total blood volume. Consequently, they are commonly thought of as the *capacitance* vessels. More importantly, *changes* in venous volume greatly influence cardiac filling and therefore cardiac pumping. Thus, peripheral veins actually play an extremely important role in controlling cardiac output.

Control of Blood Vessels


Blood flow through individual vascular beds is profoundly influenced by changes in activity of sympathetic nerves innervating arterioles. These nerves release norepinephrine from their endings which interacts with α-*adrenergic* receptors on the smooth muscle cells to cause contraction and thus arteriolar constriction. The reduction in arteriolar diameter increases vascular resistance and decreases blood flow. These neural fibers provide the most important means of *reflex* control of vascular resistance and organ blood flow.


Arteriolar smooth muscle is also very responsive to changes in the local chemical conditions within

an organ that accompany changes in the metabolic rate of the organ. For reasons to be discussed later, increased tissue metabolic rate leads to arteriolar dilation and increased tissue blood flow.

Venules and veins are also richly innervated by sympathetic nerves and constrict when these nerves are activated. The mechanism is the same as that involved with arterioles. Thus, increased sympathetic nerve activity is accompanied by decreased venous volume. The importance of this phenomenon is that venous constriction tends to increase cardiac filling and therefore cardiac output via Starling's law of the heart.

There is no important neural or local metabolic control of either the arterial or capillary vessels.

BLOOD



Blood is a complex fluid that serves as the medium for transporting substances between the tissues of the body and performs a host of other functions as well. Normally about 40% of the volume of whole blood is occupied by blood cells that are suspended in the watery fluid, *plasma,* which accounts for the rest of the volume. The fraction of blood volume occupied by cells is a clinically important parameter termed the *hematocrit:*

$$\text{Hematocrit} = \text{cell volume/total blood volume}$$

Blood Cells

Blood contains three general types of "formed elements": red cells, white cells, and platelets (see Appendix A). All are formed in bone marrow from a common stem cell. Red cells are by far the most abundant. They are specialized to carry oxygen from the lungs to other tissues by binding oxygen to *hemoglobin,* an iron-containing heme protein concentrated within red blood cells. Because of the presence of hemoglobin, blood can transport 40 to 50 times the amount of oxygen that plasma alone could carry. In addition, the hydrogen ion buffering capacity of hemoglobin is vitally important to the blood's capacity to transport carbon dioxide.

A small but important fraction of the cells in blood are white cells or *leukocytes.* Leukocytes are involved in immune processes. Appendix A gives more information on the types and function of leukocytes. Platelets are small cell fragments that are important in the blood-clotting process.

Plasma

Plasma is the liquid component of blood and, as indicated in Appendix B, is a complex solution of electrolytes and proteins. *Serum* is the fluid obtained from a blood sample after it has been allowed to clot. For all practical purposes, the composition of serum is identical to that of plasma except that it contains none of the clotting proteins.

Inorganic*electrolytes* (inorganic ions such as sodium, potassium, chloride, and bicarbonate) are the most concentrated solutes in plasma. Of these, sodium and chloride are by far the most abundant and, therefore, are primarily responsible for plasma's normal osmolarity of about 300 mOsm/L. To a first approximation, the "stock" of the plasma soup is a 150 m*M* solution of sodium chloride. Such a solution is called isotonic saline and has many clinical uses as a fluid that is compatible with cells.

Plasma normally contains many different *proteins.* Most plasma proteins can be classified as *albumins, globulins,* or *fibrinogen* on the basis of different physical and chemical characteristics used to separate them. More than 100 distinct plasma proteins have been identified and each presumably serves some specific function. Many plasma proteins are involved in blood clotting or immune/defense reactions. Many others are important carrier proteins for a variety of substances including fatty acids, iron,

copper, vitamin D, and certain hormones.

Proteins do not readily cross capillary walls and, in general, their plasma concentrations are much higher than their concentrations in the interstitial fluid. As will be discussed, plasma proteins play an important osmotic role in transcapillary fluid movement and thus the distribution of extracellular volume between the plasma and interstitial compartments. *Albumin* plays an especially strong role in this regard simply because it is by far the most abundant of the plasma proteins.

Plasma also serves as the vehicle for transporting nutrients and waste products. Thus, a plasma sample contains many small organic molecules such as glucose, amino acids, urea, creatinine, and uric acid whose measured values are useful in clinical diagnosis.

FOUNDATION FOR SUBSEQUENT CHAPTERS

This first chapter has presented an overall description of the design of the cardiovascular system. Some important, basic, bottom-line principles that should help you understand many aspects of cardiovascular function have been included. (See the study questions at the end of this chapter, for example.)

Subsequent chapters will expand these concepts in much greater detail, but we urge students not to lose sight of the overall picture presented in this chapter. It may be useful to repeatedly refer back to this material.

KEY CONCEPTS


The primary role of the cardiovascular system is to maintain homeostasis in the interstitial fluid.


The physical law that governs cardiovascular operation is that flow through any segment is equal to pressure difference across that segment divided by its resistance to flow; ie, $\dot{Q} = \Delta P/R$.


The heart pumps blood by rhythmically filling and ejecting blood from the ventricular chambers that are served by passive one-way inlet and outlet valves.


Changes in heart rate and stroke volume (and therefore cardiac output) can be accomplished by alterations in ventricular filling and by alterations in autonomic nerve activity to the heart.


Blood flow through individual organs is regulated by changes in the diameter of their arterioles.


Changes in arteriolar diameter can be accomplished by alterations in sympathetic nerve activity and by variations in local conditions.


Blood is a complex suspension of red cells, white cells, and platelets in plasma that is ideally suited to carry gases, salts, nutrients, and waste molecules throughout the system.

STUDY QUESTIONS

1–1. Which organ in the body always receives the most blood flow?

1–2. Whenever skeletal muscle blood flow increases, blood flow to other organs must decrease. True or false?

1–3. When a heart valve does not close properly, a sound called a murmur can often be detected as the valve leaks. Would you expect a leaky aortic valve to cause a systolic or diastolic murmur?

1–4. Slowing of action potential conduction through the AV node will slow heart rate. True or false?

1–5. Calculate cardiac output from the following data:

Pulmonary arterial pressure = 20 mmHg

Pulmonary venous pressure = 0 mmHg

Pulmonary vascular resistance = 4 mmHg $\times$ min/L

1–6. a. Determine the vascular resistance of a resting skeletal muscle from the following data:

Mean arterial pressure = 100 mmHg

Mean venous pressure = 0 mmHg

Blood flow to the muscle = 5 mL/min

b. Assume that when the muscle is exercising, the resistance vessels dilate so that their internal radius doubles. If blood pressure does not change, what is the blood flow through the exercising muscle?

c. What is the vascular resistance of this exercising skeletal muscle?

1–7. Usually an individual who has lost a significant amount of blood is weak and does not reason very clearly. Why would blood loss have these effects?

1–8. What direct cardiovascular consequences would you expect from an intravenous injection of norepinephrine?

1–9. What direct cardiovascular effects would you expect from an intravenous injection of a drug that stimulates α-adrenergic receptors but not β-adrenergic receptors?

1–10. Individuals with high arterial blood pressure (hypertension) are often treated with drugs that block β-adrenergic receptors. What is the rationale for such treatment?

1–11. The clinical laboratory reports a serum sodium ion value of 140 mEq/L in a blood sample you have taken from a patient. What does this tell you about the sodium ion concentration in plasma, in interstitial fluid, and in intracellular fluid?

1–12. An individual has had the "flu" for 3 days with severe vomiting and diarrhea. How is this likely to influence his or her hematocrit?

See answers.

SUGGESTED READINGS

Handbook of Physiology Series. Section 2: The Cardiovascular System, New York, NY: Oxford University Press.

Volume I: *The Heart*. Edited by Page E, Fozzard H, Solaro RJ. 2000.

Volume II: *Vascular Smooth Muscle*. Edited by Bohr DF, Somlyo AP, Sparks HV, 1980.

Volume III: *Peripheral Circulation and Organ Blood Flow*. Edited by Shepherd JT, 1983.

Volume IV: *Microcirculation*. Edited by Renkin E, Michel CC, 1984.

Harvey W. (1628). *The Movement of the Heart and Blood.* (translated by Witteridge G.) Oxford: Blackwell Scientific Publications; 1976.

Rowell LB. *Human Cardiovascular Control.* New York, NY: Oxford University Press; 1993.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.
Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.

Mc Graw Hill Medical a silverchair information system The McGraw-Hill Companies

Note: Large images and tables on this page may necessitate printing in landscape mode.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.

OBJECTIVES

The student understands the ionic basis of the spontaneous electrical activity of cardiac muscle cells:

- *Describes how membrane potentials are created across semipermeable membranes by transmembrar concentration differences.*
- *Defines equilibrium potential and knows its normal value for potassium and sodium ions.*
- *States how membrane potential reflects a membrane's relative permeability to various ions.*
- *Defines resting potential and action potential.*
- *Describes the characteristics of "fast" and "slow" response action potentials.*
- *Identifies the refractory periods of the cardiac cell electrical cycle.*
- *Defines threshold potential and describes the interaction between ion channel conditions, and membra potential during the depolarization phase of the action potential.*
- *Defines pacemaker potential and describes the basis for rhythmic electrical activity of cardiac cells.*
- *Lists the phases of the cardiac cell electrical cycle and states the membrane permeability alterations responsible for each phase.*

The student knows the normal process of cardiac electrical excitation:

- *Describes gap junctions and their role in cardiac excitation.*
- *Describes the normal pathway of action potential conduction through the heart.*
- *Indicates the timing with which various areas of the heart are electrically excited and identifies the characteristic action potential shapes and conduction velocities in each major part of the conduction s*
- *States the relationship between electrical events of cardiac excitation and the P, QRS, and T waves, tl interval, and the ST segment of the electrocardiogram.*

The student understands the factors that control heart rate and action potential conduction in the heart:

- *States how diastolic potentials of pacemaker cells can be altered to produce changes in heart rate.*
- *Describes how cardiac sympathetic and parasympathetic nerves alter heart rate and conduction of car action potentials.*
- *Defines the terms* chronotropic *and* dromotropic.

The student understands the contractile processes of cardiac muscle cells:

- *Describes the subcellular structures responsible for cardiac muscle cell contraction.*
- *Defines and describes the excitation-contraction process.*
- *Defines isometric, isotonic, and afterloaded contractions of cardiac muscle.*

- *Describes the influence of altered preload on the tension-producing and shortening capabilities of card muscle.*
- *Describes the influence of altered afterload on the shortening capabilities of cardiac muscle.*
- *Defines the terms* contractility *and* inotropic state *and describes the influence of altered contractility o tension-producing and shortening capabilities of cardiac muscle.*
- *Describes the effect of altered sympathetic neural activity on cardiac inotropic state.*
- *States the relationships between ventricular volume, muscle tension, and intraventricular pressure (La Laplace).*

ELECTRICAL ACTIVITY OF CARDIAC MUSCLE CELLS

In all striated muscle cells, contraction is triggered by a rapid voltage change called an *action potential* tha on the cell membrane. Cardiac muscle cell action potentials differ sharply from those of skeletal muscle cel three important ways that promote synchronous rhythmic excitation of the heart: (1) they can be self-gen (2) they can be conducted directly from cell to cell; and (3) they have long durations, which preclude fusio individual twitch contractions. To understand these special electrical properties of cardiac muscle and how function depends on them, the basic electrical properties of excitable cell membranes must first be reviewe

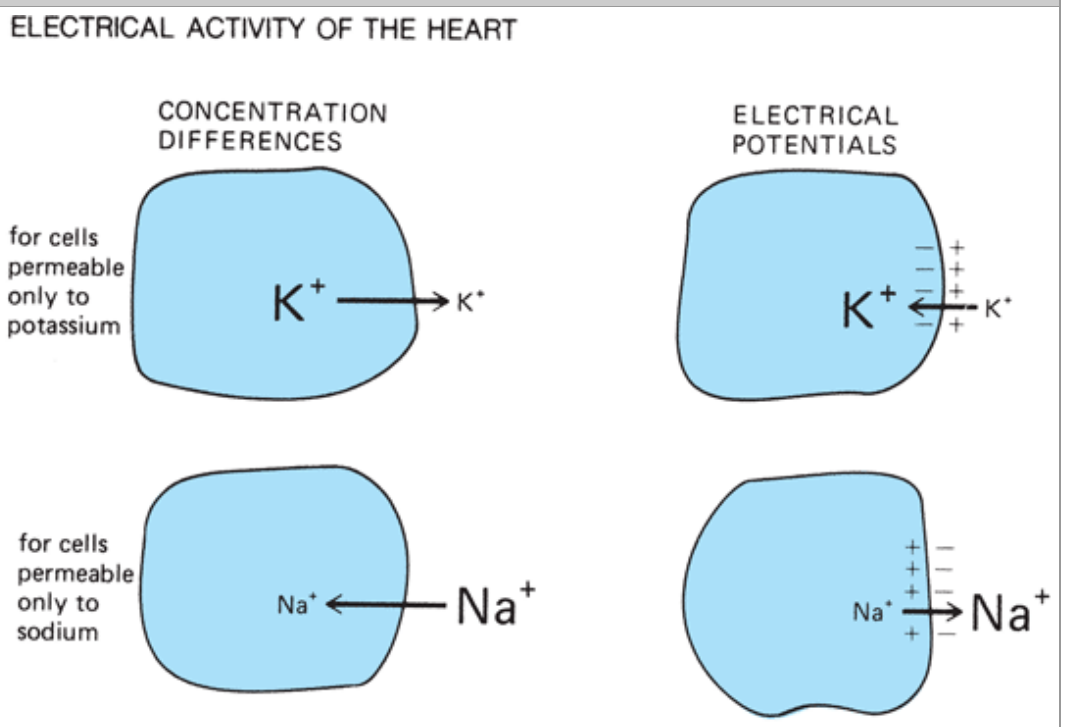
Membrane Potentials



All cells have an electrical potential (voltage) across their membranes. Such *membrane potentials* exi because the ionic concentrations of the cytoplasm are different from those of the interstitium and ions diffu down concentration gradients across semipermeable membranes generate electrical gradients. The three i are the most important determinants of cardiac membrane potential are sodium (Na^+) and calcium (Ca^{2+}) which are more concentrated in the interstitial fluid than they are inside cells, and potassium (K^+) ions, wh the opposite distribution. The diffusion of ions across the cell membrane occurs through *channels* that (1) made up of protein molecules that span the membrane, (2) are specific for an individual ion (eg, Na^+ chan and (3) exist in various configurations that are open, closed, or inactivated (unable to be opened). The *permeability* of the membrane to a specific ion is directly related to the number of open channels for that i any given time.

Figure 2–1 shows how ion concentration differences can generate an electrical potential across the cell me Consider first, as shown at the top of this figure, a cell that (1) has K^+ more concentrated inside the cell th (2) is permeable only to K^+ (ie, only K^+ channels are open), and (3) has no initial transmembrane potentia Because of the concentration difference, K^+ ions (positive charges) will diffuse out of the cell. Meanwhile, r charges, such as protein anions, cannot leave the cell because the membrane is impermeable to them. Thu K^+ efflux will make the inside of the cell more electrically negative (deficient in positively charged ions) an same time make the interstitium more electrically positive (rich in positive ions). Now K^+ ion, being positiv charged, is attracted to regions of electrical negativity. Therefore, when K^+ diffuses out of a cell, it creates electrical potential across the membrane that tends to attract it back into the cell. There exists one membr potential called the *potassium equilibrium potential* at which the electrical forces tending to pull K^+ into the exactly balance the concentration forces tending to drive K^+ out. When the membrane potential has this va there is no net movement of K^+ across the membrane. With the normal concentrations of about 145 m*M* K cells and 4 m*M* K^+ in the extracellular fluid, the K^+ equilibrium potential is roughly –90 mV (more negative than outside by nine-hundredths of a volt).[1] A membrane that is permeable only to K^+ will inherently and r (essentially instantaneously) develop the potassium equilibrium potential. In addition, membrane potentia changes require the movement of so few ions that concentration differences are not significantly affected b process.

Figure 2–1.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Electrochemical basis of membrane potentials.

As depicted in the bottom half of Figure 2–1, similar reasoning shows how a membrane permeable only to would have the *sodium equilibrium potential* across it. The sodium equilibrium potential is approximately + with the normal extracellular Na^+ concentration of 140 m*M* and intracellular concentration of 10 m*M*. Real membranes, however, are never permeable to just Na^+ or just K^+. When a membrane is permeable to both these ions, the membrane potential will lie somewhere between the Na^+ equilibrium potential and the K^+ equilibrium potential. Just what membrane potential will exist at any instant depends on the relative perm of the membrane to Na^+ and K^+. The more permeable the membrane to K^+ than to Na^+, the closer the me potential will be to –90 mV. Conversely, when the permeability to Na^+ is high relative to the permeability t the membrane potential will be closer to +70 mV.[2] Because of low or unchanging permeabilities or low concentration, roles played by ions other than Na^+ and K^+ in determining membrane potential are usually and often ignored. However, as will be discussed later, calcium ions (Ca^{2+}) do participate in the cardiac mu action potential. Like Na^+, Ca^{2+} is more concentrated outside cells than inside. The equilibrium potential fo ~ + 100 mV, and the cell membrane tends to become more positive on the inside when the membrane's permeability to Ca^{2+} rises.

Under resting conditions, most heart muscle cells have membrane potentials that are quite close to the po equilibrium potential. Thus, both electrical and concentration gradients favor Na^+ entry into the resting cel However, the very low permeability of the resting membrane to Na^+ in combination with an energy-requiri sodium pump that extrudes Na^+ from the cell prevents Na^+ from gradually accumulating inside the resting

[1] The equilibrium potential (E_{eq}) for any ion (X^z) is determined by its intracellular and extracellular concent as indicated in the Nernst equation:

$$E_{eq} = \frac{-61.5\ \text{mV}}{z} \log_{10} \frac{[X^z]\ \text{inside}}{[X^z]\ \text{outside}}$$

[2] A quantitative description of how Na^+ and K^+ concentrations and the relative permeability (P_{Na}/P_K) to the affect membrane potential (E_m) is given by the following equation:

$$E_m = -61.5\ \text{mV} \log_{10} \left(\frac{[K^+]_i + P_{Na}/P_K [Na^+]_i}{[K^+]_o + P_{Na}/P_K [Na^+]_o} \right)$$

[3] The sodium pump not only removes Na^+ from the cell but also pumps K^+ into the cell. Since more Na^+ is out than K^+ is pumped in (3:2), the pump is said to be electrogenic. The resting membrane potential beco slightly less negative than normal when the pump is abruptly inhibited.

Cardiac Cell Action Potentials

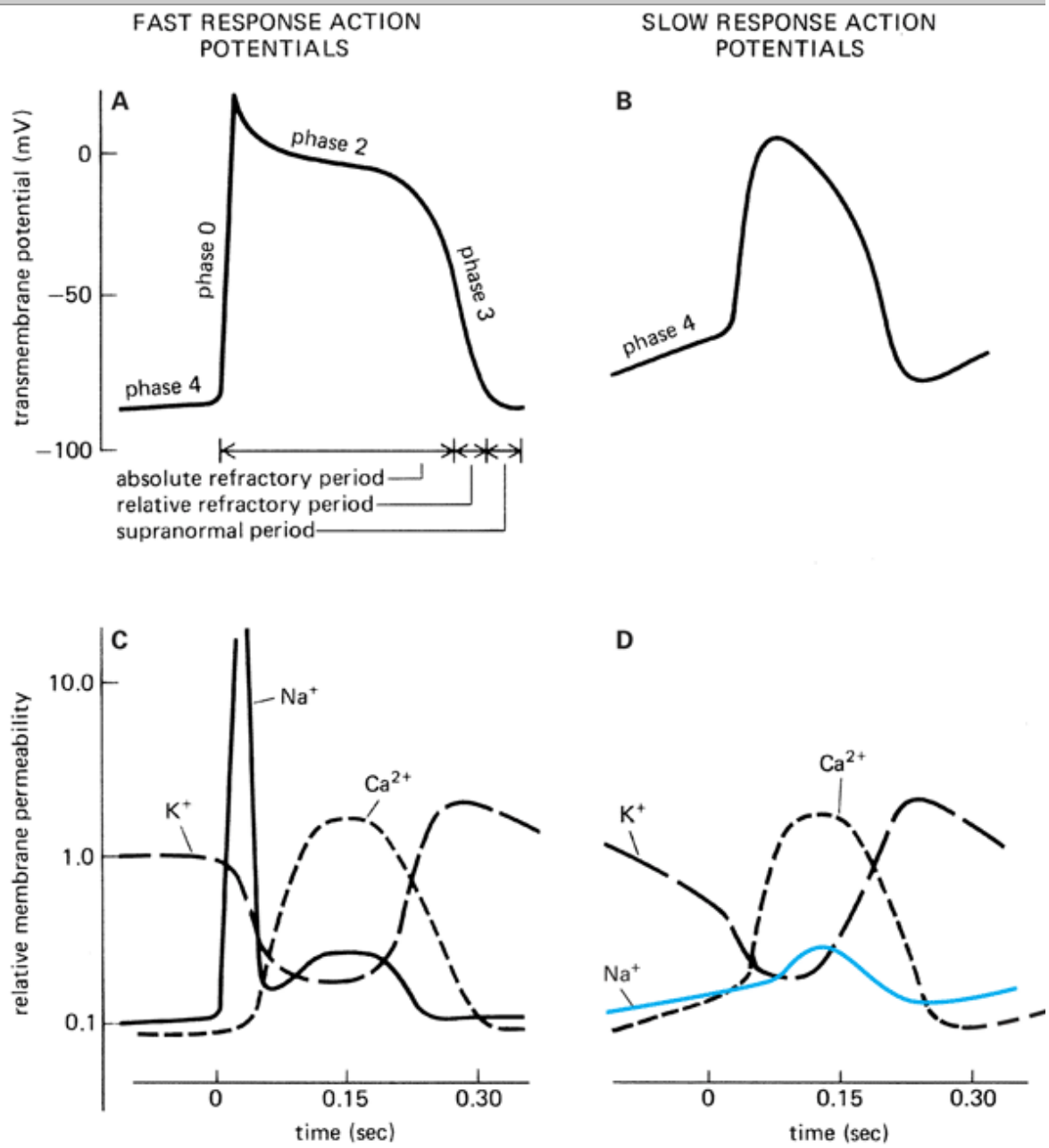


Action potentials of cells from different regions of the heart are not identical but have varying charact that are important to the overall process of cardiac excitation.



Some cells within a specialized conduction system have the ability to act as pacemakers and to sponta initiate action potentials whereas ordinary cardiac muscle cells do not (except under unusual conditions). E membrane electrical features of an ordinary cardiac muscle cell and a cardiac pacemaker-type cell are sho Figure 2–2. Action potentials from these cell types are referred to as "fast response" and "slow response" a potentials, respectively. As shown in panel A of this figure, fast response action potentials are characterize rapid depolarization (phase 0) with a substantial overshoot (positive inside voltage), a rapid reversal of the overshoot potential (phase 1), a long plateau (phase 2), and a repolarization (phase 3) to a stable, high (i negative) resting membrane potential (phase 4). In comparison, the slow response action potentials are characterized by a slower initial depolarization phase, a lower amplitude overshoot, a shorter and less stab plateau phase, and a repolarization to an unstable, slowly depolarizing "resting" potential (Figure 2–2B). T unstable resting potential seen in pacemaker cells with slow response action potentials is variously referre the *phase 4 depolarization, diastolic depolarization,* or *pacemaker potential.*

Figure 2–2.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Time course of membrane potential and ion permeability changes that occur during "fast response" (left) a "slow response" (right) action potentials.

As indicated at the bottom of Figure 2–2A, cells are in an absolute refractory state during most of the actic potential (ie, they cannot be stimulated to fire another action potential). Near the end of the action potent membrane is relatively refractory and can be reexcited only by a larger than normal stimulus. Immediately the action potential, the membrane is transiently hyperexcitable and is said to be in a "vulnerable" or "supranormal" period. Similar alterations in membrane excitability probably occur during slow action poten

at present are not fully characterized.

Recall that the membrane potential of any cell depends on the relative permeability of the cell's meml specific ions at that instant. As in all excitable cells, cardiac cell action potentials are the result of transient changes in the ionic permeability of the cell membrane, which are triggered by an initial depolarization. Pa and D of Figure 2–2 indicate the changes in membrane permeabilities to K^+, Na^+, and Ca^{2+}, which produce various phases of the fast and slow response action potentials. Note that during the resting phase, the me of both types of cells are more permeable to K^+ than to Na^+ or Ca^{2+}. Therefore, the membrane potentials to the potassium equilibrium potential (of –90 mV) during this period. In the pacemaker-type cells, at leas mechanisms are thought to contribute to the slow depolarization of the membrane observed during the dia interval. First, there is a progressive decrease in the membrane's permeability to K^+ during the resting pha second, the permeability to Na^+ increases slightly. The gradual increase in the Na^+/K^+ permeability ratio w the membrane potential to move slowly away from the K^+ equilibrium potential (–90 mV) in the direction o Na^+ equilibrium potential. Third, there is an increase in the permeability of the membrane to calcium ions, results in an inward movement of positively charged ions and also contributes to the diastolic depolarizatio

When the membrane potential depolarizes to a certain threshold potential in either type of cell, major rapi alterations in the permeability of the membrane to specific ions are triggered. Once initiated, these permea changes cannot be stopped and they proceed to completion.

The characteristic rapid rising phase of the fast response action potential is a result of a sudden increa Na^+ permeability. This produces what is referred to as the *fast inward current* of Na^+ and causes the meml potential to move rapidly toward the sodium equilibrium potential. As indicated in panel C of Figure 2–2, tl period of very high sodium permeability is short-lived. It is followed by a more slowly developed increase i membrane's permeability to Ca^{2+} and a decrease in its permeability to K^+. Also, there is a second slowly developing increase in Na^+ permeability, which is thought to be caused by a different mechanism than tha involved in the initial rapid Na^+ permeability changes. These more persistent permeability changes (which what is referred to as the *slow inward current*) prolong the depolarized state of the membrane to cause th (phase 2) of the cardiac action potential. The initial fast inward current is small (or even absent) in cells th slow response action potentials. The slow rising phase of these action potentials is therefore primarily a res an inward movement of Ca^{2+} ions. In both types of cells, the membrane is repolarized (phase 3) to its orig resting potential as the K^+ permeability increases and the Ca^{2+} and Na^+ permeabilities return to their low values. These late permeability changes produce what is referred to as the *delayed outward current.*

The overall smoothly graded permeability changes that produce action potentials are the net result of alter each of the many individual ion channels within the plasma membrane of a single cell. The experimental te of*patch clamping* has made it possible to study the operation of individual ion channels. The patch clamp d clearly indicate that a single channel is either open or closed at any instant in time; there are no graded st partial opening. What is graded is the percentage of time that a channel spends in the open state, ie, its probability of being open. While a channel may remain closed for long periods, it rarely remains open for n than a few milliseconds at a time. Thus, the probability of a channel's being open depends both on the *freq* with which it opens and how long it remains open. An increase in an ion channel's probability of being oper (channel "activation") leads to an increase in total open time and an increase in the overall membrane per to that ion.

Certain types of channels are called *voltage-gated channels* (or voltage-operated channels) because their probability of being open varies with membrane potential. Other types of channels, called *ligand-gated cha* (or receptor-operated channels), are activated by certain neurotransmitters or other specific signal molecu

Table 2–1, at the end of this section, lists some of the major currents and channel types involved in cardia electrical activity.

Table 2–1. Characteristics of Important Cardiac Ion Channels in Order of Their Participation in an Action Potential.

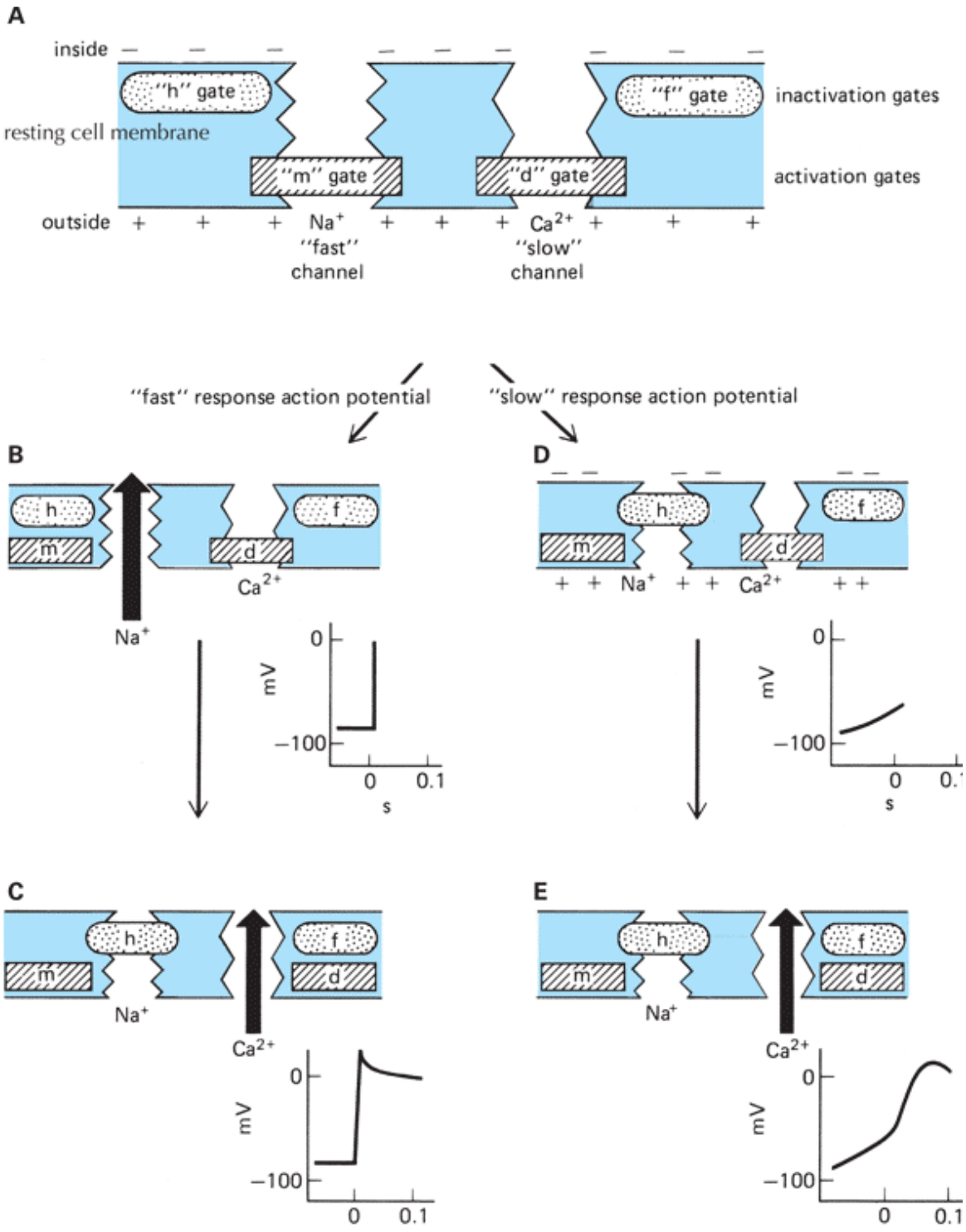
Current	Channel	Gating mechanism	Functional role
i_{K1}	K^+ channel (inward rectifier)	Voltage	Maintains high K^+ permeability during phase Its decay contributes to diastolic depolarizat Its suppression during phases 0 to 2 contrib plateau
i_{Na}	Na^+ channel (fast)	Voltage	Accounts for phase 0 of action potential Inactivation may contribute to phase 1 of ac potential
i_{To}	K^+ channel (transient outward)	Voltage	Contributes to phase 1 of action potential
i_{Ca}	Ca^{2+} channel (slow inward, L channels)	Voltage	Primarily responsible for phase 2 of action p Inactivation may contribute to phase 3 of ac potential Is enhanced by sympathetic stimulation and adrenergic agents
i_K	K^+ channel (delayed rectifier)	Voltage	Causes phase 3 of action potential May be enhanced by increased intracellular
i_{KATP}	K^+ channel (ATP-sensitive)	Ligand	Increases K^+ permeability when [ATP] is low
i_{KACh}	K^+ channel (acetylcholine-activated)	Ligand	Responsible for effects of vagal stimulation Decreases diastolic depolarization (and hea Hyperpolarizes resting membrane potential Shortens phase 2 of the action potential
i_f("funny")	Na^+ channel (pacemaker current)	Both	Contributes to the diastolic depolarization Is enhanced by sympathetic stimulation and adrenergic agents Is suppressed by vagal stimulation

Some of the voltage-gated channels respond to a sudden onset, sustained change in membrane potential brief period of activation. However, changes in membrane potential of slower onset but the same magnitu fail to activate these channels at all. To explain such behavior, it is postulated that these channels have tw independently operating "gates"—an *activation gate* and an *inactivation gate*—both of which must be open

channel as a whole to be open. These gates both respond to changes in membrane potential but do so witl different voltage sensitivities and time courses.

These concepts are illustrated in Figure 2–3. In the resting state, with the membrane polarized to near –8(the activation or *m* gate of the fast Na^+ channel is closed, but its inactivation or *h* gate is open (Figure 2–3 a rapid depolarization of the membrane to threshold, the Na^+ channels will be activated strongly to allow a of positive sodium ions that further depolarizes the membrane and thus initiates a "fast" response action p as illustrated in Figure 2–3B. This occurs because the *m* gate responds to membrane depolarization by ope more quickly than the *h* gate responds by closing. Thus a rapid depolarization to threshold is followed by a but strong period of Na^+ channel activation wherein the *m* gate is open but the *h* gate has yet to close.

Figure 2–3.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Conceptual model of cardiac membrane ion channels: at rest (A), during the initial phases of the fast resp
andC), and the slow response action potentials (D and E).

The initial membrane depolarization also causes the activation (*d*) gate of the Ca^{2+} channel to open a
brief delay. This permits the slow inward current of Ca^{2+} ions, which helps maintain the depolarization thro

plateau phase of the action potential (Figure 2–3C). Ultimately, repolarization occurs because of both a de inactivation of the Ca^{2+} channel (by closure of the *f* gates) and an opening of K^+ channels (which are not s Figure 2–3). Multiple factors influence the operation of K^+ channels. For example, high intracellular Ca^{2+} concentration contributes to activation of K^+ channels during repolarization. The *h* gates of sodium channe remain closed during the remainder of the action potential, effectively inactivating the Na^+ channel and contributing to the long cardiac refractory period which lasts until the end of phase 3. With repolarization, gates of the sodium channel return to their original position and the channel is now ready to be reactivate subsequent depolarization.

The slow response action potential shown in the right half of Figure 2–3 differs from the fast response acti potential primarily because of the lack of a strong activation of the fast Na^+ channel at its onset. This is a consequence of a slow depolarization to the threshold potential. Slow depolarization gives the inactivating time to close even as the activating *m* gates are opening (Figure 2–3D). Thus, in a slow response action p there is no initial period where all the sodium channels of a cell are essentially open at once. The depolariz beyond threshold is slow and caused primarily by the influx of Ca^{2+} through slow channels (Figure 2–3E).

While cells in certain areas of the heart typically have fast-type action potentials and cells in other areas n have slow-type action potentials, it is important to recognize that all cardiac cells are potentially capable o either type of action potential depending on how fast they depolarize to the threshold potential. As we sha rapid depolarization to the threshold potential is usually an event forced on a cell by the occurrence of an a potential in an adjacent cell. Slow depolarization to threshold occurs when a cell itself spontaneously and g loses its resting polarization, which normally happens only in the sinoatrial (SA) node. A *chronic* moderate depolarization of the resting membrane (caused, for example, by moderately high extracellular K^+ concent can inactivate the fast channels (by closing the *h* gates) without inactivating the slow Ca^{2+} channels. Unde conditions, all cardiac cell action potentials will be of the slow type. Large sustained depolarizations, howe inactivate both the fast and slow channels and thus make the cardiac muscle cells inexcitable.

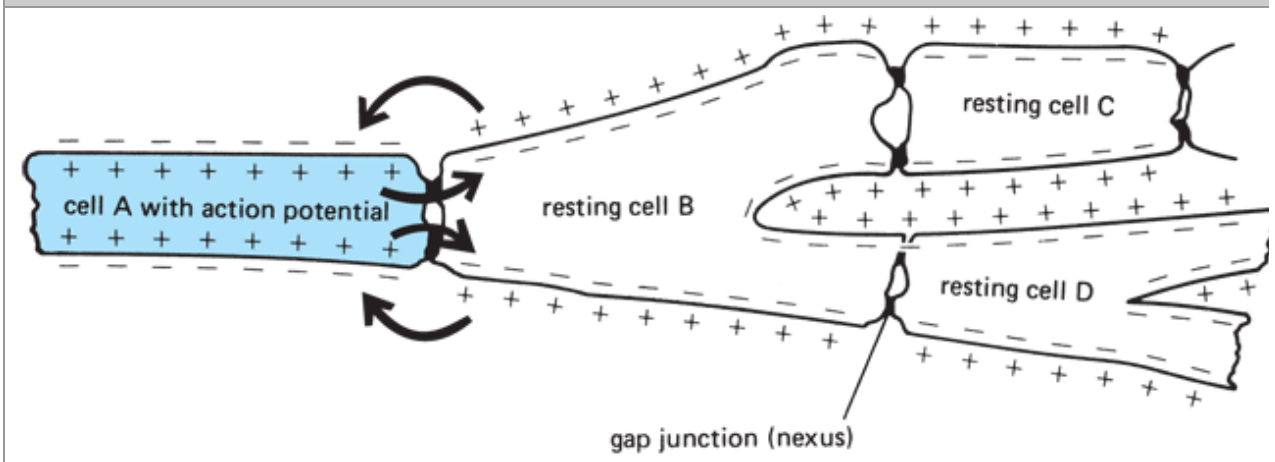
Conduction of Cardiac Action Potentials



Action potentials are conducted over the surface of individual cells because active depolarization in an area of the membrane produces local currents in the intracellular and extracellular fluids which passively d immediately adjacent areas of the membrane to their voltage threshold for active depolarization.

In the heart, cardiac muscle cells are connected end-to-end by structures called intercalated disks. These contain the following: (1) *firm mechanical attachments* between adjacent cell membranes by proteins calle adherins in structures called desmosomes and (2) *low resistance electrical connections* between adjacent through channels formed by protein called connexin in structures called gap junctions. Figure 2–4 shows schematically how these gap junctions allow action potential propagation from cell to cell.

Figure 2–4.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

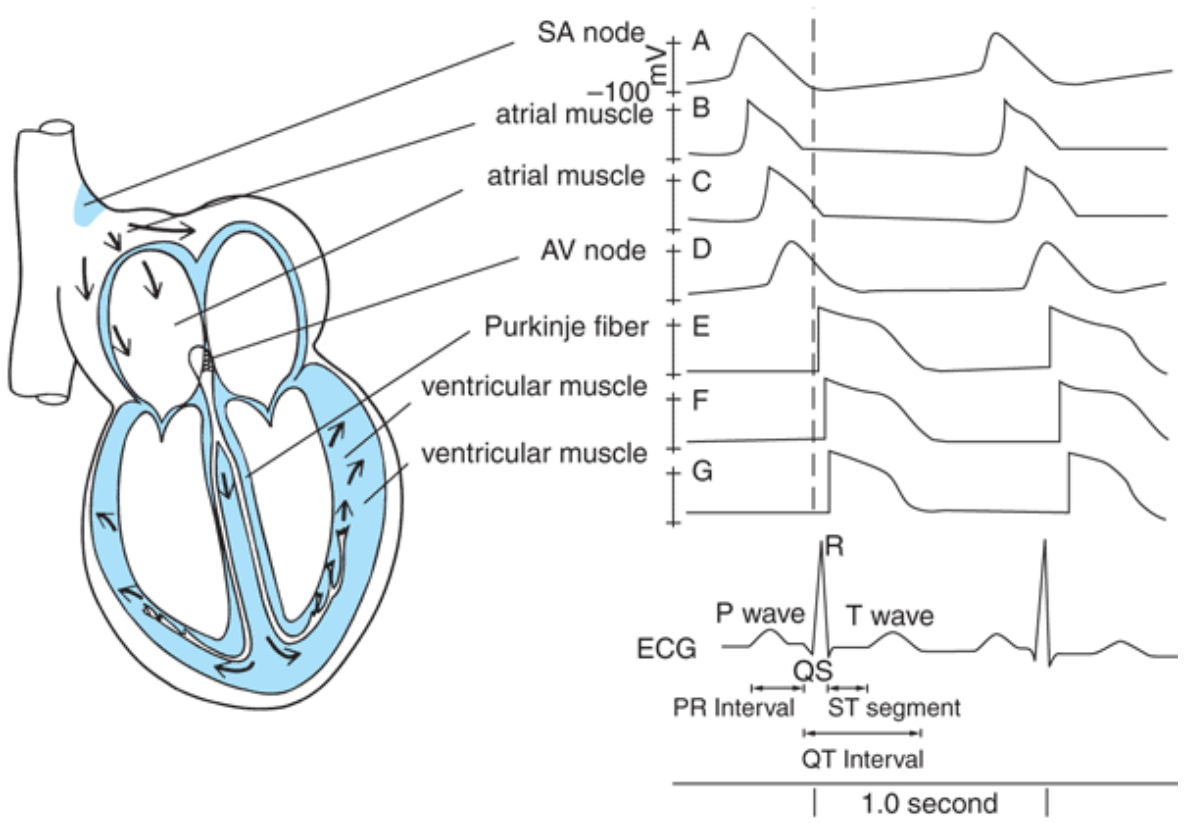
Local currents and cell-to-cell conduction of cardiac muscle cell action potentials.

Cells B, C, and D are shown in the resting phase with more negative charges on the inside than the outside is shown in the plateau phase of an action potential and has more positive charges inside than out. Becaus gap junctions, electrostatic attraction can cause a local current flow (ion movement) between the depolariz membrane of active cell A and the polarized membrane of resting cell B, as indicated by the arrows in the This ion movement tends to eliminate the charge difference across the resting membrane; ie, it depolarize membrane of cell B. Once the local currents from active cell A depolarize the membrane of cell B near the junction to the threshold level, an action potential will be triggered at that site and will be conducted over Because cell B branches (a common morphological characteristic of cardiac muscle fibers), its action poten evoke action potentials on cells C and D. This process is continued through the entire myocardium. Thus, a potential initiated at *any* site in the myocardium will be conducted from cell-to-cell throughout the entire myocardium.

The speed at which an action potential propagates through a region of cardiac tissue is called the *conducti velocity.* The conduction velocity varies considerably in different areas in the heart. This velocity is directly dependent on the diameter of the muscle fiber involved. Thus, conduction over small-diameter cells in the atrioventricular (AV) node is significantly slower than conduction over large-diameter cells in the ventricula Purkinje system. Conduction velocity is also directly dependent on the intensity of the local depolarizing cu which are in turn directly determined by the rate of rise of the action potential. Rapid depolarization favors conduction. Variations in the capacitive and/or resistive properties of the cell membranes, gap junctions, a cytoplasm are also factors that contribute to the differences in conduction velocity of action potentials thro specific areas of the heart.

Details of the cardiac conduction system are shown in Figure 2–5. Specific electrical adaptations of various the heart are reflected in the characteristic shape of their action potentials, as shown in the right half of Fi 2–5. Note that the action potentials shown in Figure 2–5 have been positioned to indicate the time at whic electrical impulse that originates in the SA node reaches other areas of the heart. Cells of the SA node act heart's normal pacemaker and determine the heart rate. This is because the spontaneous depolarization o resting membrane is most rapid in SA nodal cells, and they reach their threshold potential before cells else

Figure 2–5.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Electrical activity of the heart: single-cell voltage recordings (traces A to G) and lead II electrocardiogram

The action potential initiated by an SA nodal cell first spreads progressively through the atrial wall. Action potentials from cells in two different regions of the atria are shown in Figure 2–5: one close to the SA node one more distant from the SA node. Both cells have similarly shaped action potentials, but their temporal displacement reflects the fact that it takes some time for the impulse to spread over the atria.

As shown in Figure 2–5, action potential conduction is greatly slowed as it passes through the AV nod because of the small size of the AV nodal cells and the slow rate of rise of their action potentials. Since the node delays the transfer of the cardiac excitation from the atria to the ventricles, atrial contraction can cor to ventricular filling just before the ventricles contract. Note also that AV nodal cells have a faster spontan depolarization during the resting period than other cells of the heart except those of the SA node. The AV r sometimes referred to as a latent pacemaker, and in many pathological situations it (rather than the SA no controls the heart rhythm.

Because of sharply rising action potentials and other factors, such as large cell diameters, electrical conduc extremely rapid in Purkinje fibers. This allows the Purkinje system to transfer the cardiac impulse to cells i areas of the ventricle nearly in unison. Action potentials from muscle cells in two areas of the ventricle are in Figure 2–5. Because of the high conduction velocity in ventricular tissue, there is only a small discrepan their time of onset. Note in Figure 2–5 that the ventricular cells which are the last to depolarize have short duration action potentials and thus are the first to repolarize. The physiological importance of this unexpec

behavior is not clear but it does have an influence on the electrocardiograms that will be discussed in Chap

Electrocardiograms

Fields of electrical potential caused by the electrical activity of the heart extend through the body tissue ar be measured with electrodes placed on the body surface. *Electrocardiography* provides a record of how the between two points on the body surface changes with time as a result of the electrical events of the cardia At any instant of the cardiac cycle the electrocardiogram indicates the net electrical field that is the summa many weak electrical fields being produced by voltage changes occurring on individual cardiac cells at that When a large number of cells are simultaneously depolarizing or repolarizing, large voltages are observed electrocardiogram. Since the electrical impulse spreads through the heart tissue in a stereotyped manner, temporal pattern of voltage change recorded between two points on the body surface is also stereotyped a repeat itself with each heart cycle.

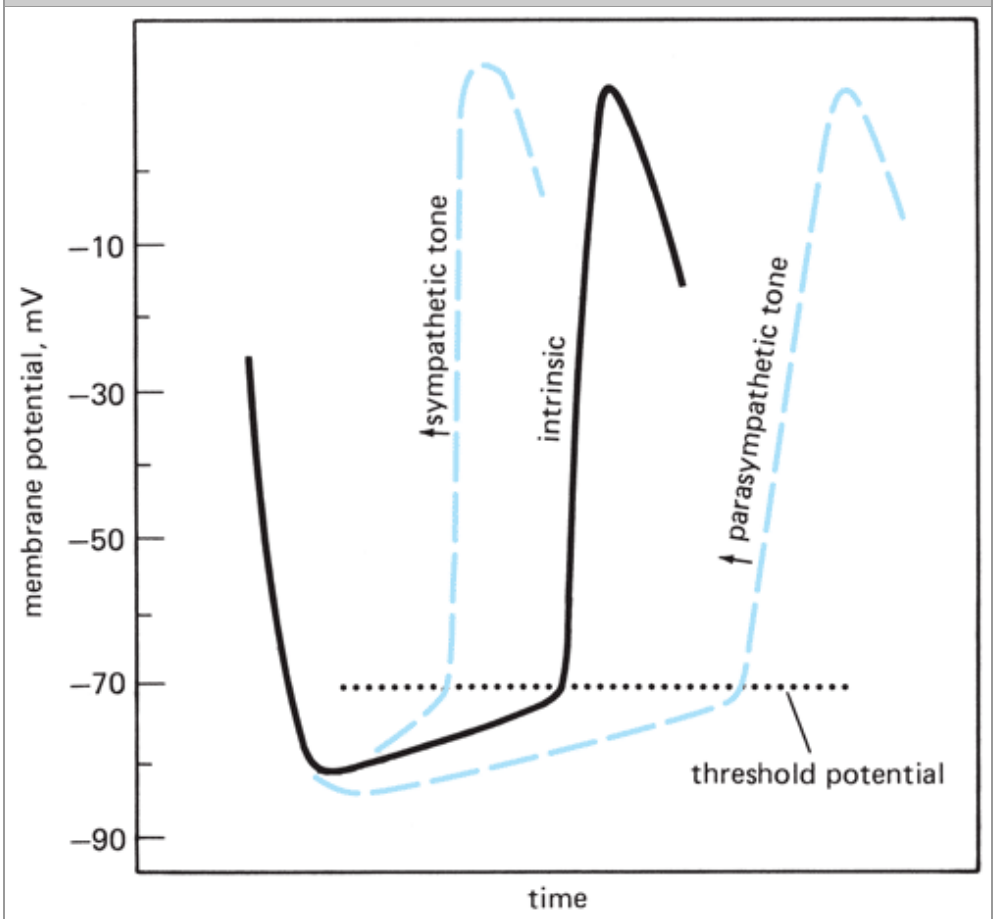
The lower trace of Figure 2–5 represents a typical recording of the voltage changes normally measured be the right arm and the left leg as the heart goes through two cycles of electrical excitation; this record is ca lead II electrocardiogram and will be discussed in detail in Chapter 4. The major features of an electrocard are the *P wave,* the *QRS complex,* and the *T wave.* The P wave corresponds to atrial depolarization, the QR complex to ventricular depolarization, and the T wave to ventricular repolarization.

Control of Heart Beating Rate

Normal rhythmic contractions of the heart occur because of spontaneous electrical pacemaker activity (automaticity) of cells in the SA node. The interval between heartbeats (and thus the heart rate) is determ how long it takes the membranes of these pacemaker cells to spontaneously depolarize to the threshold le SA nodal cells fire at a spontaneous or *intrinsic rate* (≈100 beats per minute) in the absence of any outside influences. Outside influences *are* required, however, to increase or decrease automaticity from its intrinsi

The two most important outside influences on automaticity of SA nodal cells come from the autonomi nervous system. Fibers from both the sympathetic and parasympathetic divisions of the autonomic system terminate on cells in the SA node and these fibers can modify the intrinsic heart rate. Activating the cardia sympathetic nerves (increasing cardiac sympathetic *tone*) increases the heart rate. Increasing cardiac parasympathetic tone slows the heart. As shown in Figure 2–6, the parasympathetic and sympathetic nerv influence heart rate by altering the course of spontaneous depolarization of the resting potential in SA pac cells.

Figure 2–6.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Effect of sympathetic and parasympathetic tone on pacemaker potential.

Cardiac parasympathetic fibers, which travel to the heart through the *vagus* nerves, release the transmitte substance*acetylcholine* on SA nodal cells. Acetylcholine increases the permeability of the resting membran and decreases the diastolic permeability to Na^+.[4] As indicated in Figure 2–6, these permeability changes h effects on the resting potential of cardiac pacemaker cells: (1) they cause an initial hyperpolarization of th membrane potential by bringing it closer to the K^+ equilibrium potential and (2) they slow the rate of spon depolarization of the resting membrane. Both these effects increase the time between beats by prolonging time required for the resting membrane to depolarize to the threshold level. Since there is normally some continuous*tonic* activity of cardiac parasympathetic nerves, the normal resting heart rate is approximately beats per minute.

Sympathetic nerves release the transmitter substance *norepinephrine* on cardiac cells. In addition to other discussed later, norepinephrine increases the inward currents carried by Na^+ (i_f) and by Ca^{2+} during the di interval.[5] These changes will increase heart rate by increasing the rate of diastolic depolarization as shown Figure 2–6.

In addition to sympathetic and parasympathetic nerves, there are many (usually less important) factors th alter heart rate. These include a number of ions and circulating hormones, as well as physical influences su temperature and atrial wall stretch. All act by somehow altering the time required for the resting membran

depolarize to the threshold potential. An abnormally high concentration of Ca^{2+} in the extracellular fluid, fo example, tends to decrease heart rate by shifting the threshold potential. Factors that increase heart rate to have a *positive chronotropic effect.* Those that decrease heart rate have a *negative chronotropic effect.*

Besides their effect on heart rate, autonomic fibers also influence the conduction velocity of action potentia through the heart. Increases in sympathetic activity increase conduction velocity (have a *positive dromotro effect*), whereas increases in parasympathetic activity decrease conduction velocity (have a *negative drom effect*). These effects are most notable at the AV node and can influence the duration of the PR interval.

[4] Acetylcholine interacts with a muscarinic receptor on the SA nodal cell membrane which in turn is linked inhibitory G protein, G_i. The activation of G_i has two effects: (1) an increase in K^+ conductance resulting fr increased opening of the K_{Ach} channels and (2) a suppression of adenylate cyclase leading to a fall in intrac cyclic adenosine monophosphate (cAMP) which reduces the inward-going pacemaker current carried by Na

[5] Norepinephrine interacts with β_1-adrenergic receptors on the SA nodal cell membrane which in turn are l stimulatory G proteins, G_s. The activation of G_s increases adenylate cyclase, leading to an increase in intra cyclic AMP which increases the open-state probability of the pacemaker Na^+ current channel (i_f).

MECHANICAL ACTIVITY OF THE HEART

Cardiac Muscle Contraction

Contraction of the cardiac muscle cell is initiated by the action potential signal acting on intracellular organ evoke tension generation and/or shortening of the cell. In this section, we shall describe (1) the subcellula processes involved in coupling the excitation to the contraction of the cell (E-C coupling) and (2) the mech properties of cardiac cells.

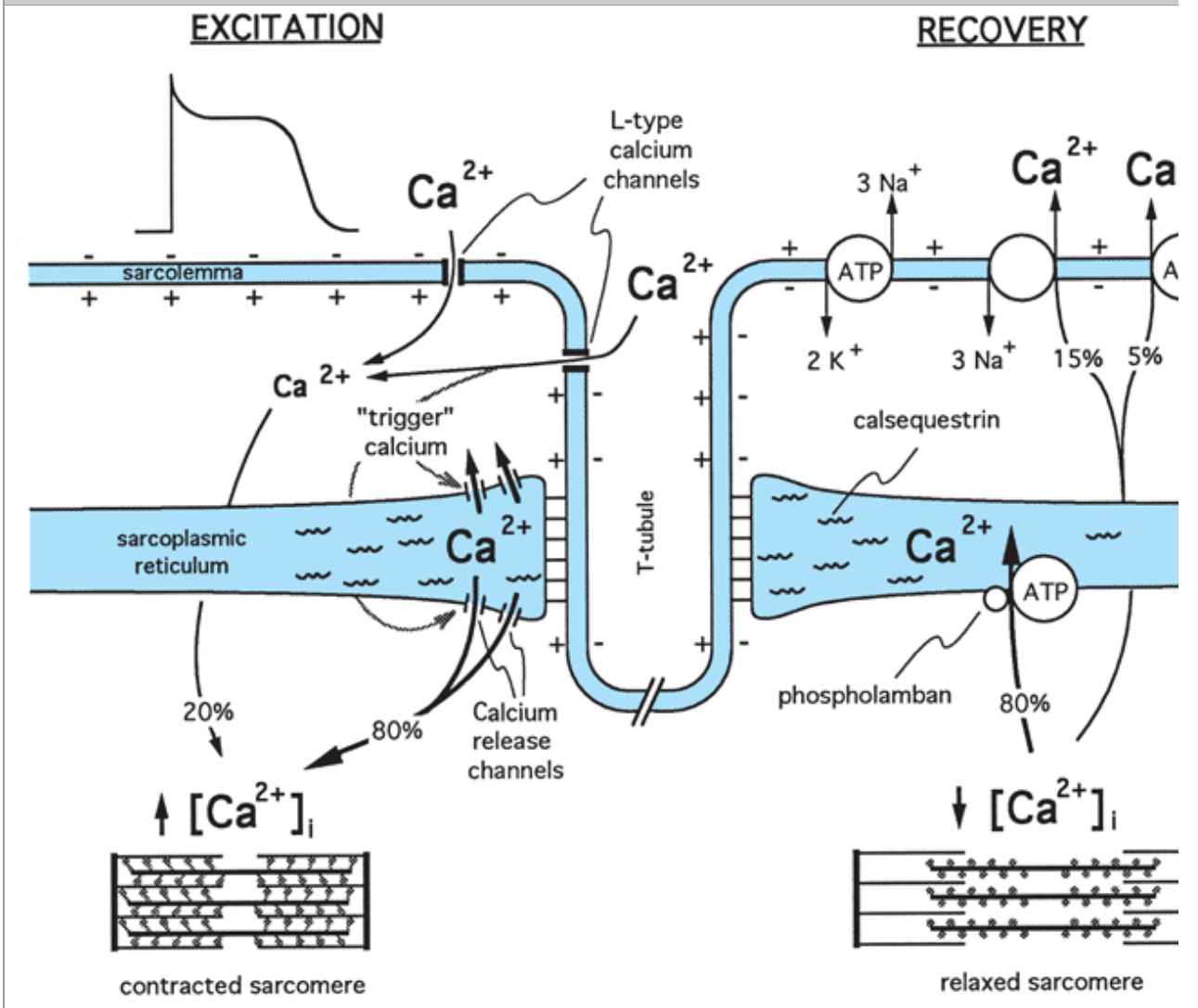
Basic histological features of cardiac muscle cells are quite similar to those of skeletal muscle cells and incl an extensive myofibrillar structure made up of parallel interdigitating thick and thin filaments arranged in s units called *sarcomeres,* which are responsible for the mechanical processes of shortening and tension development[6]; (2) an internal compartmentation of the cytoplasm by an intracellular membrane system ca *sarcoplasmic reticulum* (SR), which sequesters calcium during the diastolic interval with the help of the cal storage protein, calsequestrin; (3) regularly spaced extensive invaginations of the cell membrane (sarcole called*T tubules,* which appear to be connected to parts of the SR ("junctional" SR) by dense strands ("feet" which carry the action potential signal to the inner parts of the cell; and (4) large numbers of mitochondria provide the oxidative phosphorylation pathways needed to ensure a ready supply of adenosine triphosphat to meet the high metabolic needs of cardiac muscle. Students are encouraged to consult a histology textbo specific cellular morphological details.

[6] Proteins making up the thick and thin filaments are collectively referred to as "contractile proteins." The *filament* consists of a protein called *myosin,* which has a long straight tail with two globular heads each of contains an adenosine triphosphate (ATP)-binding site and an actin-binding site; light chains are loosely as with the heads and their phosphorylation may regulate (or modulate) muscle function. The *thin filament* co several proteins including *actin*—two α-helical strands of polymerized subunits (g-actin) with sites that inte with the heads of myosin molecules to form cross-bridges with the thick filaments; *tropomyosin*—a regulat fibrous-type protein lying in the groove of the actin α helix which prevents actin from interacting with myo the muscle is at rest; and *troponin*—a regulatory protein consisting of three subunits: *troponin C,* which bi calcium ions during activation and initiates the configurational changes in the regulatory proteins that expo actin site for cross-bridge formation; *troponin T,* which anchors the troponin complex to tropomyosin; and *I,* which participates in the inhibition of actin-myosin interaction at rest. In addition, the macromolecule tit extends from the Z disk to the M line and contributes significantly to the passive stiffness of cardiac muscle normal working range.

Excitation-Contraction Coupling

Muscle action potentials trigger mechanical contraction through a process called *excitation-contractior coupling,* which is illustrated in Figure 2–7. The major event of excitation-contraction coupling is a dramati the intracellular free Ca^{2+} concentration. The "resting" intracellular free Ca^{2+} concentration is less than 0.1 contrast, during maximum activation of the contractile apparatus, the intracellular free Ca^{2+} concentration nearly 100 μ*M.* When the wave of depolarization passes over the muscle cell membrane and down the T tu Ca^{2+} is released from the SR into the intracellular fluid.

Figure 2–7.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Excitation-contraction coupling and sarcomere shortening.

As indicated on the left side of Figure 2–7, the specific trigger for this release appears to be the entry of ca into the cell via the L-type calcium channels and an increase in Ca^{2+} concentration in the region just under sarcolemma on the surface of the cell and throughout the t-tubular system. Unlike skeletal muscle, this hig localized increase in calcium is essential for triggering the massive release of calcium from the SR. This *cal*

induced calcium release is a result of opening calcium-sensitive release channels on the SR.[7] Although the of Ca^{2+} that enters the cell during a single action potential is quite small compared with that released from it is not only essential for triggering the SR calcium release but also essential for maintaining adequate lev Ca^{2+} in the intracellular stores over the long run.

When the intracellular Ca^{2+} level is high (>1.0 μ*M*), links called *cross-bridges* form between two types of fi found within muscle. Sarcomere units, as depicted in the lower part of Figure 2–7, are joined end to end a to form *myofibrils,* which run the length of the muscle cell. During contraction, thick and thin filaments slid one another to shorten each sarcomere and thus the muscle as a whole. The bridges form when the regula spaced myosin heads from thick filaments attach to regularly spaced sites on the actin molecules in the thi filaments. Subsequent deformation of the bridges result in a pulling of the actin molecules toward the cent sarcomere. This actin-myosin interaction requires energy from ATP. In resting muscles, the attachment of to the actin sites is inhibited by troponin and tropomyosin. Calcium causes muscle contraction by interactir troponin C to cause a configurational change that removes the inhibition of the actin sites on the thin filam Since a single cross-bridge is a very short structure, gross muscle shortening requires that cross-bridges repetitively form, produce incremental movement between the myofilaments, detach, form again at a new site, and so on, in a cyclic manner.

There are several processes that participate in the reduction of intracellular Ca^{2+} that terminates the contr These processes are illustrated on the right side of Figure 2–7. Approximately 80% of the calcium is active back up into the SR by the action of Ca^{2+}-ATPase pumps located in the network part of the SR.[8] About 20% calcium is extruded from the cell into the extracellular fluid either via the Na^{+}-Ca^{2+} exchanger located in tl sarcolemma[9] or via sarcolemmal Ca^{2+}-ATPase pumps.

Excitation-contraction coupling in cardiac muscle is different from that in skeletal muscle in that it may be modulated; different intensities of actin-myosin interaction (contraction) can result from a single action po trigger in cardiac muscle. The mechanism for this seems to be dependent on variations in the amount of C reaching the myofilaments and therefore the number of cross-bridges activated during the twitch. This abil cardiac muscle to vary its contractile strength—ie, change its *contractility*—is extremely important to cardi function, as will be discussed in a later section of this chapter.

The duration of the cardiac muscle cell contraction is approximately the same as that of its action potentia Therefore, the electrical refractory period of a cardiac muscle cell is not over until the mechanical response completed. As a consequence, heart muscle cells cannot be activated rapidly enough to cause a fused (teta state of prolonged contraction. This is fortunate because intermittent contraction and relaxation are essent the heart's pumping action.

[7] These channels may be blocked by the plant alkaloid ryanodine and are activated by the methylxanthine These agents are chemical tools used to assess properties of these SR channels.

[8] The action of these pumps is regulated by the protein phospholamban. When this protein is phosphorylat example, by the action of norepinephrine) the rate of Ca^{2+} resequestration is increased and the rate of rela is enhanced.

[9] The Na^{+}-Ca^{2+} exchanger is powered by the sodium gradient across the sarcolemma which in turn is mair by the Na^{+}/K^{+} ATPase. This exchanger is electrogenic in that three Na^{+} ions move into the cell in exchange each Ca^{2+} ion that moves out. This net inward movement of positive charge may contribute to the mainter the plateau phase of the action potential. The cardiac glycoside, digitalis, slows down the Na^{+}/K^{+} pump an reduces the sodium gradient which in turn results in an increase in intracellular Ca^{2+}. This mechanism cont to the positive effect of cardiac glycosides on the contractile force of the failing heart.

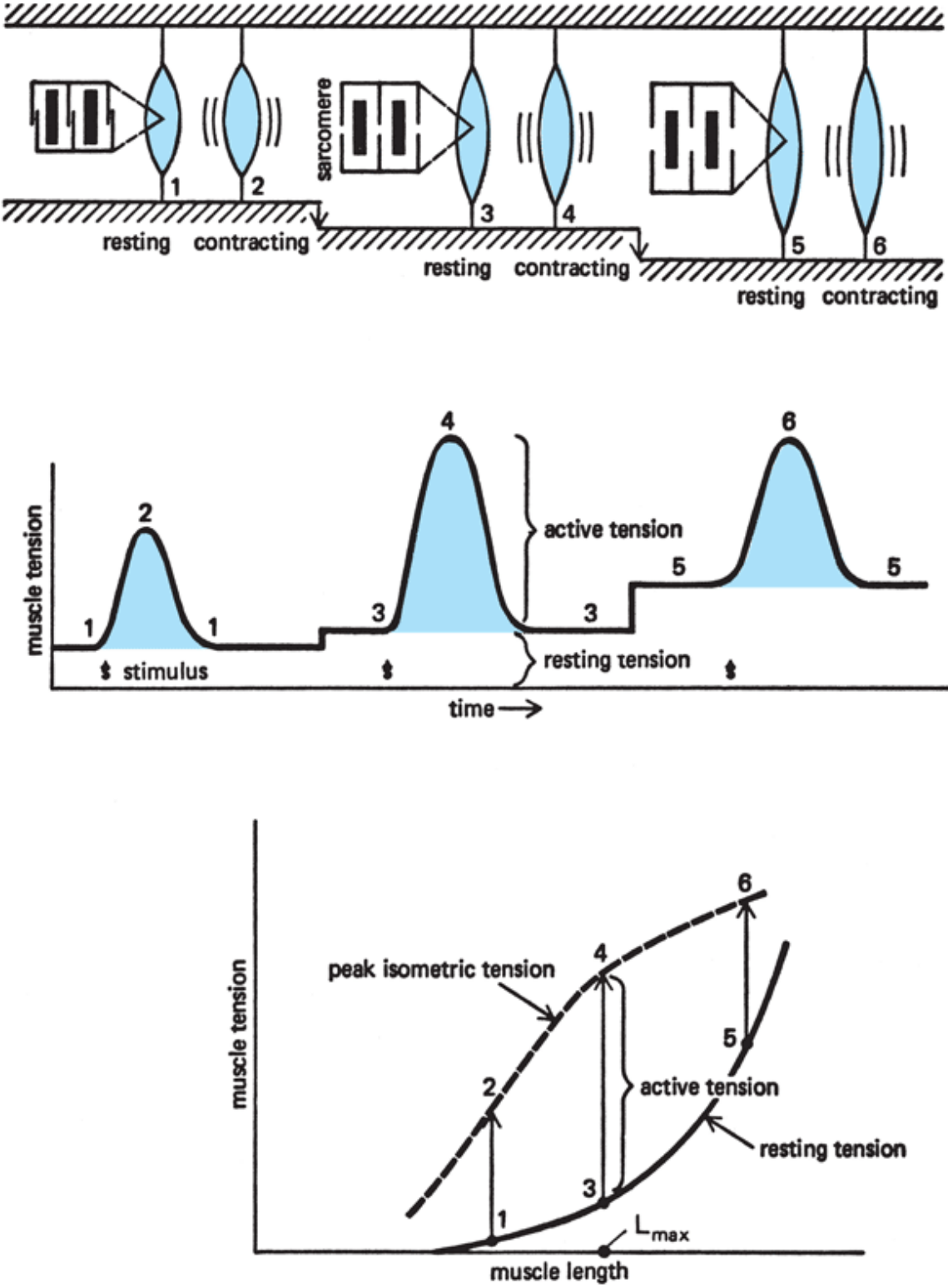
Cardiac Muscle Cell Mechanics

The cross-bridge interaction that occurs after a muscle is activated to contract gives the muscle the p to develop force and/or shorten. Whether it does one, the other, or some combination of the two depends primarily on what is allowed to happen by the external constraints placed on the muscle during the contrac example, activating a muscle whose ends are held rigidly causes it to develop tension, but it cannot shorte is called an *isometric* ("fixed length") contraction. The force that a muscle produces during an isometric co indicates its maximum ability to develop tension. At the other extreme, activating an unrestrained muscle to shorten without force development because it has nothing to develop force against. This type of contrac called an *isotonic* ("fixed tension") contraction. Under such conditions, a muscle shortens with its maximun possible velocity (called V_{max}), which is determined by the maximum possible rate of cross-bridge cycling. load to the muscle decreases the velocity and extent of its shortening. Thus, the course of a muscle contra depends both on the inherent capabilities of the muscle and the external constraints placed on the muscle contraction. Muscle cells in the ventricular wall operate under different constraints during different phases cardiac cycle. To understand ventricular function, the manner in which cardiac muscle behaves when const several different ways must first be examined.

Isometric Contractions: Length-Tension Relationships

The influence of muscle length on the behavior of cardiac muscle during isometric contraction is illustrated Figure 2–8. The top panel shows the experimental arrangement for measuring muscle force at rest and du contraction at three different lengths. The middle panel shows time records of muscle tensions recorded at the three lengths in response to an external stimulus, and the bottom panel shows a graph of the resting a tension results plotted against muscle length.

Figure 2–8.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Isometric contractions and the effect of muscle length on resting tension and active tension development.

The first important fact illustrated in Figure 2–8 is that force is required to stretch a resting muscle to diffe

lengths. This force is called the *resting tension.* The lower curve in the graph in Figure 2–8 shows the resti tension measured at different muscle lengths and is referred to as the *resting length-tension curve.* When is stimulated to contract while its length is held constant, it develops an additional component of tension c *active*or *developed tension.* The *total tension* exerted by a muscle during contraction is the sum of the acti resting tensions.

The second important fact illustrated in Figure 2–8 is that the active tension developed by cardiac muscle the course of an isometric contraction depends very much on the muscle length at which the contraction o Active tension development is maximum at some intermediate length referred to as L_{max}. Little active tens developed at very short or very long muscle lengths. Normally, cardiac muscle operates at lengths well bel so that increasing muscle length increases the tension developed during an isometric contraction.

There are three separate mechanisms that have been proposed to explain the relationship between muscle and developed tension. The first mechanism to be identified suggests that this relationship depends on the *of overlap* of the thick and thin filaments in the sarcomere at rest. Histological studies indicate that the cha the resting length of the whole muscle are associated with proportional changes in the individual sarcomer tension development occurs at sarcomere lengths of 2.2 to 2.3 μm. At sarcomere lengths shorter than ~ 2. the opposing thin filaments may overlap or buckle and thus interfere with active tension development as s the top of Figure 2–8. At long sarcomere lengths, overlap may be insufficient for optimal cross-bridge form

The second (and perhaps more important) mechanism is based on a length-dependent change in *sensitivit* myofilaments to calcium. At short lengths only a fraction of the potential cross-bridges are apparently activ a given increase in intracellular calcium. At longer lengths, more of the cross-bridges become activated, le an increase in active tension development. This change in calcium sensitivity occurs immediately after a ch length with no time delay. The "sensor" responsible for the length-dependent activation of cardiac muscle reside with the troponin C molecule, but how it happens is not fully understood.

The third mechanism rests on the observation that within several minutes after increasing the resting leng cardiac muscle, there is an increase in the *amount* of calcium that is released with excitation, which is coup further increase in force development. It is thought that stretch-sensitive ion channels in the cell membrar be responsible for this delayed response.

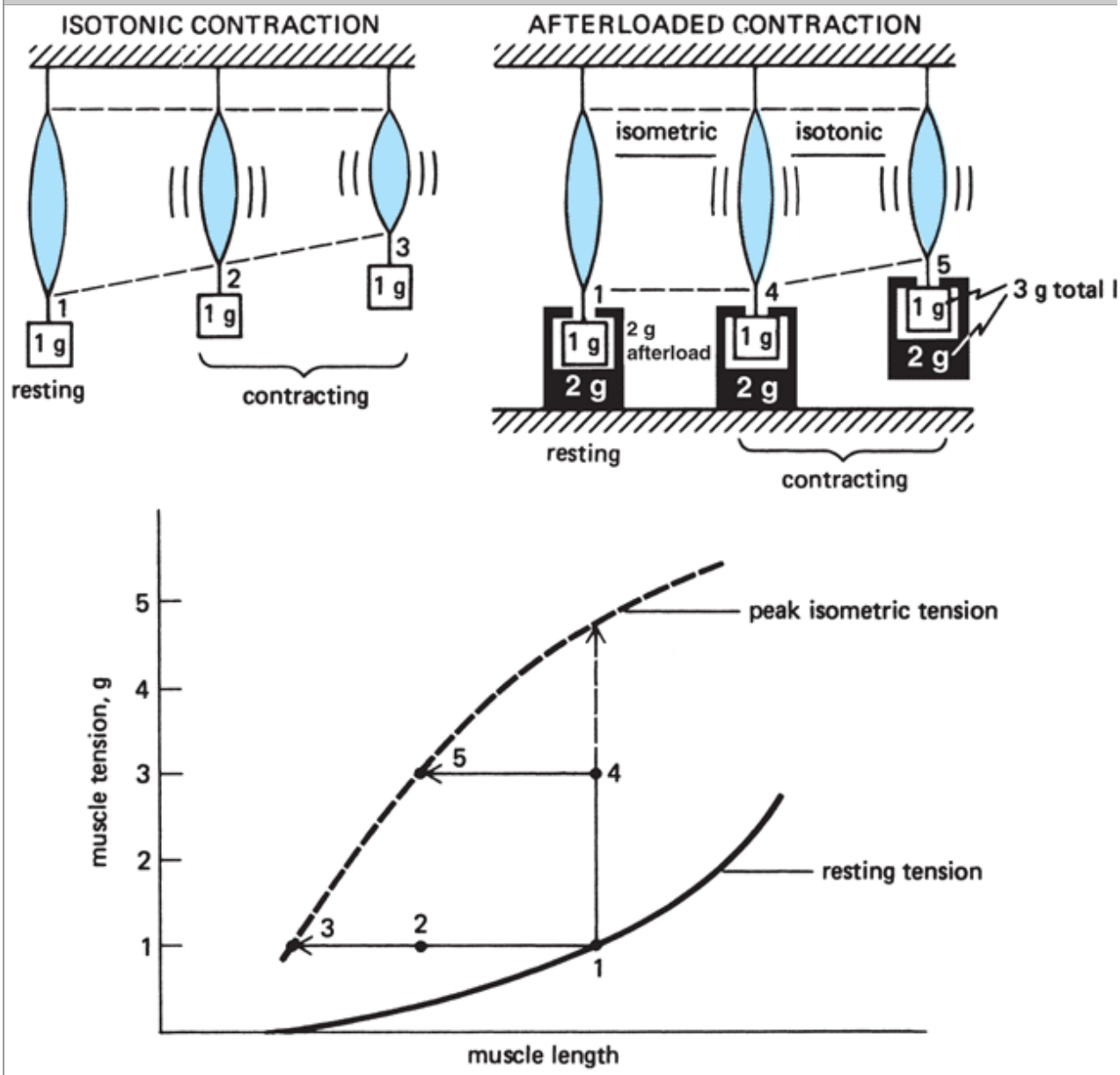
To what extent each of these mechanisms is contributing to the length-dependency of cardiac contractile f any instant is not clear, nor very important in this discussion. The important point is that the dependence tension development on muscle length is a fundamental property of cardiac muscle that has extremely pov effects on heart function.

Isotonic & Afterloaded Contractions

During what is termed *isotonic* ("fixed load") contraction, a muscle shortens against a constant load. A mu contracts isotonically when lifting a fixed weight such as the 1-g load shown in Figure 2–9. Such a 1-g weig placed on a resting muscle will result in some specific resting muscle length, which is determined by the m resting length-tension curve. If the muscle were to contract isometrically at this length, it would be capabl generating a certain amount of tension, eg, 4.5 g as indicated by the dashed line in the graph of Figure 2– contractile tension of 4.5 g obviously cannot be generated while lifting a 1-g weight. When a muscle has c potential in excess of the tension it is actually developing, it shortens. Thus in an isotonic contraction, mus length decreases at constant tension, as illustrated by the horizontal arrow from point 1 to point 3 in Figur As the muscle shortens, however, its contractile potential inherently decreases, as indicated by the downw slope of the peak isometric tension curve in Figure 2–9. There exists some short length at which the muscl capable of generating only 1 g of tension, and when this length is reached, shortening must cease.[10] Thus curve on the cardiac muscle length-tension diagram that indicates how much isometric tension a muscle ca

develop at various lengths also establishes the limit on how far muscle shortening can proceed with differe

Figure 2–9.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Relationship of isotonic and afterloaded contractions to the cardiac muscle length-tension diagram.

Figure 2–9 also shows a complex type of muscle contraction called an *afterloaded isotonic contraction,* in v load on the muscle at rest, the *preload,* and the load on the muscle during contraction, the *total load,* are In the example of Figure 2–9 the preload is equal to 1 g, and because an additional 2-g weight (the *afterlo* engaged during contraction, the total load equals 3 g.

Since preload determines the resting muscle length, both isotonic contractions shown in Figure 2–9 begin same length. Because of the different loading arrangement, however, the afterloaded muscle must increas

total tension to 3 g before it can shorten. This initial tension will be developed isometrically and can be rep as going from point 1 to point 4 on the length-tension diagram. Once the muscle generates enough tensio equal the total load, its tension output is fixed at 3 g and it will now shorten isotonically because its contra potential still exceeds its tension output. This isotonic shortening is represented as a horizontal movement length-tension diagram along the line from point 4 to point 5. As in any isotonic contraction, shortening m cease when the muscle's tension-producing potential is decreased sufficiently by the length change to be e the load on the muscle. Note that the afterloaded muscle shortens less than the nonafterloaded muscle ev though both muscles began contracting at the same initial length. The factors that affect the extent of car muscle shortening during an afterloaded contraction are of special interest to us, because, as we shall see, volume is determined by how far cardiac muscle shortens under these conditions.

[10] In reality, muscle shortening requires some time and the duration of a muscle twitch contraction is limit because intracellular Ca^{2+} levels are elevated only briefly following the initiation of a membrane action pot For this and possibly other reasons, isotonic shortening may not actually proceed quite as far as the isome tension development curve on the length-tension diagram suggests is possible. Since this complication doe alter the general correspondence between a muscle's isometric and isotonic performance, we choose to ign

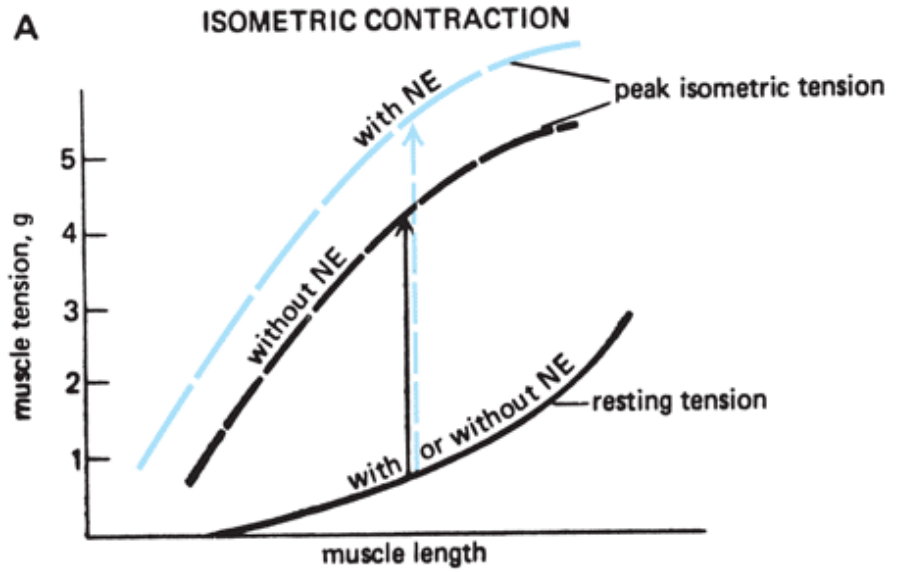
Cardiac Muscle Contractility

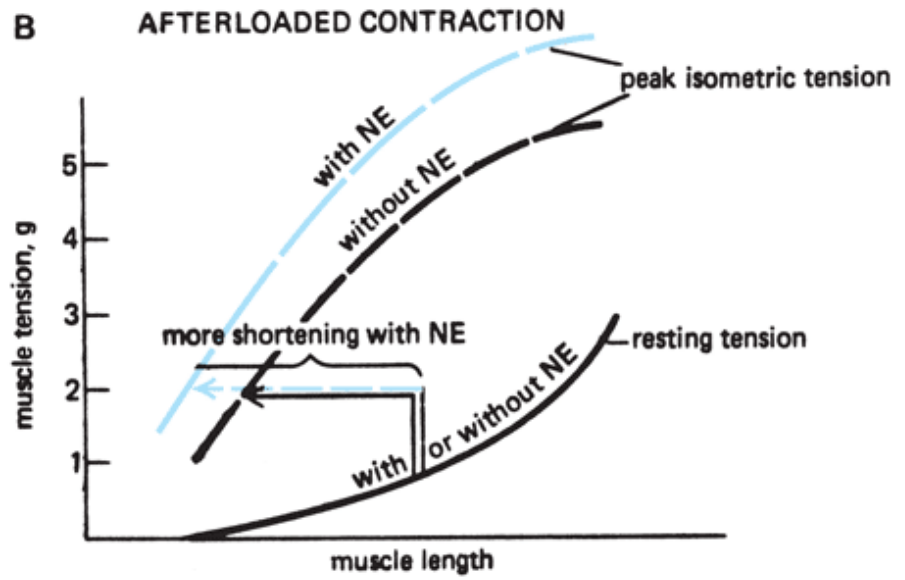
A number of factors in addition to initial muscle length can affect the tension-generating potential of cardia muscle.*Any intervention that increases the peak isometric tension that a muscle can develop at a* fixed len *said to increase cardiac muscle contractility.* Such an agent is said to have a *positive inotropic effect* on th

The most important physiological regulator of cardiac muscle contractility is norepinephrine. When norepin is released on cardiac muscle cells from sympathetic nerves, it has not only the chronotropic effect on hea discussed earlier but also a pronounced positive inotropic effect that causes cardiac muscle cells to contrac rapidly and forcefully.

The positive effect of norepinephrine on the isometric tension-generating potential is illustrated in Figure 2 When norepinephrine is present in the solution bathing cardiac muscle, the muscle will, *at every length,* de more isometric tension when stimulated than it would in the absence of norepinephrine. In short, norepine raises the peak isometric tension curve on the cardiac muscle length-tension graph. Norepinephrine is said increase cardiac muscle contractility because it enhances the forcefulness of muscle contraction *even when is constant.* Changes in contractility and initial length can occur simultaneously, but by definition a change *contractility* must involve a shift from one peak isometric length-tension curve to another.

Figure 2–10.





Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Effect of norepinephrine (NE) on isometric (A) and afterloaded (B) contractions of cardiac muscle.

Figure 2–10B shows how raising the peak isometric length-tension curve with norepinephrine increases the of shortening in afterloaded contractions of cardiac muscle. With preload and total load constant, more shc occurs in the presence of norepinephrine than in its absence. This is because when contractility is increase tension-generating potential is equal to the total load at a shorter muscle length. Note that norepinephrine effect on the resting length-tension relationship of cardiac muscle. Thus norepinephrine causes increased shortening by changing the final but not the initial muscle length associated with afterloaded contractions.

The cellular mechanism of the norepinephrine effect on contractility is mediated by its interaction with a β_1 adrenergic receptor. The signaling pathway involves an activation of the G_s protein-cAMP-protein kinase A, then phosphorylates the Ca^{2+} channel increasing the inward calcium current during the plateau of the actio potential. This increase in calcium influx not only contributes to the magnitude of the rise in intracellular C given beat but also loads the internal calcium stores, which allows more to be released during subsequent depolarizations. This increase in free Ca^{2+} during activation allows more cross-bridges to be formed and gr tension to be developed.

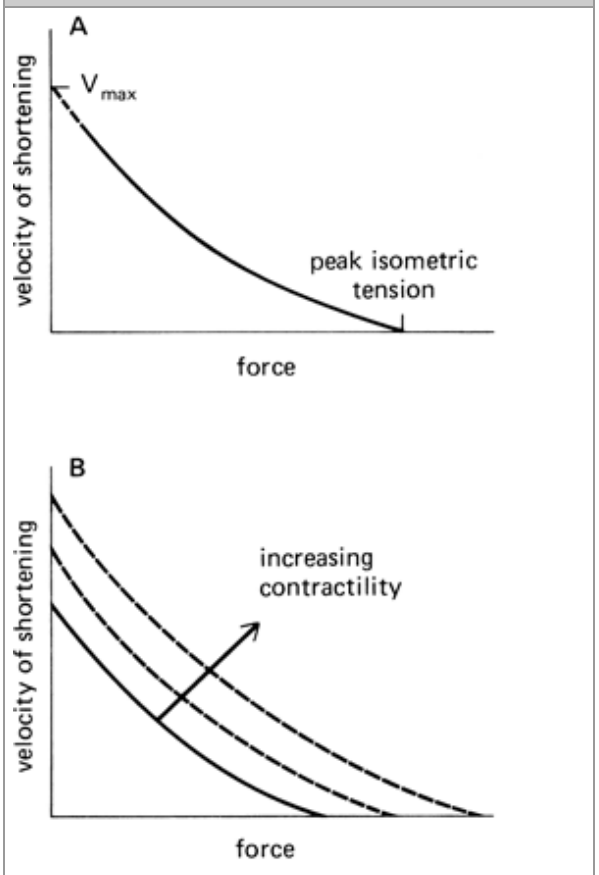
Because norepinephrine also causes phosphorylation of the regulatory protein, phospholamban, on the sarcoplasmic reticular Ca^{2+} ATPase pump, the rate of calcium retrapping into the SR is enhanced and the r relaxation is increased. This is called a *positive lusitropic effect.* In addition to more rapid calcium retrappi SR, there is also a norepinephrine-induced decrease in the action potential duration. This effect is achieved potassium channel alteration, occurring in response to the elevated intracellular[Ca^{2+}], that increases pota permeability, terminates the plateau phase of the action potential and contributes to the early relaxation. shortening of the systolic interval is helpful in the presence of elevated heart rates that might otherwise significantly compromise diastolic filling time.

Enhanced parasympathetic activity has been shown to have a small negative inotropic effect upon the hea atria, where this effect is most pronounced, the negative inotropic effect is thought to be due to a shorteni the action potential and a decrease in the amount of Ca^{2+} that enters the cell during the action potential.

Changes in heart rate also influence cardiac contractility. Recall that a small amount of extracellular Ca^{2+} e the cell during the plateau phase of each action potential. As the heart rate increases, more Ca^{2+} enters th per minute. There is a buildup of intracellular Ca^{2+} and a greater amount of Ca^{2+} is released into the sarco with each action potential. Thus, a sudden increase in beating rate is followed by a progressive increase in contractile force to a higher plateau. This behavior is called the *staircase phenomenon* (or treppe). Change contractility produced by this intrinsic mechanism are sometimes referred to as *homeometric autoregulatio* importance of such rate-dependent modulation of contractility in normal ventricular function is not clear at

The contractility of isolated cardiac muscle is often assessed by first determining the peak velocity of short the preparation during isotonic contractions against several different total loads. The data obtained are use construct what is known as the muscle *force-velocity* relationship as shown in Figure 2–11A. The force-velo relationship indicates the trade-off between force development and shortening velocity, which is inherent i contractile machinery of all muscle. The isometric force generating capability of the muscle is indicated by point where the curve intersects the force axis. The point where the force-velocity curve intersects the velo is called V_{max}. This V_{max} point has been shown to be closely correlated with the actin-myosin ATPase activi muscle and is thought to indicate the maximum possible rate of interaction between thick and thin filamen the sarcomere. The V_{max} value is commonly used as an index of the contractility of isolated cardiac muscle 2–11B shows the effect of norepinephrine (or other inotropic agents) on the force-velocity relationship. No both peak isometric tension and V_{max} become elevated with increases in the contractility of the preparatio

Figure 2–11.



Copyright ©2006 by The McGraw-Hill Companies, Inc. All rights reserved.

Cardiac muscle force-velocity relationship.

RELATING CARDIAC MUSCLE CELL MECHANICS TO VENTRICULAR FUNCT

Certain geometric factors dictate how the length-tension relationships of cardiac muscle fibers in the ventricular wall determine the volume and pressure relationships of the ventricular chamber. The actual relationships are complex because the shape of the ventricle is complex. The ventricle is often modeled as cylinder or a sphere, although its actual shape lies somewhere between the two. Because cardiac muscle c oriented circumferentially in the ventricular wall, either model can be used to illustrate three important fun points:

1. An increase in ventricular volume causes an increase in ventricular circumference and therefore an incre the length of the individual cardiac muscle cells (and vice-versa).

2. At any given ventricular volume, an increase in the tension of individual cardiac muscle cells in the wall an increase in intraventricular pressure (and vice versa).

3. As ventricular volume increases (ie, as the ventricular radius increases), a greater force is required from individual muscle cell to produce any given intraventricular pressure.

The last point is a reflection of the *law of Laplace*, which is a statement of the relationship that exists betw forces within the walls of any curved fluid container and pressure of its contents. If the ventricle is modele

cylinder where changes in ventricular volume occur only by changes in radius, the law of Laplace states tha tension on the muscle of the ventricular wall (T) depends both on the intraventricular pressure (P) and the intraventricular radius (r) as $T = P \times r$.

The importance of these relationships will become more apparent in the subsequent chapter as we conside cardiac muscle cell behavior determines how the heart functions as a pump.

KEY CONCEPTS


Cardiac myocyte membrane potentials are a result of the relative permeability of the membrane to va ions and their concentration differences across the membrane.


Action potentials of cardiac myocytes are a result of changes in the membrane permeability to various


Action potentials of cardiac myocytes have long plateau phases that generate long refractory periods preclude summated or tetanic contractions.


Action potentials are spontaneously generated by pacemaker cells in the SA node and are conducted f to cell via gap junctions throughout the entire heart.


The rate of spontaneous diastolic depolarization of the SA nodal cells (and thus the heart rate) is mod by the autonomic nervous system.


Excitation of the cardiac myocyte initiates contraction by increasing the cytostolic calcium level that a the contractile apparatus.


Mechanical response of the myocyte depends on preload (determined by the initial resting length), aft (determined by the tension that needs to be developed) and contractility (the degree of activation of the contractile apparatus dependent upon the amount of calcium released upon activation).


The cardiac myocyte length-tension relationships are correlated with changes in volume and pressure intact ventricle.

STUDY QUESTIONS

2–1. Small changes in extracellular potassium ion concentrations have major effects on cell membrane pot

a. What will happen to the potassium equilibrium potential of cardiac muscle cells when interstitial $[K^+]$ ($[K^+]_O$) is elevated?

b. What effect will this have on the cells' resting membrane potential?

c. What effect will this have on the cells' excitability?

2–2. Cardiac survival during cardiac transplantation is improved by perfusing donor hearts with cardioplegi solutions containing ~ 20 mM KCl. Why is this high potassium concentration helpful?

2–3. There are several classes of drugs that are useful for treating various cardiac arrhythmias. Identify th primary effects of each of the following classes of drugs on cardiac myocyte characteristics.

a. What are the effects of sodium channel blockers on the PR interval of the ECG? On the duration of the complex?

b. What are the effects of calcium channel blockers on the rate of firing of SA nodal cells? On the rate of conduction of the action potential through the AV node? On myocardial contractility?

c. What are the effects of potassium channel blockers on action potential duration? On refractory periods

2–4. Very high sympathetic neural activity to the heart can lead to tetanic concentration of the cardiac mu True or false?

2–5. An increase in which of the following (with the others held constant) will result in an increase in the a active shortening of a cardiac muscle cell?

a. Preload

b. Afterload

c. Contractility

See answers.

SUGGESTED READINGS

Blaustein MP, Lederer WJ. Sodium/calcium exchange: its physiological implications. *Physiol Rev.* 1999;79:763–854. [PMID: 10390518]

Brady AJ. Mechanical properties of isolated cardiac myocytes. *Physiol Rev.* 1991;71:413–422. [PMID: 2006

Brutsaert DL. Cardiac endothelial-myocardial signaling: its role in cardiac growth, contractile performance rhythmicity.*Physiol Rev*. 2003;83:59–115. [PMID: 12506127]

Carmeliet E. Cardiac ionic currents and acute ischemia: from channels to arrhythmias. *Physiol Rev.* 1999;79:917–1017. [PMID: 10390520]

Catterall WA. Cellular and molecular biology of voltage-gated sodium channels. *Physiol Rev.* 1992;72(Suppl):S15–S48.

Deal KK, England SK, Tamkun MM. Molecular physiology of cardiac potassium channels. *Physiol Rev.* 1996;76:49–67. [PMID: 8592732]

DiFrancesco D. Pacemaker mechanisms in cardiac tissue. *Annu Rev Physiol.* 1993;55:451–467.

Fukuda N, Wu Y, Nair P, Granzier HL. Phosphorylation of titin modulates passive stiffness of cardiac muscle titin isoform-dependent manner. *J Gen Physiol*. 2005;125:257–271. [PMID: 15738048]

Gordon AM, Regnier M, Homsher E. Skeletal and cardiac muscle contractile activation: Tropomyosin "Rocks Rolls."*News Physiol Sci.* 2000;16:49–56.

Hamilton SL, Serysheva I, Strasburg GM. Calmodulin and excitation-contraction coupling. *News Physiol Sci* 2000;15:281–284. [PMID: 11390927]

Hiraoka M, Furukawa T. Functional modulation of cardiac ATP-sensitive K^+ channels. *News Physiol Sci.* 1998;13:131–137. [PMID: 11390776]

Hume JR, Duan D, Collier ML, et al. Anion transport in the heart. *Physiol Rev*. 2000;80:31–81. [PMID: 106

Irisawa H, Brown HF, Giles W. Cardiac pacemaking in the sinoatrial node. *Physiol Rev.* 1993;73:197–227. [8380502]

Kleber AG, Rudy Y. Basic mechanisms of cardiac impulse propagation and associated arrhythmias. *Physiol* 2003;84:431–488.

Kolbayashi T, Solaro RJ. Calcium, thin filaments and the integrative biology of cardiac contractility. *Annu R Physiol.* 2005;67:39–67.

Korzick DH. Regulation of cardiac excitation-contraction coupling: a cellular update. *Adv Physiol Educ.* 2003;27:192–200. [PMID: 14627617]

Lipsius SL, Huser J, Blatter LA. Intracellular Ca^{2+} release sparks atrial pacemaker activity. *News Physiol Sci* 2001;16:101–109. [PMID: 11443225]

McDonald TF, Pelzer S, Trautwein W, Pelzer DJ. Regulation and modulation of calcium channels in cardiac, and smooth muscle cells. *Physiol Rev.* 1994;74:365–507. [PMID: 8171118]

Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. *Physiol Rev.* 2005;85:1205–1253. [16183911]

Niggli E. Ca^{2+} sparks in cardiac muscle: is there life without them? *News Physiol Sci.* 2000;14:281–284.

Noble D. Modeling the heart—from genes to cells to the whole organ. *Science.* 2002;295:1678–1682. [PMI 11872832]

Pallotta BS, Wagoner PK. Voltage-dependent potassium channels since Hodgkin and Huxley. *Physiol Rev.* 1992;72(Suppl):S49–S67.

Philipson KD, Nicoll DA. Sodium-calcium exchange: a molecular perspective. *Annu Rev Physiol.* 2000;62:1
[PMID: 10845086]

Pongs O. Molecular biology of voltage-dependent potassium channels. *Physiol Rev.* 1992;72(Suppl):S69–S

Protas L, Qu J, Robinson RB. Neuropeptide Y: neurotransmitter or trophic factor in the heart? *News Physiol*
2003;18:181–185. [PMID: 14500795]

Roden DM, Balser JR, George AL Jr, Anderson ME. Cardiac ion channels. *Annu Rev Physiol.* 2002;64:431–4
[PMID: 11826275]

Salama G, Choi BR. Images of action potential propagation in the heart. *News Physiol Sci.* 1999;15:129–1

Saul JP. Beat-to-beat variations of heart rate reflect modulation of cardiac autonomic outflow. *News Physio*
1990;5:32–37.

Wehrens XHT, Lehnart SE, Marks AR. Intracellular calcium release and cardiac disease. *Annu Rev Physiol.*
2005;67:69–98. [PMID: 15709953]

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.
Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.

Medical a silverchair information system The McGraw-Hill Companies

McGraw-Hill's ACCESSMedicine

Print Close Window

Note: Large images and tables on this page may necessitate printing in landscape mode.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.

OBJECTIVES

The student knows the basic electrical and mechanical events of the cardiac cycle:

- *Correlates the electrocardiographic events with the mechanical events during the cardiac cycle.*
- *Lists the major distinct phases of the cardiac cycle as delineated by valve opening and closure.*
- *Describes the pressure and volume changes in the atria, the ventricles, and the aorta during each phase of the cardiac cycle.*
- *Defines and states normal values for (1) ventricular end-diastolic volume, end-systolic volume, stroke volume, diastolic pressure, and peak systolic pressure, and (2) aortic diastolic pressure, systolic pressure, and pulse pressure.*
- *States similarities and differences between mechanical events in the left and right heart pump.*
- *States the origin of the heart sounds.*
- *Diagrams the relationship between left ventricular pressure and volume during the cardiac cycle.*

The student understands the factors that determine cardiac output:

- *Defines cardiac output and cardiac index.*
- *States the relationship between cardiac output, heart rate, and stroke volume.*
- *Identifies the major determinants of stroke volume.*
  - *States the Frank-Starling law of the heart.*
  - *Predicts the effect of altered ventricular preload on stroke volume and the ventricular pressure-volume relationship.*
  - *Predicts the effect of altered ventricular afterload on stroke volume and the ventricular pressure-volume relationship.*
  - *Predicts the effect of altered ventricular contractility (inotropic state) on stroke volume and the ventricular pressure-volume relationship.*
- *Draws a family of cardiac function curves describing the relationship between filling pressure and cardiac output under various levels of sympathetic tone.*
- *Given data, calculates cardiac output using the Fick principle.*
- *Defines ejection fraction and identifies methods to determine it.*
- *Describes the end-systolic pressure-volume relationship.*

THE HEART PUMP: INTRODUCTION

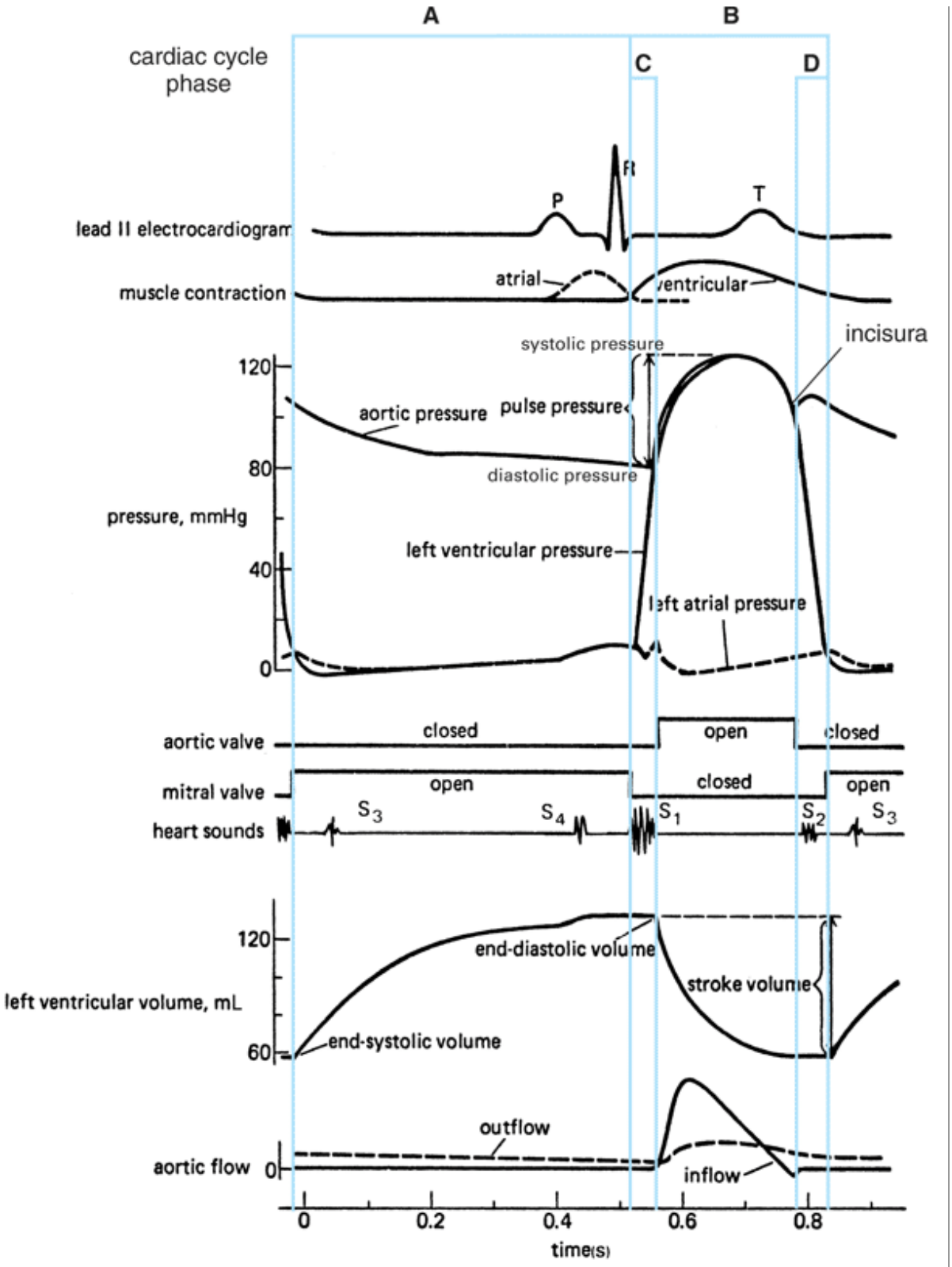
The repetitive, synchronized contraction and relaxation of the cardiac muscle cells provide the forces necessary to pump blood through the systemic and pulmonary circulations. In this chapter, we shall describe (1) basic mechanical features of this cardiac pump, (2) factors that influence and/or regulate the cardiac output, and (3) various methods for estimating cardiac mechanical function.

CARDIAC CYCLE

Left Pump

The mechanical function of the heart can be described by the pressure, volume, and flow changes that occur within it during one cardiac cycle. A cardiac cycle is defined as one complete sequence of contraction and relaxation. The normal mechanical events of a cycle of the left heart pump are correlated in Figure 3–1. This important figure summarizes a great deal of information and should be studied carefully.

Figure 3–1.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Cardiac cycle—left heart. Cardiac cycle phases: A, diastole; B, systole; C, isovolumetric contraction; andD, isovolumetric relaxation.

VENTRICULAR DIASTOLE

The*diastolic phase* [1] of the cardiac cycle begins with the opening of the atrioventricular (AV) valves. As shown in Figure 3–1, the mitral valve opens when left ventricular pressure falls below left atrial pressure and the period of ventricle filling begins. Blood that had previously accumulated in the atrium behind the closed mitral valve empties rapidly into the ventricle and this causes an initial drop in atrial pressure. Later, the pressures in both chambers slowly rise together as the atrium and ventricle continue passively filling in unison with blood returning to the heart through the veins.

Atrial contraction is initiated near the end of ventricular diastole by the depolarization of the atrial muscle cells, which causes the P wave of the electrocardiogram. As the atrial muscle cells develop tension and shorten, atrial pressure rises and an additional amount of blood is forced into the ventricle. At normal heart rates, atrial contraction is not essential for adequate ventricular filling. This is evident in Figure 3–1 from the fact that the ventricle has nearly reached its maximum or *end-diastolic volume* before atrial contraction begins. Atrial contraction plays an increasingly significant role in ventricular filling as heart rate increases because the time interval between beats for passive filling becomes progressively shorter with increased heart rate. Note that throughout diastole, atrial and ventricular pressures are nearly identical. This is because a normal open mitral valve has very little resistance to flow and thus only a very small atrial-ventricular pressure difference is necessary to produce ventricular filling.

[1] The atria and ventricles do not beat simultaneously. Usually, and unless otherwise noted, systole and diastole denote phases of ventricular operation.

VENTRICULAR SYSTOLE

Ventricular systole begins when the action potential breaks through the AV node and sweeps over the ventricular muscle—an event heralded by the QRS complex of the electrocardiogram. Contraction of the ventricular muscle cells causes intraventricular pressure to rise above that in the atrium, which causes abrupt closure of the AV valve.

Pressure in the left ventricle continues to rise sharply as the ventricular contraction intensifies. When the left ventricular pressure exceeds that in the aorta, the aortic valve opens. The period of time between mitral valve closure and aortic valve opening is referred to as the *isovolumetric contraction phase* because during this interval the ventricle is a closed chamber with a fixed volume. Ventricular ejection begins with the opening of the aortic valve. In early ejection, blood enters the aorta rapidly and causes the pressure there to rise. Pressure builds simultaneously in both the ventricle and the aorta as the ventricular muscle cells continue to contract in early systole. This period is often called the *rapid ejection phase.*

Left ventricular and aortic pressures ultimately reach a maximum called *peak systolic pressure.* At this point the strength of ventricular muscle contraction begins to wane. Muscle shortening and ejection continue, but at a reduced rate. Aortic pressure begins to fall because blood is leaving the aorta and large arteries faster than blood is entering from the left ventricle. Throughout ejection, very small pressure differences exist between the left ventricle and the aorta because the aortic valve orifice is so large that it presents very little resistance to flow.

Eventually, the strength of the ventricular contraction diminishes to the point where intraventricular pressure falls below aortic pressure. This causes abrupt closure of the aortic valve. A dip, called the *incisura* or *dicrotic notch,* appears in the aortic pressure trace because a small volume of aortic blood must flow backward to fill the aortic valve leaflets as they close. After aortic valve closure, intraventricular pressure falls rapidly as the ventricular muscle relaxes. For a brief interval, called the *isovolumetric relaxation phase,* the mitral valve is also closed. Ultimately, intraventricular pressure

falls below atrial pressure, the AV valve opens, and a new cardiac cycle begins.

Note that atrial pressure progressively rises during ventricular systole because blood continues to return to the heart and fill the atrium. The elevated atrial pressure at the end of systole promotes rapid ventricular filling once the AV valve opens to begin the next heart cycle.

The ventricle has reached its minimum or *end-systolic volume* at the time of aortic valve closure. The amount of blood ejected from the ventricle during a single beat, the *stroke volume,* is equal to ventricular end-diastolic volume minus ventricular end-systolic volume.

The aorta distends or balloons out during systole because more blood enters the aorta than leaves it. During diastole, the arterial pressure is maintained by the elastic recoil of walls of the aorta and other large arteries. Nonetheless, aortic pressure gradually falls during diastole as the aorta supplies blood to the systemic vascular beds. The lowest aortic pressure, reached at the end of diastole, is called *diastolic pressure.* The difference between diastolic and peak systolic pressure in the aorta is called the arterial*pulse pressure.* Typical values for systolic and diastolic pressures in the aorta are 120 and 80 mmHg, respectively.

At a normal resting heart rate of about 70 beats per minute, the heart spends approximately two thirds of the cardiac cycle in diastole and one third in systole. When increases in heart rate occur, both diastolic and systolic intervals become shorter. Action potential durations are shortened and conduction velocity is increased. Contraction and relaxation rates are also enhanced. This shortening of the systolic interval tends to blunt the potential adverse effects of increases in heart rate on diastolic filling time.

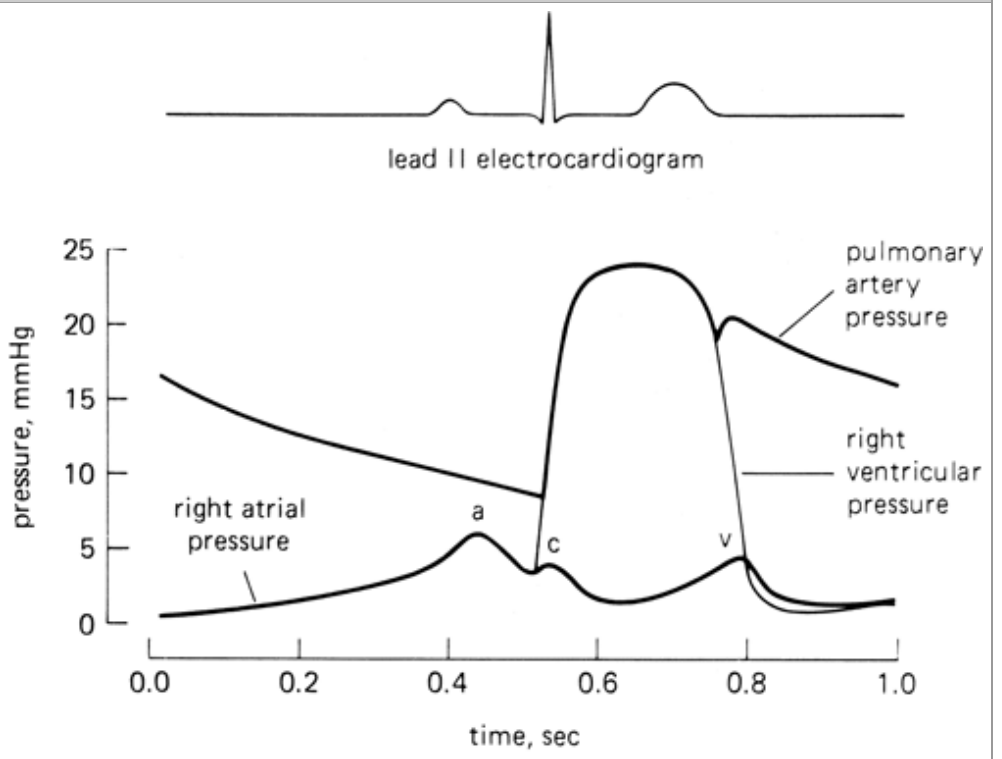
Right Pump



Because the entire heart is served by a single electrical excitation system, similar mechanical events occur essentially simultaneously in both the left heart and the right heart. Both ventricles have synchronous systolic and diastolic periods and the valves of the right and left heart normally open and close nearly in unison. Because the two sides of the heart are arranged in series in the circulation, they must pump the same amount of blood and therefore must have identical stroke volumes.

The major difference between the right and left pumps is in the magnitude of the peak systolic pressure. The pressures developed by the right heart as shown in Figure 3–2 are considerably lower than those for the left heart (Figure 3–1). The lungs provide considerably less resistance to blood flow than that offered collectively by the systemic organs. Therefore, less arterial pressure is required to drive the cardiac output through the lungs than through the systemic organs. Typical pulmonary artery systolic and diastolic pressures are 24 and 8 mmHg, respectively.

Figure 3–2.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Cardiac cycle—right heart.

The pressure pulsations that occur in the right atrium are transmitted in retrograde fashion to the large veins near the heart. These pulsations, shown on the atrial pressure trace of Figure 3–2, can be visualized in the neck over the jugular veins in a recumbent individual and can provide clinically useful information about the heart. Atrial contraction produces the first pressure peak called the *a* wave. The *c* wave, which follows shortly thereafter, coincides with the onset of ventricular systole and is caused by an initial bulging of the tricuspid valve into the right atrium. Right atrial pressure falls after the *c* wave because of atrial relaxation and a downward displacement of the tricuspid valve during ventricular emptying. Right atrial pressure then begins to increase toward a third peak, the *v* wave, as the central veins and right atrium fill behind a closed tricuspid valve with blood returning to the heart from the peripheral organs. With the opening of the tricuspid valve at the conclusion of ventricular systole, right atrial pressure again falls as blood moves into the relaxed right ventricle. Shortly afterward, right atrial pressure begins to rise once more toward the next *a* wave as returning blood fills the central veins, the right atrium, and right ventricle together during diastole.

Heart Sounds

A phonocardiographic record of the heart sounds, which occur in the cardiac cycle, is included in Figure 3–1. The first heart sound, S_1,occurs at the beginning of systole because of the abrupt closure of the AV valves, which produces vibrations of the cardiac structures and the blood in the ventricular chambers. S_1 can be heard most clearly by placing the stethoscope over the apex of the heart. Note that this sound occurs immediately after the QRS complex of the electrocardiogram.

The second heart sound, S_2, arises from the closure of the aortic and pulmonic valves at the beginning of the period of isovolumetric relaxation. This sound is heard at about the time of the T wave in the electrocardiogram. The pulmonic valve usually closes slightly after the aortic valve. Because this discrepancy is enhanced during the inspiratory phase of the respiratory cycle, inspiration causes what is referred to as the *physiological splitting of the second heart sound.* The discrepancy in valve closure during inspiration may range from 30 to 60 ms. One of the factors that leads to prolonged ejection of the right ventricle during inspiration is that the decreased intrathoracic pressure that accompanies inspiration transiently enhances venous return and diastolic filling of the right heart. For reasons that will be detailed later in this chapter, this extra filling volume will be ejected but a little extra time is required to do so.

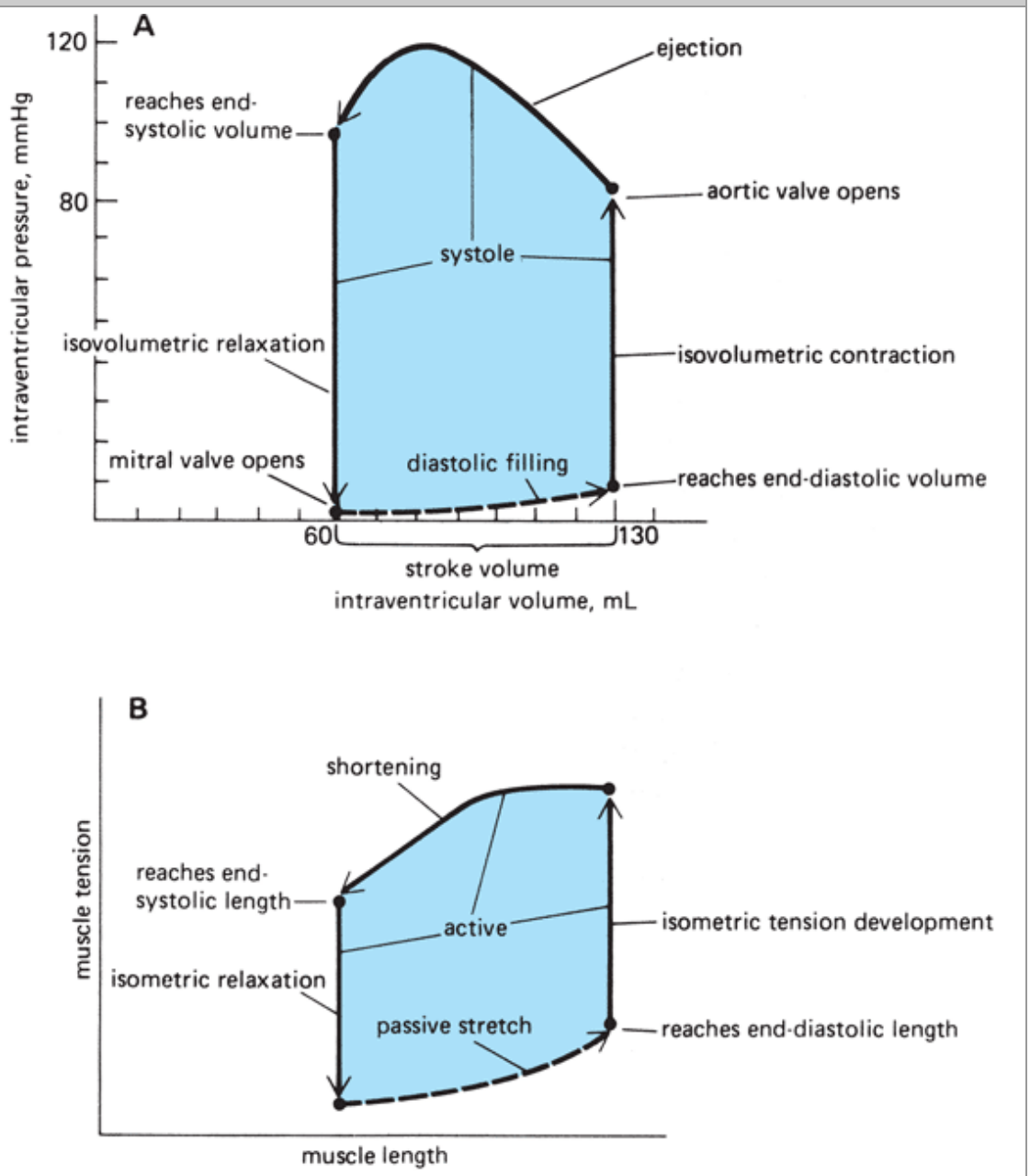
The third and fourth heart sounds, shown in Figure 3–1, are not normally present. When they are present, however, they, along with S_1 and S_2, produce what are called *gallop rhythms* (resembling the sound of a galloping horse). When present, the third heart sound occurs shortly after S_2 during the period of rapid passive ventricular filling and, in combination with heart sounds S_1 and S_2, produces what is called *ventricular gallop rhythm.* Although S_3 may sometimes be detected in normal children, it is heard more commonly in patients with left ventricular failure. The fourth heart sound, which occasionally is heard shortly before S_1, is associated with atrial contraction and rapid active filling of the ventricle. Thus, the combination of S_1, S_2, and S_4 sounds produces what is called an *atrial gallop rhythm.* The presence of S_4 often indicates an increased ventricular diastolic stiffness, which can occur with several cardiac disease states.

Cardiac Cycle Pressure-Volume & Length-Tension Relationships



Intraventricular pressure and volume are intimately linked to the tension and length of the cardiac muscle cells in the ventricular wall through purely geometric and physical laws. Figures 3–3A and 3–3B show the correspondence between a ventricular pressure-volume loop and a cardiac muscle length-tension loop during one cardiac cycle. This fact makes it clear that cardiac muscle length-tension behavior is the underlying basis for ventricular function. Note that in Figure 3–3, each major phase of the ventricular cardiac cycle has a corresponding phase of cardiac muscle length and tension change. During diastolic ventricular filling, for example, the progressive increase in ventricular pressure causes a corresponding increase in muscle tension, which passively stretches the resting cardiac muscle to greater lengths along its resting length-tension curve. End-diastolic ventricular pressure is referred to as*ventricular preload* because it sets the end-diastolic ventricular volume and therefore the resting length of the cardiac muscle fibers at the end of diastole.

Figure 3–3.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Ventricular pressure-volume cycle A, and corresponding cardiac muscle length-tension cycle B.

At the onset of systole, the ventricular muscle cells develop tension isometrically and intraventricular pressure rises accordingly. After the intraventricular pressure rises sufficiently to open the outlet valve, ventricular ejection begins as a consequence of ventricular muscle shortening. Systemic arterial pressure is often referred to as the *ventricular afterload* because it determines the tension that must be developed by cardiac muscle fibers before they can shorten.[2]

During cardiac ejection, cardiac muscle is simultaneously generating active tension *and* shortening (ie, an afterloaded isotonic contraction). The magnitude of ventricular volume change during ejection (ie, stroke volume) is determined simply by how far ventricular muscle cells are able to shorten during contraction. This, as already discussed, depends on the length-tension relationship of the cardiac muscle cells and the load against which they are shortening. Once shortening ceases and the output valve closes, the cardiac muscle cells relax isometrically. Ventricular wall tension and intraventricular pressure fall in unison during isovolumetric relaxation.

[2] This designation is somewhat misleading for at least two reasons. First, arterial pressure is more analogous to ventricular total load than to ventricular afterload. Second, because of the law of Laplace, the actual wall tension that needs to be generated to attain a given intraventricular pressure also depends on the ventricular radius (tension = pressure x radius). Thus, the larger the end-diastolic volume, the greater the tension required to develop sufficient intraventricular pressure to open the outflow valve. We choose, however, to ignore these complications.

DETERMINANTS OF CARDIAC OUTPUT



Cardiac output (liters of blood pumped by *each* of the ventricles per minute) is an extremely important cardiovascular variable that is continuously adjusted so that the cardiovascular system operates to meet the body's moment-to-moment transport needs. In going from rest to strenuous exercise, for example, the cardiac output of an average person will increase from approximately 5.5 to perhaps 15 L/min. The extra cardiac output provides the exercising skeletal muscles with the additional nutritional supply needed to sustain an increased metabolic rate. To understand the cardiovascular system's response not only to exercise but to all other physiological or pathological demands placed on it, we must understand what determines and therefore controls cardiac output.

As stated in Chapter 1, cardiac output is the product of heart rate and stroke volume (CO = HR x SV). Therefore, all changes in cardiac output must be produced by changes in heart rate and/or stroke volume.

Factors influencing heart rate do so by altering the characteristics of the diastolic depolarization of the pacemaker cells as discussed in Chapter 2 (Figure 2–6). Recall that variations in activity of the sympathetic and parasympathetic nerves leading to cells of the sinoatrial (SA) node constitute the most important regulators of heart rate. Increases in sympathetic activity increase heart rate whereas increases in parasympathetic activity decrease heart rate. These neural inputs have immediate effects (within one beat) and therefore can cause very rapid adjustments in cardiac output.

INFLUENCES ON STROKE VOLUME

Effect of Changes in Ventricular Preload: Frank-Starling Law of the Heart

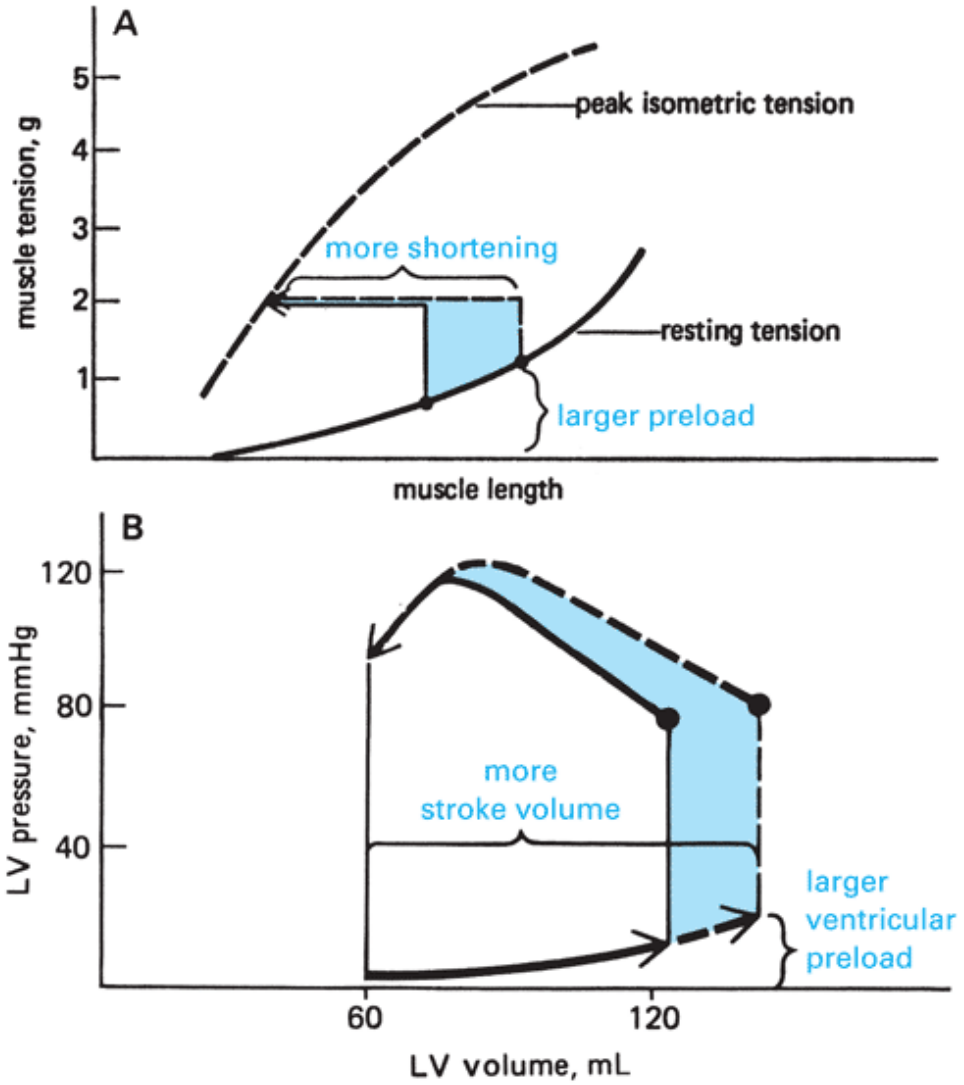


The volume of blood that the heart ejects with each beat can vary significantly. One of the most important factors responsible for these variations in stroke volume is the extent of cardiac filling during diastole. This concept was introduced in Chapter 1 (Figure 1–7) and is known as Starling's law of the heart. To review (and to reemphasize its importance), this law states that, with other factors equal, *stroke volume increases as cardiac filling increases*. As we will now show, this phenomenon is based on the intrinsic mechanical properties of myocardial muscle.

Figure 3–4A illustrates how increasing muscle preload will increase the extent of shortening during a subsequent contraction with a fixed total load. Recall from the nature of the resting length-tension relationship that an increased preload is necessarily accompanied by increased initial muscle fiber

length. As was described in Chapter 2, when a muscle starts from a greater length, it has more room to shorten before it reaches the length at which its tension-generating capability is no longer greater than the load upon it. The same behavior is exhibited by cardiac muscle cells when they are actually operating in the ventricular wall. Increases in ventricular preload increase both end-diastolic volume and stroke volume almost equally, as illustrated in Figure 3–4B.

Figure 3–4.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Effect of changes in preload on cardiac muscle shortening during after-loaded contractions A and on ventricular stroke volume B.

The precise relationship between cardiac preload (cardiac filling pressure) and end-diastolic volume has especially important physiological and clinical consequences. Whereas the actual relationship is somewhat curvilinear, especially at very high filling pressures, it is nearly linear over the normal operating range of the heart. The low slope of this relationship indicates the incredible distensibility of the normal ventricle during diastole. (For example, a change in filling pressure of only 1 mmHg

normally will change end-diastolic volume by about 25 mL!) As will be discussed in the final chapter of this book, one major form of cardiac failure is called "diastolic failure" and is characterized by a decidedly abnormal relationship between cardiac filling pressure and end-diastolic volume.

It should be noted in Figure 3–4A that increasing preload increases initial muscle length without significantly changing the final length to which the muscle shortens against a constant total load. Thus, increasing ventricular filling pressure increases stroke volume primarily by increasing end-diastolic volume. As shown in Figure 3–4B, this is not accompanied by a significant alteration in end-systolic volume.

Effect of Changes in Ventricular Afterload

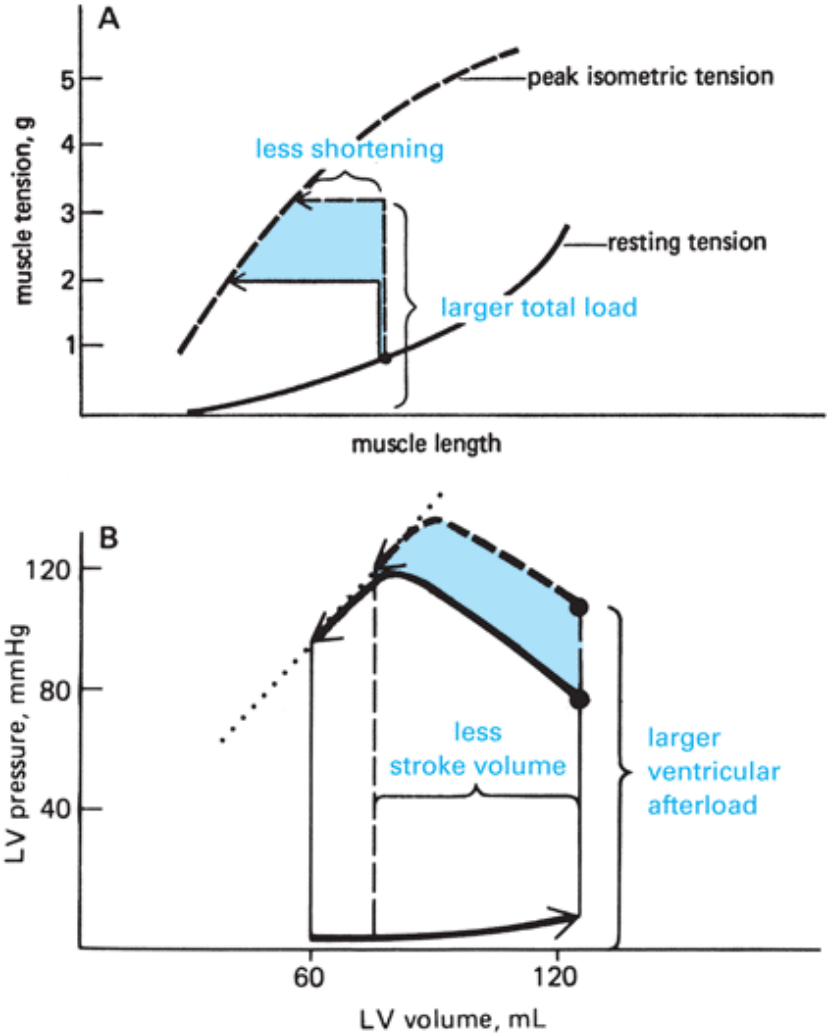
As stated previously, systemic arterial pressure (ventricular afterload) is analogous to total load in isolated muscle experiments. A slight complication is that arterial pressure varies between a diastolic value and a systolic value during each cardiac ejection. Usually, however, we are interested in *mean* ventricular afterload and take this to be *mean* arterial pressure.



Figure 3–5A shows how increased afterload, at constant preload, has a negative effect on cardiac muscle shortening. Again, this is simply a consequence of the fact that muscle cannot shorten beyond the length at which its peak isometric tension-generating potential equals the total load upon it. Thus, shortening must stop at a greater muscle length when afterload is increased.

Normally, mean ventricular afterload is quite constant, because mean arterial pressure is held within tight limits by the cardiovascular control mechanisms described later. In many pathological situations such as hypertension and aortic valve obstruction, however, ventricular function is adversely influenced by abnormally high ventricular afterload. When this occurs, stroke volume is decreased as shown by the changes in the pressure-volume loop in Figure 3–5B. Under these conditions, note that stroke volume is decreased because end-systolic volume is increased.

Figure 3–5.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Effect of changes in afterload on cardiac muscle shortening during afterloaded contractions A and on ventricular stroke volume B.

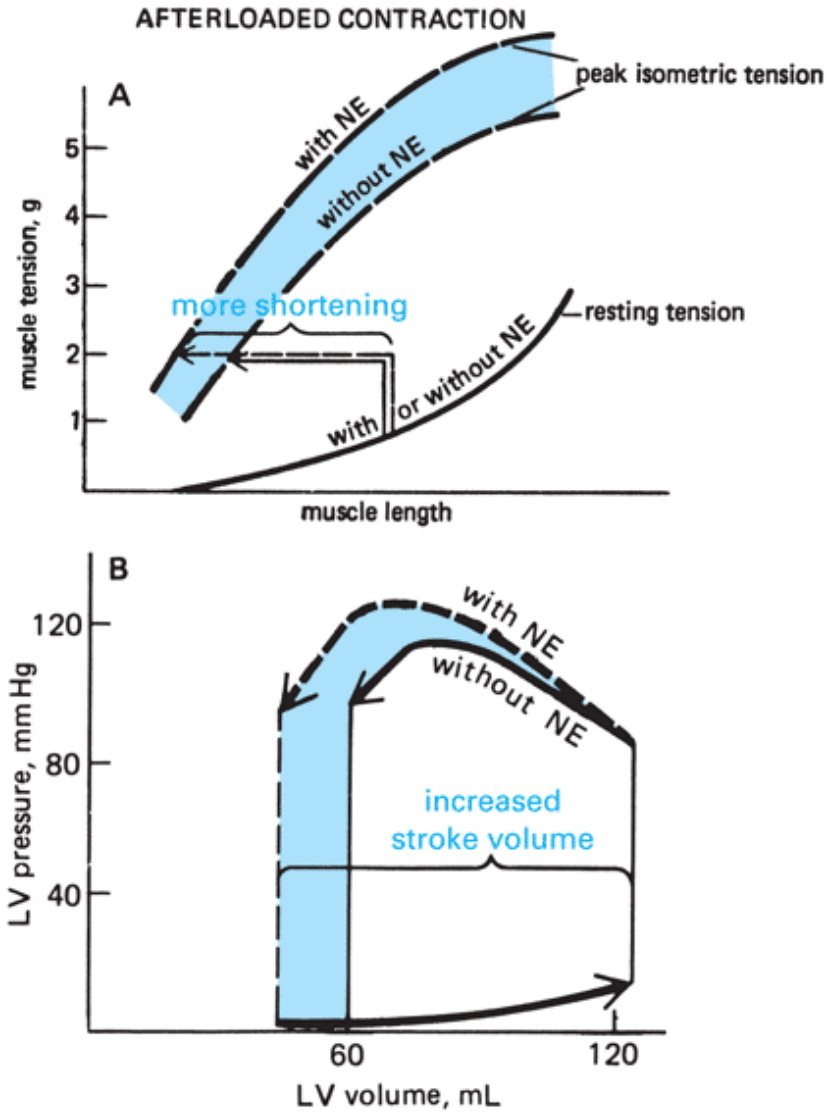
The relationship between end-systolic pressure and end-systolic volume obtained at a constant preload but different afterloads is indicated by the dotted line in Figure 3–5B. In a normally functioning heart, the effect of changes in afterload on end-systolic volume (and therefore stroke volume) is quite small (about 0.5 mL/mmHg). However, in what is termed "systolic cardiac failure" the effect of afterload on end-systolic volume is greatly enhanced. Thus, the slope of this line can be used clinically to assess the systolic function of the heart.

Effect of Changes in Cardiac Muscle Contractility

Recall that activation of the sympathetic nervous system results in release of norepinephrine from cardiac sympathetic nerves which increases contractility of the individual cardiac muscle cells. This results in an upward shift of the peak isometric length-tension curve. As shown in Figure 3–6A, such a shift will result in an increase in the shortening of a muscle contracting with constant preload and total load. Thus, as shown in Figure 3–6B, the norepinephrine released by sympathetic nerve stimulation will increase ventricular stroke volume by decreasing the end-systolic volume without directly

influencing the end-diastolic volume.

Figure 3–6.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Effect of norepinephrine (NE) on afterloaded contractions on cardiac muscle A and on ventricular stroke volume B.

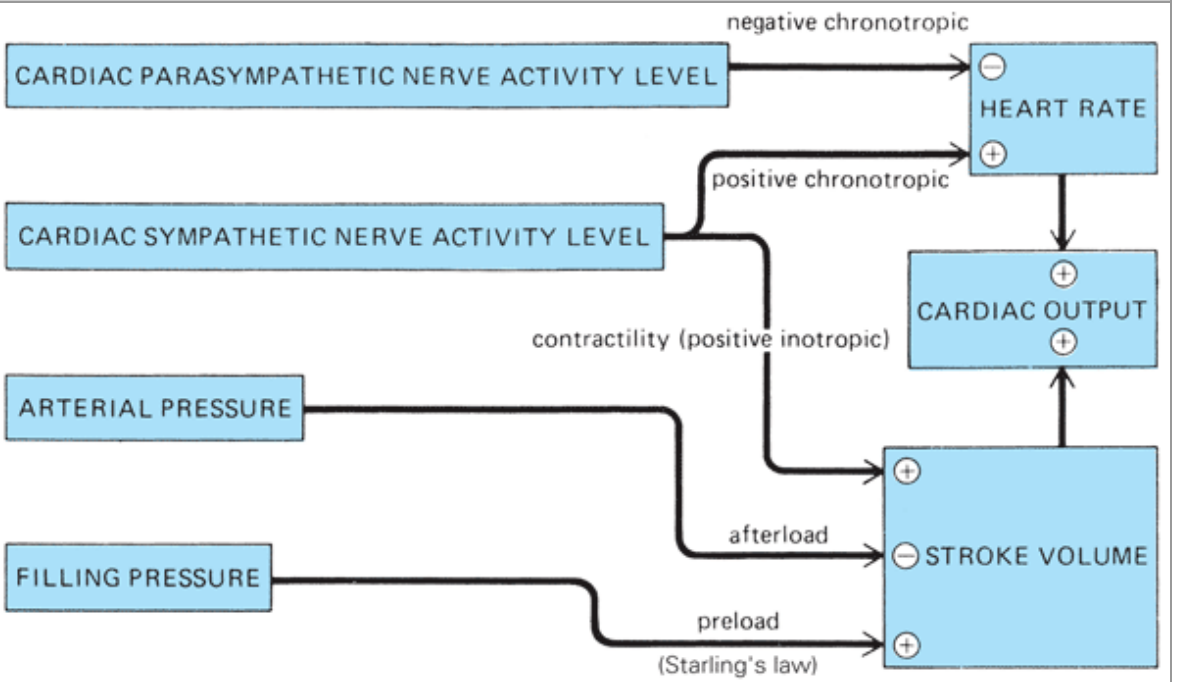
As previously discussed, the V_{max} value is commonly used as an index of the state of contractility of isolated cardiac muscle. Myocardial contractility cannot be directly measured in patients. However, several indirect methods are used to obtain clinically useful information about this important determinant of cardiac function. In one method, cardiac catheters are placed in the ventricle and the maximum rate of pressure development (dP/dt_{max}) during the isovolumetric contraction is measured. This may be used as an index of contractility on the grounds that, in isolated cardiac muscle preparations, changes in contractility and V_{max} cause changes in the rate of tension development in an isometric contraction. Decreases in left ventricular dP/dt_{max} below the normal values of 1500 to 2000 mmHg/s indicate that myocardial contractility is below normal. Other methods of assessing

contractility that use information derived from cardiac imaging techniques are discussed at the end of this chapter.

SUMMARY OF DETERMINANTS OF CARDIAC OUTPUT

The major influences on cardiac output are summarized in Figure 3–7. Heart rate is controlled by chronotropic influences on the spontaneous electrical activity of SA nodal cells. Cardiac parasympathetic nerves have a negative chronotropic effect, and sympathetic nerves have a positive chronotropic effect on the SA node. Stroke volume is controlled by influences on the contractile performance of ventricular cardiac muscle—in particular its degree of shortening in the afterloaded situation. The three distinct influences on stroke volume are contractility, preload, and afterload. Increased cardiac sympathetic nerve activity tends to increase stroke volume by increasing the contractility of cardiac muscle. Increased arterial pressure tends to decrease stroke volume by increasing the afterload on cardiac muscle fibers. Increased ventricular filling pressure increases end-diastolic volume, which tends to increase stroke volume through Starling's law.

Figure 3–7.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

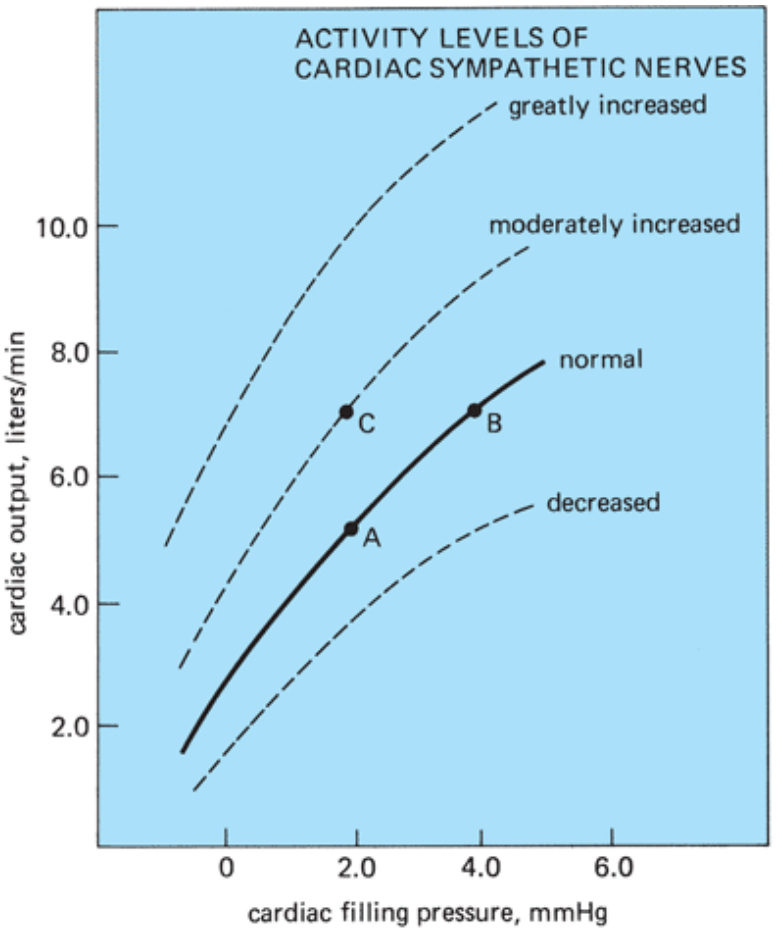
Influences on cardiac output.

It is important to recognize at this point that both heart rate and stroke volume are subject to more than one influence. Thus, the fact that increased contractility tends to increase stroke volume should not be taken to mean that, in the intact cardiovascular system, stroke volume is always high when contractility is high. Following blood loss caused by hemorrhage, for example, stroke volume may be low in spite of a high level of sympathetic nerve activity and increased contractility. The only other possible causes for low stroke volume are high arterial pressure and low cardiac filling pressure. Because arterial pressure is normal or low following hemorrhage, the low stroke volume associated with severe blood loss must be (and is) the result of low cardiac filling pressure.

Cardiac Function Curves

One very useful way to summarize the influences on cardiac function and the interactions between them is by cardiac function curves such as those shown in Figure 3–8.

Figure 3–8.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Influence of cardiac sympathetic nerves on cardiac function curves.

In this case, cardiac output is treated as the dependent variable and is plotted on the vertical axis in Figure 3–8, while cardiac filling pressure is plotted on the horizontal axis.[3]

Different curves are used to show the influence of alterations in sympathetic nerve activity. Thus, Figure 3–8 shows how the cardiac filling pressure and the activity level of cardiac sympathetic nerves interact to determine cardiac output. When cardiac filling pressure is 2 mmHg and the activity of cardiac sympathetic nerves is normal, the heart will operate at point A and will have a cardiac output of 5 L/min. Each single curve in Figure 3–8 shows how cardiac output would be changed by changes in cardiac filling pressure if cardiac sympathetic nerve activity were held at a fixed level. For example, if cardiac sympathetic nerve activity remained normal, increasing cardiac filling pressure from 2 to 4 mmHg would cause the heart to shift its operation from point A to point B on the cardiac function diagram. In this case, cardiac output would increase from 5 to 7 L/min solely as a result of the

increased filling pressure (Starling's law). If, on the other hand, cardiac filling pressure were fixed at 2 mmHg while the activity of cardiac sympathetic nerves was moderately increased from normal, the heart would change from operating at point A to operating at point C. Cardiac output would again increase from 5 to 7 L/min. In this instance, however, cardiac output does not increase through the length-dependent mechanism because cardiac filling pressure did not change. Cardiac output increases at constant filling pressure with an increase in cardiac sympathetic activity for two reasons. First, increased cardiac sympathetic nerve activity increases heart rate. Second, but just as important, increased sympathetic nerve activity increases stroke volume by increasing cardiac contractility.

Cardiac function graphs thus consolidate knowledge of many mechanisms of cardiac control, and are most helpful in describing how the heart interacts with other elements in the cardiovascular system. Furthermore, these graphs reemphasize the important point that a change in cardiac filling pressure alone will have a very potent effect on cardiac output at any level of sympathetic activity.

[3] Other variables may appear on the axes of these curves. The vertical axis may be designated as stroke volume or stroke work whereas the horizontal axis may be designated as central venous pressure, right (or left) atrial pressure, or ventricular end-diastolic volume (or pressure). In all cases, the curves describe the relationship between preload and cardiac function.

Summary of Sympathetic Neural Influences on Cardiac Function

Because of its importance in overall control of cardiac function, it is appropriate at this point to summarize the major direct effects that the sympathetic nervous system exerts upon electrical and mechanical properties of cardiac muscle and thus upon cardiac pumping ability. These effects are initiated by norepinephrine interaction with β_1-adrenergic receptors on cardiac muscle cells resulting in an increase in cytosolic cyclic adenosine monophosphate (cAMP). Various intracellular signaling pathways are then triggered, which evoke improvements in pumping capabilities of the heart. These improvements include the following:

1. An increase in heart rate (positive chronotropic effect);

2. A decrease in cardiac action potential duration, which minimizes the detrimental effect of high heart rates on diastolic filling time;

3. An increase in rate of action potential conduction, particularly evident in the AV node (positive dromotropic effect);

4. An increase in cardiac contractility (positive inotropic effect), which increases the contractile ability of cardiac muscle at any given preload; and

5. An increase in rate of cardiac relaxation (positive lusitropic effect), which also helps minimize the detrimental effect of high heart rates on diastolic filling time.[4,5]

As we will see in subsequent chapters, increases in sympathetic activity can have *indirect* influences on cardiac function that are a consequence of sympathetic-induced alterations in arteriolar and venous tone (ie, alterations in afterload and preload, respectively).

[4] Most catecholamine effects on the heart are a result of increases in sympathetic neural activity. Although circulating catecholamines of adrenal origin can potentially evoke similar effects, their concentrations are normally so low that their contributions are negligible.

[5] All of the effects of catecholamines on cardiac muscle can be blocked by specific drugs called β-adrenergic receptor blockers. The drugs may be useful in the treatment of coronary artery disease to thwart increased metabolic demands placed on the heart by activity of sympathetic nerves.

CARDIAC ENERGETICS

Energy Sources

In order for the heart to operate properly, it must have an adequate supply of chemical energy in the form of adenosine triphosphate (ATP). The relatively low ATP content of cardiac tissue combined with a relatively high rate of ATP hydrolysis at rest suggests that the myocardial ATP pool will completely turn over every 10 seconds. The substrates from which ATP is formed by the heart depend partly on which are in the greatest supply at a particular instant. For example, after a high carbohydrate meal, the heart will take up and metabolize glucose and pyruvate, whereas between meals, the heart can switch to metabolize free fatty acids, triglycerides, and ketones. In addition, the choice of substrate also depends on the metabolic phenotype of the cardiac muscle. Fetal and newborn hearts derive most of their ATP from metabolism of glucose and lactate, whereas, within a few weeks of birth, a switch toward fatty acid oxidation occurs so that by adulthood, 60 to 90% of cardiac ATP is derived from fatty acids. A switch back toward the fetal phenotype accompanies severe heart failure. Glycogen is stored in myocardial cells as a reserve energy supply and can be mobilized via the glycolytic pathway to provide extra substrate under conditions of increased sympathetic stimulation.[6] The end-product of metabolism of glycogen, glucose, fatty acids, triglycerides, pyruvate, and lactate is acetyl CoA, which enters the citric acid (Krebs) cycle in the mitochondria, where, by a process of oxidative phosphorylation, the molecules are degraded to carbon dioxide and water and the energy is converted to ATP. (The student is encouraged to consult a biochemistry textbook for further details of these important metabolic pathways.)

The anaerobic sources of energy in the heart (eg, glycolysis, creatine phosphate) are not adequate to sustain the metabolic demand for more than a few minutes. The heavy (nearly total) reliance of the heart on the aerobic pathways for ATP production is evident by (1) the high number of mitochondria and (2) the presence of high concentrations of the oxygen-binding protein myoglobin within the cardiac muscle cells. Myoglobin can release its oxygen to the mitochondrial cytochrome oxidase system when intracellular oxygen levels are lowered. In these regards, cardiac muscle resembles "red" skeletal muscle that is adapted for sustained contractile activity as opposed to "white" skeletal muscle that is adapted for high-intensity, short-duration contractile activity.

[6] Catecholamines interacting with membrane β receptors increase intracellular cyclic adenosine monophosphate (cAMP), which then activates phosphorylase b to stimulate glycogen metabolism.

Determinants of Myocardial Oxygen Consumption

In many pathological situations, such as obstructive coronary artery disease, the oxygen requirements of the myocardial tissue may exceed the capacity of coronary blood flow to deliver oxygen to the heart muscle. It is important, therefore, to understand what factors determine the myocardial oxygen consumption rate because reduction of the oxygen demand may be of significant clinical benefit to the patient.

Because the heart derives its energy almost entirely from aerobic metabolism, myocardial oxygen consumption is directly related to myocardial energy use (ie, ATP splitting). Understanding the determinants of myocardial oxygen consumption essentially means understanding the myocardial processes that require ATP.

The *basal metabolism* of the heart tissue normally accounts for about 25% of myocardial ATP use and therefore myocardial oxygen consumption in a resting individual. Because basal metabolism represents the energy consumed in cellular processes other than contraction (eg, energy-dependent ion

pumping), little can be done to reduce it.

The processes associated with *muscle contraction* account for about 75% of myocardial energy use. Primarily this reflects ATP splitting associated with cross-bridge cycling during the isovolumetric contraction and ejection phases of the cardiac cycle. Some ATP is also used for Ca^{2+} sequestration at the termination of each contraction.

The energy expended during the isovolumetric contraction phase of the cardiac cycle accounts for the largest portion (~50%) of total myocardial oxygen consumption despite the fact that the heart does no external work during this period. The energy needed for isovolumetric contraction depends heavily on the intraventricular pressure that must develop during this time, ie, on the cardiac afterload. *Cardiac afterload* then is a major determinant of myocardial oxygen consumption. Reductions in cardiac afterload can produce clinically significant reductions in myocardial energy requirements and therefore myocardial oxygen consumption.

Energy utilization during isovolumetric contraction is actually more directly related to isometric *wall tension* development than to intraventricular pressure development. Recall that wall tension is related to intraventricular pressure *and* ventricular radius through the law of Laplace ($T = P \times r$). Consequently, reductions in cardiac preload (ie, end-diastolic volume, radius) will also tend to reduce the energy required for isovolumetric contraction.

It is during the ejection phase of the cardiac cycle that the heart actually performs external work and the energy the heart expends during ejection depends on how much *external work* it is doing. In a fluid system, work (force x distance) is equal to pressure (force/distance^2) x volume (distance ^{3}). The external physical work done by the left ventricle in one beat, called *stroke work,* is equal to the area enclosed by the left ventricular pressure-volume loop (see Figure 3–3). Stroke work is increased either by an increase in stroke volume (increased "volume" work) or by an increase in afterload (increased "pressure" work). In terms of ATP utilization and oxygen consumption, increases in the pressure work of the heart are more costly than increases in volume work. Thus, reductions in afterload are especially helpful in reducing the myocardial oxygen requirements for doing external work.

Changes in *myocardial contractility* can have important consequences on the oxygen requirement for basal metabolism, isovolumic wall tension generation, and external work. Heart muscle cells use more energy in rapidly developing a given tension and shortening by a given amount than in doing the same thing more slowly. Also, with increased contractility, more energy is expended in active Ca^{2+} transport. The net result of these influences is often referred to as the "energy wasting" effect of increased contractility.

Heart rate is also one of the more important determinants of myocardial oxygen consumption because the energy costs per minute must equal the energy cost per beat times the number of beats per minute. In general, it has been found that it is more efficient (less oxygen is required) to achieve a given cardiac output with low heart rate and high stroke volume than with high heart rate and low stroke volume. This again appears to be related to the relatively high energy cost of the pressure development phase of the cardiac cycle. The less pressure (wall tension) developed and the less often pressure development occurs, the better.

Many attempts have been made to develop clinically practical methods for estimating myocardial oxygen requirements from routinely measured cardiovascular variables. While none of these take into account all the factors that can influence myocardial oxygen consumption and therefore do not give 100% accurate predictions in all situations, many methods have proved to be of some usefulness. Perhaps the simplest "index" of the energy demands of the heart is obtained by multiplying peak

systolic arterial pressure times heart rate. This *pressure-rate product* takes into account two of the most important factors in cardiac energy use (the magnitude and frequency of pressure development) and requires no invasive measures. Another formula, the *tension-time index,* is defined as summed areas under the systolic portions of a ventricular pressure recording for 1 minute. A continuous high-fidelity recording of intraventricular pressure such as that obtained during cardiac catheterization is required to calculate the tension-time index. It is debatable whether the tension-time index predicts myocardial oxygen consumption with any more certainty than the simple pressure-rate product. The quest for a reliable index of myocardial oxygen consumption continues as cardiac imaging techniques (described near the end of this chapter) make cardiac volume and dimension information more routinely available. For example, this additional information makes it possible to construct ventricular pressure-volume loops whose area accurately indicates external cardiac work. As yet, however, no simple method has been found for assessing all the factors that affect myocardial energy use and using them to predict myocardial oxygen consumption.

MEASUREMENT OF CARDIAC FUNCTION

Cardiac Output/Cardiac Index



Establishing the *absolute* value of a patient's cardiac output is a relatively difficult task. It is, however, possible to estimate the *relative change* in a patient's cardiac output between two situations from the changes in heart rate (HR) and arterial pressure that occur. Recall (from Figure 3–1) that arterial pulse pressure (P_p) is defined as the difference between the arterial systolic (P_s) and diastolic (P_d) pressures. For reasons that will be explained in Chapter 6, acute changes in pulse pressure occur primarily because of changes in stroke volume (SV). If one assumes a linear relationship between changes in stroke volume and pulse pressure, then one can reason that since CO=HR x SV, the fractional change in CO that occurs in going from situation 1 to situation 2 is approximately equal to the product of the fractional changes in HR and P_p between these situations. For example, if heart rate increased by 10% and pulse pressure increased by 10%, one would estimate that cardiac output increased by 21% (1.1 x 1.1 = 1.21).

One of the most accurate methods of measuring cardiac output makes use of the Fick principle, which is discussed in detail in Chapter 6. Briefly, this principle states that the amount of a substance consumed by the tissues, X_{tc}, is equal to what goes in minus what goes out [which is the arterial-venous concentration difference in the substance ($[X]_a - [X]_v$) times the blood flow rate, $\dot{Q}$]. This relationship can be algebraically arranged to solve for blood flow:

$$\dot{Q} = \frac{\dot{X}_{tc}}{[X]_a - [X]_v}$$

A common method of determining cardiac output is to use the Fick principle to calculate the collective flow through the systemic organs from (1) the whole body oxygen consumption rate ($\dot{X}_{tc}$), (2) the oxygen concentration in arterial blood ($[X]_a$), and (3) the concentration of oxygen in mixed venous blood ($[X]_v$). Of the values required for this calculation, the oxygen content of mixed venous blood is the most difficult to obtain. Generally, the sample for venous blood oxygen measurement must be taken from venous catheters positioned in the right ventricle or pulmonary artery to ensure that it is a mixed sample of venous blood from all systemic organs.

The calculation of cardiac output from the Fick principle is best illustrated by an example. Suppose a

patient is consuming 250 mL of O_2 per minute when his or her systemic arterial blood contains 200 mL of O_2 per liter and the right ventricular blood contains 150 mL of O_2 per liter. This means that, on the average, each liter of blood loses 50 mL of O_2 as it passes through the systemic organs. In order for 250 mL of O_2 to be consumed per minute, 5 L of blood must pass through the systemic circulation each minute:

$$\dot{Q} = \frac{250 \text{ mL } O_2/\text{min}}{(200 - 150) \text{ mL } O_2/\text{L blood}}$$

$$\dot{Q} = 5 \text{ L blood/min}$$

Dye dilution and thermal dilution (dilution of heat) are other clinical techniques commonly employed for estimating cardiac output. Usually a known quantity of indicator (dye or heat) is rapidly injected into the blood as it enters the right heart and appropriate detectors are arranged to continuously record the concentration of the indicator in blood as it leaves the left heart. It is possible to estimate the cardiac output from the quantity of indicator injected and the time record of indicator concentration in the blood that leaves the left heart.

The normal cardiac output for an individual is obviously dependent on his or her size. For example, the cardiac output of 50-kg woman will be significantly lower than that of a 90-kg man. It has been found, however, that cardiac output correlates better with body surface area than with body weight. Therefore, it is common to express the cardiac output per square meter of surface area. This value is called the *cardiac index;* at rest it is normally approximately 3 (L/min)/m^2.

Cardiac Contractility Estimates

Imaging Techniques

It is often important to assess an individual's cardiac function without using major invasive procedures. Advances in several techniques have made it possible to obtain two- and three-dimensional images of the heart throughout the cardiac cycle. Visual or computer-aided analysis of such images provides information useful in clinically evaluating cardiac function. These techniques are especially suited for detecting abnormal operation of cardiac valves or contractile function in portions of the heart walls. They also can provide estimates of heart chamber volumes at different times in the cardiac cycle which, as described later, are used in a number of ways to assess cardiac function.

Echocardiography is the most widely used of the three cardiac imaging techniques currently available. This noninvasive technique is based on the fact that sound waves reflect back toward the source when encountering abrupt changes in the density of the medium through which they travel. A transducer, placed at specified locations on the chest, generates pulses of ultrasonic waves and detects reflected waves that bounce off the cardiac tissue interfaces. The longer the time between the transmission of the wave and the arrival of the reflection, the deeper the structure is in the thorax. Such information can be reconstructed by computer in various ways to produce a continuous image of the heart and its chambers throughout the cardiac cycle. *Cardiac angiography* involves the placement of catheters into the right or left ventricle and injection of radiopaque contrast medium during high speed x-ray filming (cineradiography).*Radionuclide ventriculography* involves the intravenous injection of a radioactive isotope that stays in the vascular space (usually technitium that binds to red blood cells) and the measurement of the changes in intensity of radiation detected over the ventricles during the cardiac cycle.

Information derived from these various imaging techniques can be used to evaluate myocardial

contractility, a critically important component of cardiac function that is somewhat difficult to measure in a clinical setting.

EJECTION FRACTION

Ejection fraction (EF) is an extremely useful clinical measurement. It is defined as the ratio of stroke volume (SV) to end-diastolic volume (EDV):

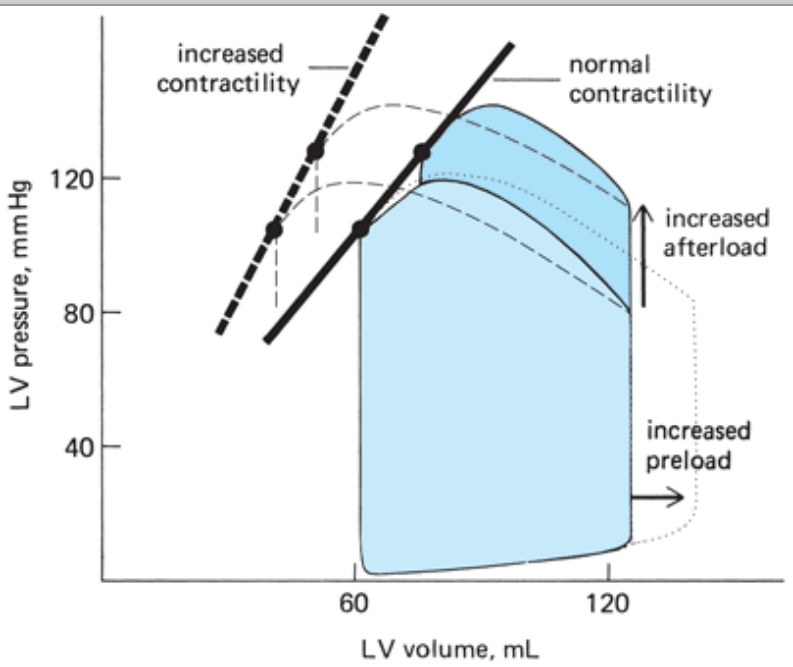
$$EF = SV/EDV$$

Ejection fraction is commonly expressed as a percentage and normally ranges from 55% to 80% (mean 67%) under resting conditions. Ejection fractions of less than 55% indicate depressed myocardial contractility.

END-SYSTOLIC PRESSURE-VOLUME RELATIONSHIP

This relationship was first described in Figure 3–5B. End-systolic volume for a given cardiac cycle is estimated by one of the imaging techniques described above while end-systolic pressure for that cardiac cycle is obtained from the arterial pressure record at the point of the closure of the aortic valve (the incisura). Values for several different cardiac cycles are obtained during infusion of a vasoconstrictor (which increases afterload), and the data are plotted. As shown in Figure 3–9, increases in myocardial contractility are associated with a leftward shift in this relationship. Decreases in contractility (as may be caused by heart disease) are associated with a downward shift of the line and will be discussed further in Chapter 11. This method of assessing cardiac function is particularly important because it provides an estimate of contractility that is independent of the end-diastolic volume (preload). Recall from Figure 3–4 and from the pressure-volume loop described by the dotted line in Figure 3–9 that increases in preload cause increases in stroke volume without changing the end-systolic volume. Thus only alterations in contractility will cause shifts in the end-systolic pressure-volume relationship.

Figure 3–9.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

The effect of increased contractility upon the left ventricular end-systolic pressure-volume relationship.

KEY CONCEPTS

1. Effective cardiac pumping of blood requires coordinated filling of the chambers, excitation and contraction of the cardiac muscle cells, pressure generation within the chambers, opening and closing of cardiac valves, and one-way movement of blood through the chambers into the aorta or pulmonary artery.

2. Except for lower ejection pressures, events of the right side of the heart are identical to those of the left side.

3. Heart sounds associated with valve movements and detected upon auscultation can be used to identify the beginnings of diastolic and systolic phases of the cardiac cycle.

4. The events of a single ventricular cardiac cycle can be displayed as a record against time or as a record of volume against pressure.

5. Cardiac output is defined as the amount of blood pumped by either of the ventricles per minute and is determined by the product of heart rate and stroke volume.

6. Stroke volume can be altered by changes in ventricular preload (filling), ventricular afterload (arterial pressure), and/or cardiac muscle contractility.

7. A cardiac function curve describes the relationship between ventricular filling and cardiac output and can be shifted up (left) or down (right) by changes in sympathetic activity to the heart or by changes in cardiac muscle contractility.

8. Energy for cardiac muscle contraction is derived primarily from aerobic metabolic pathways such that cardiac work is tightly related to myocardial oxygen consumption.

9. A variety of methods are available for measuring various aspects of cardiac function (cardiac output, cardiac index, ejection fraction). These methods are based on the Fick principle, dye-dilution techniques, and various imaging techniques.

STUDY QUESTIONS

3–1. If pulmonary artery pressure is 24/8 mmHg (systolic/diastolic), what are the respective systolic and diastolic pressures of the right ventricle?

3–2. Because pulmonary artery pressure is so much lower than aortic pressure, the right ventricle has a larger stroke volume than the left ventricle. True or false?

3–3. Which of the following interventions will increase cardiac stroke volume?

a. Increased ventricular filling pressure

b. Decreased arterial pressure

c. Increased activity of cardiac sympathetic nerves

d. Increased circulating catecholamine levels

3–4. Given the following information, calculate cardiac output:

Systemic arterial blood oxygen concentration, $[O_2]_{SA}$ = 200 mL/L

Pulmonary arterial blood oxygen concentration, $[O_2]_{PA}$ = 140 mL/L

Total body oxygen consumption, $\dot{V}_{O_2}$ = 600 mL/min

3–5. In which direction will cardiac output change if central venous pressure is lowered while cardiac sympathetic tone is increased?

3–6. Increases in sympathetic neural activity to the heart will result in an increase in stroke volume by causing a decrease in end-systolic volume for any given end-diastolic volume. True or false?

See answers.

SUGGESTED READINGS

Chemla D, Coirault C, Hebert JL, Lecarpentier Y. Mechanics of relaxation of the human heart. *News Physiol Sci.* 2000;15:78–89. [PMID: 11390883]

Elzinga G. Starling's "law of the heart": Rise and fall of the descending limb. *News Physiol Sci.* 1992;7:134–137.

Howell WH, Donaldson F. Experiments upon the heart of the dog with reference to the maximum volume of blood sent out by the left ventricle in a single beat and the influence of variations in venous pressure, arterial pressure, and pulse rate upon the work done by the heart. *Philos Trans R Soc.* 1884;175:139–160.

Koch WJ, Lefkowitz RJ, Rockman HA. Functional consequences of altering myocardial adrenergic receptor signaling. *Annu Rev Physiol.* 2000;62:237–260. [PMID: 10845091]

Millard RK. Indicator-dilution dispersion models and cardiac output computing methods. *Am J Physiol.* 1997;272:H2004–2012.

Sagawa K. The end-systolic pressure-volume relationship of the ventricles: Definition, modification and clinical use. *Circulation.* 1981;63:1223–1227. [PMID: 7014027]

Sarnoff SJ. Myocardial contractility as described by ventricular function curves. *Physiol Rev.* 1955;35:107. [PMID: 14356923]

Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart.*Physiol Rev.* 2005;85:1093–1129. [PMID: 15987803]

Starling EH. *The Linacre Lecture on the Law of the Heart.* London, England: Longmans Green; 1918.

Zimmer HG. The isolated perfused heart and its pioneers. *News Physiol Sci.* 1999;13:203–210.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.
Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.

Medical a silverchair information system The McGraw-Hill Companies

Note: Large images and tables on this page may necessitate printing in landscape mode.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.

OBJECTIVES

The student understands the physiological basis of the electrocardiogram:

- *States the relationship between electrical events of cardiac excitation and the P, QRS, and T waves, the PR and QT intervals, and the ST segment of the electrocardiogram.*
- *States Einthoven's basic electrocardiographic conventions and, given data, determines the mean electrical axis of the heart.*
- *Describes the standard 12-lead electrocardiogram.*

BASIC FEATURES OF THE ELECTROCARDIOGRAM

A typical electrocardiographic record is indicated in Figure 4–1. As briefly described in Chapter 2, the major features of the electrocardiogram are the P, QRS, and T waves that are caused by atrial depolarization, ventricular depolarization, and ventricular repolarization, respectively. The period of time from the initiation of the P wave to the beginning of QRS complex is designated as the PR interval and indicates the time it takes for an action potential to spread through the atria and the atrioventricular (AV) node. During the latter portion of the PR interval (PR segment), no voltages are detected on the body surface. This is because atrial muscle cells are depolarized (in the plateau phase of their action potentials), ventricular cells are still resting, and the electrical field set up by the action potential progressing through the small AV node is not intense enough to be detected. The duration of the normal PR interval ranges from 120 to 200 ms. Shortly after the cardiac impulse breaks out of the AV node and into the rapidly conducting Purkinje system, all the ventricular muscle cells depolarize within a very short period of time and cause the QRS complex. The R wave is the largest event in the electrocardiogram because ventricular muscle cells are so numerous and because they depolarize nearly in unison. The normal QRS complex lasts between 60 and 100 ms. [The repolarization of atrial cells is also occurring during the time period in which ventricular depolarization generates the QRS complex on the electrocardiogram (see Figure 2–5). Atrial repolarization is not evident on the electrocardiogram because it is a poorly synchronized event in a relatively small mass of heart tissue and is completely overshadowed by the major electrical events occurring in the ventricles at this time.]

Figure 4–1.



Typical electrocardiogram.

The QRS complex is followed by the *ST segment.* Normally, no electrical potentials are measured on the body surface during the ST segment because no rapid changes in membrane potential are occurring in any of the cells of the heart; atrial cells have already returned to the resting phase,

whereas ventricular muscle cells are in the plateau phase of their action potentials. (Myocardial injury or inadequate blood flow, however, can produce elevations or depressions in the ST segment.) When ventricular cells begin to repolarize, a voltage once again appears on the body surface and is measured as the T wave of the electrocardiogram. The T wave is broader and not as large as the R wave because ventricular repolarization is less synchronous than depolarization. At the conclusion of the T wave all the cells in the heart are in the resting state. The *QT interval* roughly approximates the duration of the ventricular myocyte depolarization and thus the period of ventricular systole. At a normal heart rate of 60 beats/min, the QT interval is normally less than 380 ms. No body surface potential is measured until the next impulse is generated by the sinoatrial (SA) node.

It should be recognized that the operation of the specialized conduction system is a primary factor in determining the normal electrocardiographic pattern. For example, the AV nodal transmission time determines the PR interval. Also, the effectiveness of the Purkinje system in synchronizing ventricular depolarization is reflected in the large magnitude and short duration of the QRS complex. It should also be noted that nearly every heart muscle cell is inherently capable of rhythmicity and that all cardiac cells are electrically interconnected through gap junctions. Thus a functional heart rhythm can and often does occur without the involvement of part or all of the specialized conduction system. Such a situation is, however, abnormal, and the existence of abnormal conduction pathways would produce an abnormal electrocardiogram.

Basic Electrocardiographic Conventions

Recording electrocardiograms is a routine diagnostic procedure, which is standardized by universal application of certain conventions. The conventions for recording and analysis of electrocardiograms from the three standard bipolar limb leads are briefly described here.

Recording electrodes are placed on both arms and the left leg—usually at the wrists and ankle. The appendages are assumed to act merely as extensions of the recording system, and voltage measurements are assumed to be made between points that form an equilateral triangle over the thorax, as shown in Figure 4–2. This conceptualization is called *Einthoven's triangle* in honor of the Dutch physiologist who devised it at the turn of the century. Any single electrocardiographic trace is a recording of the voltage difference measured between any two vertices of Einthoven's triangle. An example of the lead II electrocardiogram measured between the right arm and the left leg has already been shown in Figure 4–1. Similarly, lead I and lead III electrocardiograms represent voltage measurements taken along the other two sides of Einthoven's triangle, as indicated in Figure 4–2. The + and – symbols in Figure 4–2 indicate polarity conventions that have been universally adopted. For example, an upward deflection in a lead II electrocardiogram (as normally occurs during the P, R, and T waves) indicates that an electrical polarity exists at that instant between the left leg and the right shoulder electrodes, with the left leg electrode being positive. Conversely, a downward deflection in a lead II record indicates that a polarity exists between the electrodes at that instant, with the left leg electrode being negative. Similar polarity conventions have been established for lead I and lead III recordings and are indicated by the + and – symbols in Figure 4–2. In addition, electrocardiographic recording equipment is often standardized so that a 1 cm deflection on the vertical axis always represents a potential difference of 1 mV, and that 25 mm on the horizontal axis of any electrocardiographic record represents 1 second. Most electrocardiographic records contain calibration signals so that abnormal rates and wave amplitudes can be easily detected.

Figure 4–2.



Einthoven's electrocardiographic conventions.

As shown in the next chapter, many cardiac electrical abnormalities can be detected in recordings from a single electrocardiographic lead. However, certain clinically useful information can only be derived by combining the information obtained from two electrocardiographic leads. To understand these more complex electrocardiographic analyses, a close examination of how voltages appear on the body surface as a result of the cardiac electrical activity must be done.

CARDIAC DIPOLES & ELECTROCARDIOGRAPHIC RECORDS

Einthoven's conceptualization of how cardiac electrical activity causes potential differences on the surface of the body is illustrated in Figure 4–3. In this example, the heart is shown at one instant in the atrial depolarization phase. The cardiac impulse, after having arisen in the SA node, is spreading as a wavefront of depolarization through the atrial tissue. At each point along this wavefront of electrical activity, a small charge separation exists in the extracellular fluid between polarized membranes (positive outside) and depolarized membranes (negative outside). Thus, the wavefront may be thought of as a series of individual *electrical dipoles* (regions of charge separation). Each individual dipole is oriented in the direction of local wavefront movement. The large black arrow in Figure 4–3 represents the total *net* dipole created by the summed contributions of all the individual dipoles distributed along the wavefront of depolarization. The salty extracellular fluid acts as an excellent conductor, allowing these instantaneous net dipoles generated on the surface of the heart muscle to be recorded by electrodes on the surface of the body.

Figure 4–3.



Net cardiac dipole during atrial depolarization and its components on the limb leads.

The net dipole that exists at any instant is oriented (ie, points) in the general direction of wavefront movement at that instant. The magnitude or strength of the dipole (represented here by the arrow length) is determined by: (1) how extensive the wavefront is (ie, how many cells are simultaneously depolarizing at the instant in question) and (2) the consistency of orientation between individual dipoles at different points in the wavefront (dipoles with the same orientation reinforce each other; dipoles with opposite orientation cancel each other).

The net dipole in the example of Figure 4–3 causes the lower-left portion of the body to be generally positive with respect to the upper-right portion. This particular dipole will cause positive voltages to exist on all three of the electrocardiogram limb leads. As shown in the right half of Figure 4–3, this can be deduced from Einthoven's triangle by observing that the net dipole has some component that points in the positive direction of leads I, II, and III. As illustrated in Figure 4–3, the component that a cardiac dipole has on a given electrocardiogram lead is found by drawing perpendicular lines from the appropriate side of Einthoven's triangle to the tip and tail of

the dipole. (It may be helpful to think of the component on each lead as the "shadow" cast by the dipole on that lead as a result of a "sun" located far beyond the corner of Einthoven's triangle that is opposite the lead.) Note that the dipole in this example is most parallel to lead II and therefore has a large component in the lead II direction. Thus, it will create a larger voltage on lead II than on leads I or III. This dipole has a rather small component on lead III because it is oriented nearly perpendicular to lead III.

The limb lead configuration may be thought of as a way to view the heart's electrical activity from three different perspectives (or axes). The vector representing the heart's instantaneous dipole strength and orientation is the object under observation, and its appearance depends on the position from which it is viewed. The instantaneous voltage measured on the axis of lead I, for example, indicates how the dipole being generated by the heart's electrical activity at that instant appears when viewed from directly above. A cardiac dipole that is oriented horizontally appears large on lead I, whereas a vertically oriented cardiac dipole, however large, produces no voltage on lead I. Thus, it is necessary to have views from two directions to establish the magnitude and orientation of the heart's dipole. A vertically oriented dipole would be invisible on lead I but would be readily apparent if viewed from the perspective of lead II or lead III.

It is important to recognize that the example of Figure 4–3 pertains only to one instant during atrial depolarization. The net cardiac dipole continually changes in magnitude and orientation during the course of atrial depolarization. The nature of these changes will determine the shape of the P wave on each of the electrocardiogram leads.

The P wave terminates when the wave of depolarization, as illustrated in Figure 4–3, reaches the nonmuscular border between the atria and the ventricles and the number of individual dipoles becomes very small. At this time, the cardiac impulse is still being slowly transmitted toward the ventricles through the AV node. However, the electrical activity in the AV node involves so few cells that it generates no detectable net cardiac dipole. Thus, no voltages are measured on the surface of the body for a brief period following the P wave. A net cardiac dipole reappears only when the depolarization completes its passage through the AV node, enters the Purkinje system, and begins its rapid passage over the ventricular muscle cells. Because the Purkinje fibers terminate in the intraventricular septum and in the endocardial layers at the apex of the ventricles, ventricular depolarization occurs first in these areas and then proceeds outward and upward through the ventricular myocardium.

Ventricular Depolarization & the QRS Complex

It is the rapid and large changes in the magnitude and direction of the net cardiac dipole that exist during ventricular depolarization that cause the QRS complex of the electrocardiogram. The normal process is illustrated in Figure 4–4. The initial ventricular depolarization usually occurs on the left side of the intraventricular septum as diagrammed in the upper panel of the figure. Analysis of the cardiac dipole formed by this initial ventricular depolarization with the aid of Einthoven's triangle shows that this dipole has a negative component on lead I, a small negative component on lead II, and a positive component on lead III. The upper right panel shows the actual deflections on each of the electrocardiographic limb leads that will be produced by this dipole. Note that it is possible for a given cardiac dipole to produce opposite deflections on different leads. For example, in Figure 4–4, Q waves appear on leads I and II but not on lead III.

Figure 4–4.



Ventricular depolarization and the generation of the QRS complex.

The second row of panels in Figure 4–4 shows the ventricles during the instant in ventricular depolarization when the number of individual dipoles is greatest and/or their orientation is most similar. This phase generates the large net cardiac dipole, which is responsible for the R wave of the electrocardiogram. In Figure 4–4, the net cardiac dipole is nearly parallel to lead II. As indicated, such a dipole produces large positive R waves on all three limbs leads.

The third row of diagrams in Figure 4–4 shows the situation near the end of the spread of depolarization through the ventricles and indicates how the small net cardiac dipole present at this time produces the S wave. Note that an S wave does not necessarily appear on all electrocardiogram leads (as in lead I of this example).

The bottom row of diagrams in Figure 4–4 shows that during the ST segment, all ventricular muscle cells are in a depolarized state. There are no waves of electrical activity moving through the heart tissue. Consequently, no net cardiac dipole exists at this time and no voltage differences exist between points on the body surface. All electrocardiographic traces will be flat at the *isoelectric* (zero voltage) level.

Ventricular Repolarization & the T Wave

As illustrated in Figure 4–1, the T wave is normally positive on lead II as is the R wave. This indicates that the net cardiac dipole generated during ventricular repolarization is oriented in the same general direction as that which exists during ventricular depolarization. This may be somewhat surprising since the individual dipoles generated along a wavefront of repolarization have exactly the opposite polarity as those that exist along a wavefront of depolarization. However, recall from Figure 2–5 that the last ventricular cells to depolarize are the first to repolarize. The reasons for this are not well understood but the result is that the wavefront of electrical activity during ventricular repolarization tends to retrace, in *reverse direction,* the course followed during ventricular depolarization. The combination of reversed individual dipole polarity and reversed wavefront propagation pathway during ventricular repolarization would be a positive T wave recorded, for example, on lead II. The T wave is broader and smaller than the R wave because the repolarization of ventricular muscle cells is less well synchronized than is their depolarization.

MEAN ELECTRICAL AXIS & AXIS DEVIATIONS

The orientation of the cardiac dipole during the most intense phase of ventricular depolarization (ie, at the instant the R wave reaches its peak) is called the *mean electrical axis* of the heart. It is used clinically as an indicator of whether or not ventricular depolarization is proceeding over normal pathways. The mean electrical axis is reported in degrees according to the convention indicated in Figure 4–5. (Note that the downward direction corresponds to *plus* 90 degrees in this system.) As indicated, a mean electrical axis that lies anywhere in the patient's lower left-hand quadrant is considered normal. A *left axis deviation* exists when the mean electrical axis falls in the patient's upper left-hand quadrant and may indicate a physical displacement of the heart to the left, left ventricular hypertrophy, or loss of electrical activity in

the right ventricle. A *right axis deviation* exists when the mean electrical axis falls in the patient's lower right-hand quadrant and may indicate a physical displacement of the heart to the right, right ventricular hypertrophy, or loss of electrical activity in the left ventricle.

Figure 4–5.



Mean electrical axis and axis deviations.

The mean electrical axis of the heart can be determined from the electrocardiogram. The process involves determining what single net dipole orientation will produce the R wave amplitudes recorded on any two leads. For example, if the R waves on leads II and III are both positive (upright) and of equal magnitude, the mean electrical axis must be +90 degrees. As should be obvious, in this case, the amplitude of the R wave on lead I will be zero.[1] Alternatively, one can scan the electrocardiographic records for the lead tracing with the largest R waves and then deduce that the mean electrical axis must be nearly parallel to that lead. In Figure 4–4, for example, the largest R wave occurs on lead II. Lead II has an orientation of +60 degrees, which is very close to the actual mean electrical axis in this example.

Another analysis technique called *vectorcardiography* is based on continuously following the magnitude and orientation of the heart's dipole throughout the cardiac cycle. A typical vectorcardiogram is illustrated in Figure 4–6 and is a graphical record of the dipole amplitude in the*x* and *y* directions throughout a single cardiac cycle. If one imagines the heart's electrical dipole as a vector with its tail always positioned at the center of Einthoven's triangle, then the vectorcardiogram can be thought of as a complete record of all the various positions that the head of the dipole assumes during the course of one cardiac cycle. A vectorcardiogram starts from an isoelectric diastolic point and traces three loops during each cardiac cycle. The first small loop is caused by atrial depolarization, the second large loop is caused by ventricular depolarization, and the final intermediate-sized loop is caused by ventricular repolarization. The mean electrical axis of the heart is immediately apparent in a vectorcardiographic reading.

Figure 4–6.



Typical vectorcardiogram.

[1]An accurate, albeit tedious, way to determine the mean electrical axis is to follow these steps: (1) determine the algebraic sum of the R and S wave amplitude on each of the two leads, (2) plot these magnitudes as components on the appropriate sides of Einthoven's equilateral triangle according to the standardized polarity conventions, (3) project perpendicular lines from the heads and tails of these components into the interior of the triangle to find the position of the head and tail of the cardiac dipole which produced the R waves, and (4) measure the angular orientation of this dipole.

THE STANDARD 12-LEAD ELECTROCARDIOGRAM

The standard clinical electrocardiogram involves voltage measurements recorded from 12 different leads. Three of these are the bipolar limb leads I, II, and III, which have already been discussed. The other nine leads are unipolar leads. Three of these leads are generated by using the limb electrodes. Two of the electrodes are electrically connected to form an *indifferent electrode* while the third limb electrode is made the positive pole of the pair. Recordings made from these electrodes are called *augmented unipolar limb leads.* The voltage record ob-tained between the electrode at the right arm and the indifferent electrode is called a lead aVR electrocardiogram. Similarly, lead aVL is recorded from the electrode on the left arm and lead aVF is recorded from the electrode on the left leg.

The standard limb leads (I, II, and III) and the augmented unipolar limb leads (aVR, aVL, and aVF) record the electrical activity of the heart as it appears from six different "perspectives," all in the frontal plane. As shown in Figure 4–7A, the axes for leads I, II, and III are those of the sides of Einthoven's triangle, while those for aVR, aVL and aVF are specified by lines drawn from the center of Einthoven's triangle to each of its vertices. As indicated in Figure 4–7B, the six limb leads can be thought of as a hexaxial reference system for observing the cardiac vectors in the frontal plane.

Figure 4–7.



The standard 12-lead electrocardiogram. A and B: Leads in the frontal plane. C: Electrode positions for precordial leads in the transverse plane.

The other six leads of the standard 12-lead electrocardiogram are also unipolar leads that "look" at the electrical vector projections in the transverse plane. These potentials are obtained by placing an additional (*exploring*) electrode in six specified positions on the chest wall as shown in Figure 4–7C. The indifferent electrode in this case is formed by electrically connecting the limb electrodes. These leads are identified as *precordial* or *chest* leads and are designated as V1 through V6. As shown in this figure, when the positive electrode is placed in position 1 and the wave of ventricular excitation sweeps away from it, the resultant deflection will be downward. When the electrode is in position 6 and the wave of ventricular excitation sweeps toward it, the deflection will be upward.

KEY CONCEPTS

The electrocardiogram is a record of the voltage changes that occur on the surface of the body as a result of the propagation of the action potential through the heart during a cardiac cycle.

There are standardized conventions used for recording electrocardiograms.

The magnitude and direction of the net dipole formed by the wavefront of the action potential at any instant in time can be deduced from the magnitude and orientation of the electrocardiographic deflections.

The mean electrical axis describes the orientation of the net dipole at the instant of maximum wavefront propagation during ventricular depolarization and normally falls between 0 degrees and +90 degrees on a polar coordinate system.

The standard 12-lead electrocardiogram is widely used to evaluate cardiac electrical activity and consists of a combination of bipolar and unipolar records from limb electrodes and chest electrodes.

STUDY QUESTIONS

4–1. A decrease in atrioventricular nodal conduction velocity will

a. Decrease heart rate

b. Increase P wave amplitude

c. Increase the PR interval

d. Widen the QRS complex

e. Increase the ST segment duration

4–2. The P wave on lead aVR of the normal electrocardiogram will be

a. An upward deflection

b. A downward deflection

c. Not detectable

d. Highly variable

4–3. If the R wave is upright and equally large on leads I and aVF, what is the mean electrical axis of the heart? Is it within normal range? Which lead(s) will have the smallest R wave amplitude?

See answers.

SUGGESTED READINGS

Fisch C. Centennial of the string galvanometer and the electrocardiogram. *J Am Coll Cardiol.* 2000;36(6):1737–1745. [PMID: 11092639]

James TN. Structure and function of the sinus node, AV node and His bundle of the human heart: parts I and II. *Prog Cardiovasc Dis.* 2002;45:235–267, 2003;45;327–360.

Meek S, Morris F. ABC of clinical electrocardiography. Introduction. I-Leads, rate, rhythm, and cardiac axis. *BMJ.* 2002;324(7334):415–418. [PMID: 11850377]

Moss AJ. The electrocardiogram: from Einthoven to molecular genetics. *Ann Noninvasive Electrocardiol.* 2001;Jul 6(3):181–182.

Nobel D. The surprising heart: a review of recent progress in cardiac electrophysiology. *J Physiol.* 1984;353: 1–50.

Raju TN. The Nobel chronicles. 1924: Willem Einthoven (1860–1927). *Lancet.* 1998;352:1560. [PMID: 9820341]

Zipes DP, Jalife, J. *Cardiac Electrophysiology*, 4th ed. Philadelphia, Pa: WB Saunders and Company, 2004.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.
Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.

McGraw-Hill Education | A Silverchair Information System | The McGraw-Hill Companies

Note: Large images and tables on this page may necessitate printing in landscape mode.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.

OBJECTIVES

The student, through understanding normal cardiac function, diagnoses and appreciates the consequences common cardiac abnormalities:

- *Detects common cardiac arrhythmias from the electrocardiogram, identifies their physiological bases, describes their physiological consequences.*
- *Lists four common valvular abnormalities for the left heart and describes the alterations in heart soun intracardiac pressures, and flow patterns that accompany them.*

CARDIAC ABNORMALITIES: INTRODUCTION

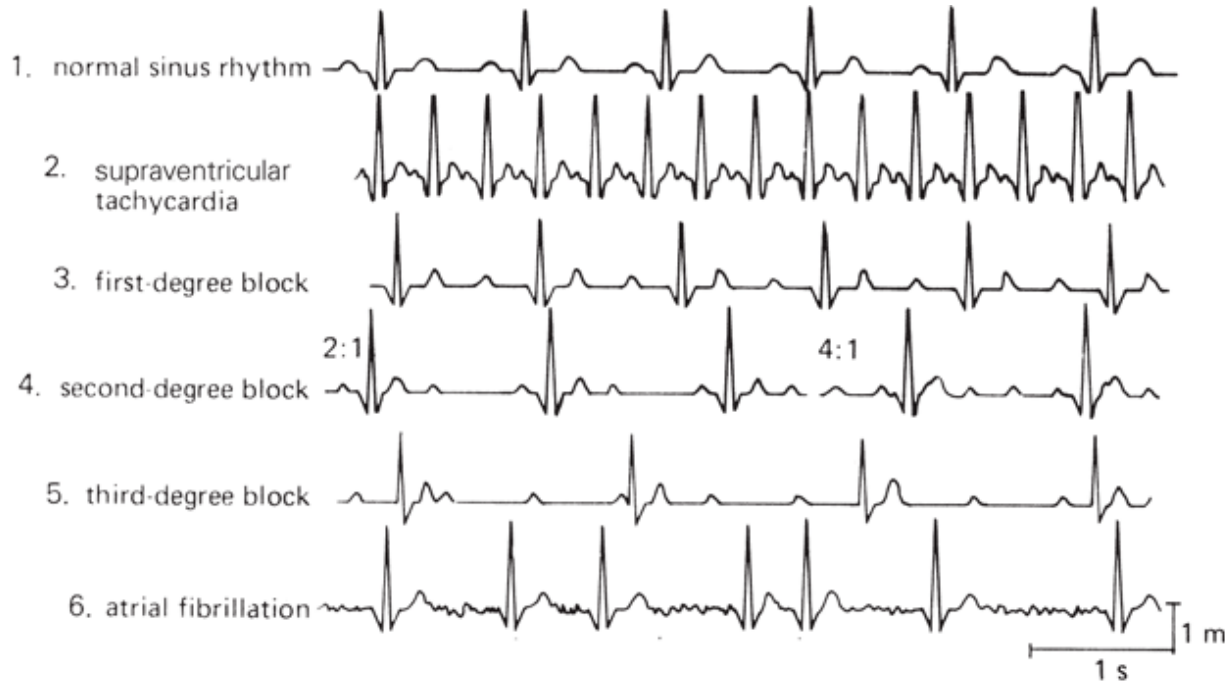
Recall that effective, efficient ventricular pumping action depends on proper cardiac function in five basic respects. This chapter will focus on the abnormalities in three of these respects: (1) abnormal cardiac exci and rhythmicity, (2) valvular stenosis (inadequate valve opening), and (3) valvular insufficiency (incomple closure). Discussion of abnormalities in myocardial force production and cardiac filling will be presented in chapter.

ELECTRICAL ABNORMALITIES & ARRHYTHMIAS



Many cardiac excitation problems can be diagnosed from the information in a single lead of an electrocardiogram. The lead II electrocardiogram trace at the top of Figure 5–1 is identified as normal sinu rhythm based on the following characteristics: (1) the frequency of QRS complexes are ~1 per second indi normal beating rate, (2) the shape of the QRS complex is normal for lead II and its duration is less than 1 indicating rapid depolarization of the ventricles via normal conduction pathways, (3) each QRS complex is preceded by a P wave of proper configuration indicating sinoatrial (SA) nodal origin of the excitation, (4) tl interval is less than 200 ms indicating proper conduction delay of the impulse propagation through the atrioventricular (AV) node, (5) the QT interval is less than half of the R-to-R interval indicating normal ven repolarization, and (6) there are no extra P waves indicating that no AV nodal conduction block is present. subsequent electrocardiographic tracings in Figures 5–1 and 5–3 represent irregularities commonly found i clinical practice. Examination of each of these traces with the above characteristics in mind will aid in the differential diagnosis. The physiological consequences of abnormal excitation and conduction in the heart d on whether the electrical abnormality evokes a *tachycardia,* which will limit the time for cardiac filling betw beats; evokes a *bradycardia,* which is inadequate to support sufficient cardiac output; or decreases the coordination of myocyte contraction, which will reduce stroke volume.

Figure 5–1.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Supraventricular arrhythmias.

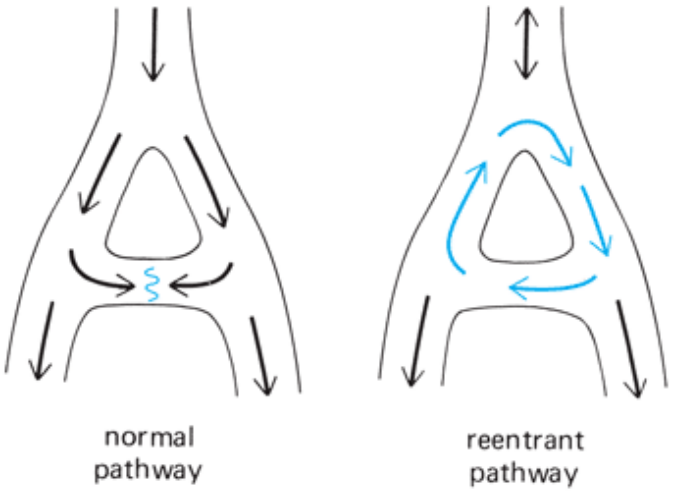
Supraventricular Abnormalities

Traces 2 through 6 below the normal trace in Figure 5–1 represent typical supraventricular arrhythmia originating in the atria or AV node). *Supraventricular tachycardia* (shown in trace 2 of Figure 5–1 and some called paroxysmal atrial tachycardia) occurs when the atria are abnormally excited and drive the ventricles very rapid rate. These paroxysms begin abruptly, last for a few minutes to a few hours, and then, just as abruptly, disappear and heart rate reverts to normal. QRS complexes appear normal (albeit frequent) with paroxysmal atrial tachycardia because the ventricular conduction pathways operate normally. The P and T may be superimposed because of the high heart rate. Low blood pressure and dizziness may accompany b this arrhythmia because the extremely high heart rate does not allow sufficient diastolic time for ventricula filling.

There are two mechanisms that may account for supraventricular tachycardia. First, an atrial region, u outside the SA node, may become irritable (perhaps because of local interruption in blood flow) and begin rapidly to take over the pacemaker function. Such an abnormal pacemaker region is called an *ectopic focus* Alternatively, atrial conduction may become altered so that a single wave of excitation does not die out bu continually travels around some abnormal atrial conduction loop. In this case, the continual activity in the conduction loop may drive the atria and AV node at a very high frequency. This self-sustaining process is c *reentry phenomenon* and is diagramed in Figure 5–2. This situation may develop as a result of abnormal repolarization and altered refractory periods in local areas of the myocardium. *Atrial flutter* is a special forr tachycardia of atrial origin in which a large reentrant pathway drives the atria at very fast rates (250 to 30 beats/min) and normal refractory periods of AV nodal tissue are overwhelmed. Thus, ventricular rate is oft

some fixed ratio of the atrial rate (2:1, 4:1) with frequencies often 150 to 220 beats/min. The electrocardi often shows a sawtooth pattern of merged P waves with intermittent normal QRS complexes.

Figure 5–2.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Normal and reentrant (circus) cardiac excitation pathways.

Conduction blocks occur at the AV node and generally represent impaired conduction through this tiss *first-degree heart block* (trace 3 of Figure 5–1), the only electrical abnormality is unusually slow conductio through the AV node. This condition is detected by an abnormally long PR interval (> 0.2 seconds). Otherv the electrocardiogram may be completely normal. At normal heart rates, the physiological effects of a first block are inconsequential. The danger, however, is that the slow conduction may deteriorate to an actual interruption of conduction.

A*second-degree heart block* (trace 4 of Figure 5–1) is said to exist when some but not all atrial impulses a transmitted through the AV node to the ventricle. Impulses are blocked in the AV node if the cells of the re are still in a refractory period from a previous excitation. The situation is aggravated by high atrial rates ar slower than normal conduction through the AV nodal region. In second-degree block, some but not all P w are accompanied by corresponding QRS complexes and T waves. Atrial rate is often faster than ventricular a certain ratio (eg, 2:1, 3:1, 4:1). This condition may not represent a serious clinical problem as long as th ventricular rate is adequate to meet the pumping needs.

In*third-degree heart block* (trace 5 of Figure 5–1), no impulses are transmitted through the AV node. In th event, some area in the ventricles—often in the common bundle or bundle branches near the exit of the AV node—assumes the pacemaker role for the ventricular tissue. Atrial rate and ventricular rate are completel independent, and P waves and QRS complexes are totally dissociated in the electrocardiogram. Ventricular likely to be slower than normal (bradycardia) and sometimes is slow enough to impair cardiac output.

Atrial fibrillation (trace 6 of Figure 5–1) is characterized by a complete loss of the normally close synchron excitation and resting phases between individual atrial cells. Cells in different areas of the atria depolarize, repolarize, and are excited again randomly. Consequently, no P waves appear in the electrocardiogram alt there may be rapid irregular small waves apparent throughout diastole. The ventricular rate is often very i in atrial fibrillation because impulses enter the AV node from the atria at unpredictable times. Fibrillation is

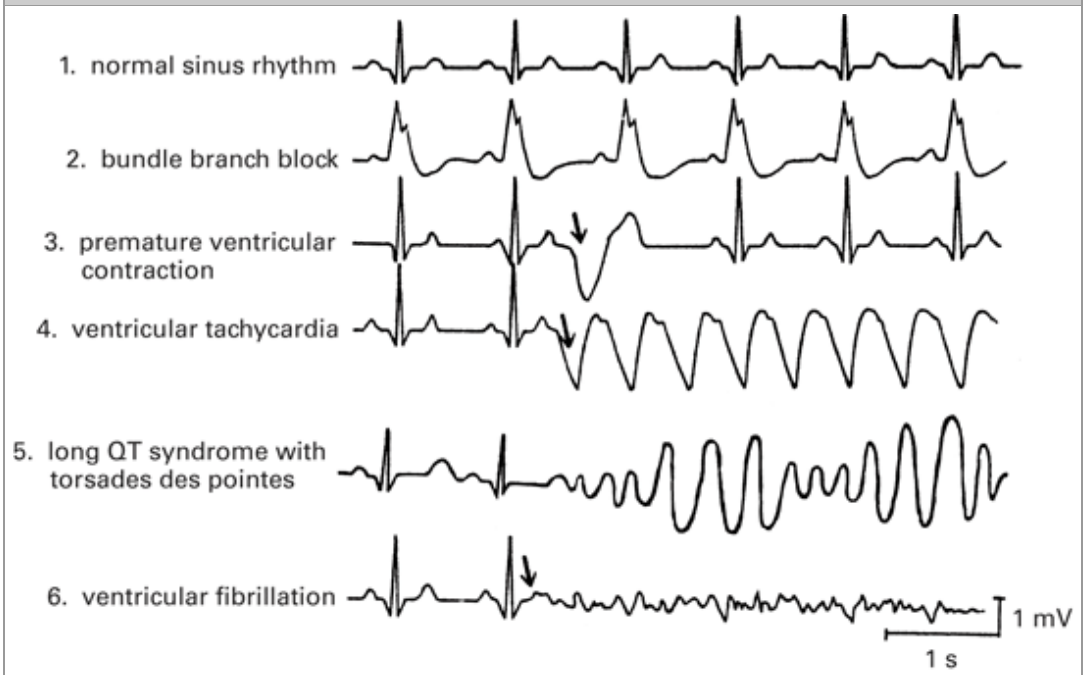
sustaining process. The mechanisms behind it are not well understood, but impulses are thought to progre repeatedly around irregular conduction pathways (sometimes called circus pathways, which imply a reentr phenomenon as described earlier and in Figure 5–2). However, because atrial contraction usually plays a negligible role in ventricular filling, atrial fibrillation may be well tolerated by most patients as long as vent rate is sufficient to maintain the cardiac output.[1]

[1] The real danger with atrial fibrillation lies in the tendency for blood to form clots in the atria in the absen the normal vigorous coordinated atrial contraction. These clots can fragment and move out of the heart to in small artries throughout the systemic circulation. These emboli can have devastating effects on critical o function. Consequently, anticoagulant therapy is usually prescribed for patients in atrial fibrillation.

Ventricular Abnormalities

Traces 2 through 6 below the normal trace in Figure 5–3 show typical ventricular electrical abnormalit Conduction blocks called *bundle branch blocks* or *hemiblocks* (trace 2 of Figure 5–3) can occur in either of branches of the Purkinje system of the intraventricular septum often as a result of a myocardial infarction. Ventricular depolarization is less synchronous than normal in the half of the heart with the nonfunctional P system. This results in a widening of the QRS complex (> 0.12 seconds) because a longer time is required ventricular depolarization to be completed. The direct physiological effects of bundle branch blocks are usu inconsequential.

Figure 5–3.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Ventricular arrhythmias.

Premature ventricular contractions (trace 3 of Figure 5–3) are caused by action potentials initiated by and propagated away from an ectopic focus in the ventricle. As a result, the ventricle depolarizes and contracts it normally would. A premature ventricular contraction is often followed by a missed beat (called a *compen*

pause) because the ventricular cells are still refractory when the next normal impulse emerges from the SA The highly abnormal ventricular depolarization pattern of a premature ventricular contraction produces the amplitude, long-duration deflections on the electrocardiogram. The shapes of the electrocardiographic recc these extra beats are highly variable and depend on the ectopic site of their origin and the depolarization pathways involved. The volume of blood ejected by the premature beat itself is smaller than normal, where stroke volume of the beat following the compensatory pause is larger than normal. This is partly due to the differences in filling times and partly to an inherent phenomenon of cardiac muscle called *postextrasystolic potentiation.* Single premature ventricular contractions (PVC) occur occasionally in most individuals and, al sometimes alarming to the individual experiencing them, are not dangerous. Frequent occurrence of PVCs, however, may be a signal of possible myocardial damage or perfusion problems.



Ventricular tachycardia (trace 4 of Figure 5–3) occurs when the ventricles are driven at high rates, usi impulses originating from a ventricular ectopic focus. Ventricular tachycardia is a very serious condition. N is diastolic filling time limited by the rapid rate, but the abnormal excitation pathways make ventricular contraction less synchronous and therefore less effective than normal. In addition, ventricular tachycardia precedes ventricular fibrillation.

Prolonged QT intervals (left side of trace 5 in Figure 5–3) are a result of delayed ventricular myocyte repolarization, which may be due to inappropriate opening of sodium channels or prolonged closure of pota channels during the action potential plateau phase. Although the normal QT interval varies with heart rate, normally less than 40% of the cardiac cycle length (except at very high heart rates). Long QT syndrome (i the interval is greater than 50% of the cycle duration) may be congenital in origin, may arise from several electrolyte disturbances (low blood levels of Ca^{2+}, Mg^{2+} or K^{+}) or may be induced by several pharmacolog agents (including some antiarrhythmic drugs). The prolongation of the myocyte refractory period, which accompanies the long QT syndrome, extends the vulnerable period during which extra stimuli can evoke tachycardia or fibrillation. Patients with long QT syndrome are predisposed to a particularly dangerous type ventricular tachycardia called *torsades de pointes* ("twisting of points" as shown on the right side of trace 5 Figure 5–3). This differs from the ordinary ventricular tachycardia in that the ventricular electrical complex cyclically vary in amplitude around the baseline and can deteriorate rapidly into ventricular fibrillation.

In*ventricular fibrillation* (trace 6 of Figure 5–3), various areas of the ventricle are excited and contract asynchronously. The mechanisms are similar to those in atrial fibrillation. The ventricle is especially suscep fibrillation whenever a premature excitation occurs at the end of the T wave of the previous excitation, ie, most ventricular cells are in the "hyperexcitable" or "vulnerable" period of their electrical cycle. In addition because some cells are repolarized and some are still refractory, circus pathways can be triggered easily a time. Since no pumping action occurs with ventricular fibrillation, the situation is fatal unless quickly corre *cardiac conversion*. During conversion, the artificial application of large currents to the entire heart (via pa electrodes applied across the chest) may be effective in depolarizing all heart cells simultaneously and thus allowing a normal excitation pathway to be reestablished.

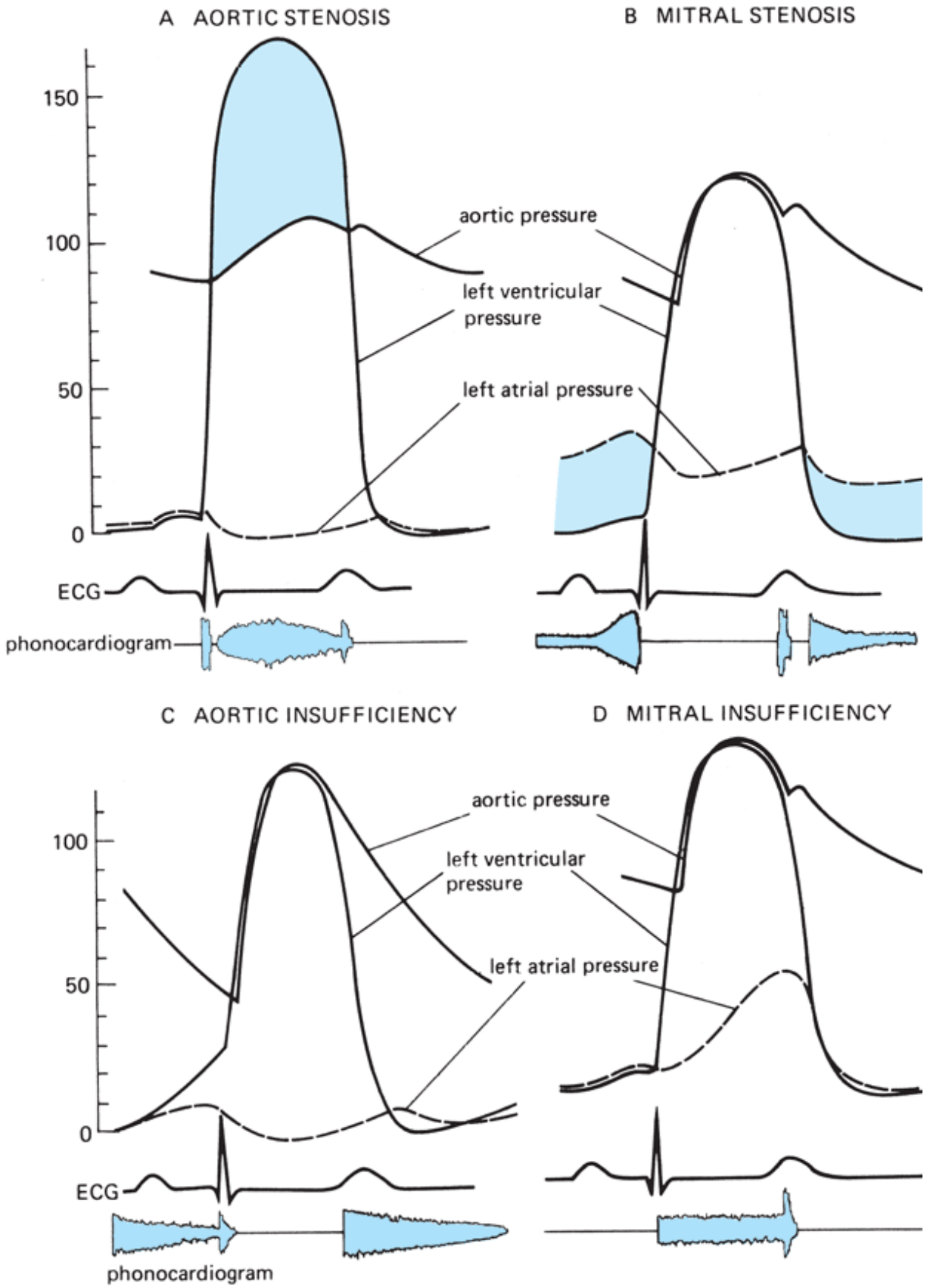
VALVULAR ABNORMALITIES



Pumping action of the heart is impaired when the valves do not function properly. Abnormal heart sou which usually accompany cardiac valvular defects, are called *murmurs.* These sounds are caused by abnor pressure gradients and turbulent blood flow patterns that occur during the cardiac cycle. A number of tech ranging from simple auscultation (listening to the heart sounds) to echocardiography or cardiac catheteriza are used to obtain information about the nature and extent of the malfunction. A brief overview of four of t common valve defects influencing left ventricular function is given in Figure 5–4. (Similar abnormalities ca

in right ventricular valve function.)

Figure 5–4.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Common valvular abnormalities. A: Aortic stenosis. B: Mitral stenosis. C: Aortic regurgitation (insufficienc
Mitral insufficiency.

Aortic Stenosis

Some consequences of aortic stenosis are shown in Figure 5–4A. Normally, the aortic valve opens widely a offers a pathway of very low resistance through which blood leaves the left ventricle. If this opening is nar (stenotic), resistance to flow through the valve increases. A significant pressure difference between the lef ventricle and the aorta may be required to eject blood through a stenotic aortic valve. As shown in Figure intraventricular pressures may rise to very high levels during systole while aortic pressure rises more slowl normal to a systolic value that is subnormal. Pulse pressure is usually low with aortic stenosis. High intraventricular pressure development is a strong stimulus for cardiac muscle cell hypertrophy, and an incr left ventricular muscle mass invariably accompanies aortic stenosis. This tends to produce a leftward devia the electrical axis. (The mean electrical axis will fall in the upper right-hand quadrant of the diagram in Fig 4–5.) Blood being ejected through the narrowed orifice may reach very high velocities, and turbulent flow occur as blood enters the aorta. This abnormal turbulent flow can be heard as a *systolic* (or ejection) *murn* with a properly placed stethoscope.

Mitral Stenosis

Some consequences of mitral stenosis are shown in Figure 5–4B. A pressure difference of more than a few millimeters of mercury across the mitral valve during diastole is distinctly abnormal and indicates that this is stenotic. The high resistance mandates an elevated pressure difference to achieve normal flow across th ($\dot{Q} = \Delta P/R$). Consequently, as shown in Figure 5–4B, left atrial pressure is elevated with mitral stenosis. Th left atrial pressure is reflected back into the pulmonary bed and, if high enough, causes pulmonary conges and "shortness of breath." A *diastolic murmur* associated with turbulent flow through the stenotic mitral va often be heard.

Aortic Insufficiency

Typical consequences of aortic regurgitation (insufficiency) are shown in Figure 5–4C. When the leaflets of aortic valve do not provide an adequate seal, blood regurgitates from the aorta back into the left ventricle the diastolic period. Aortic pressure falls faster and further than normal during diastole, which causes a lov diastolic pressure and a large pulse pressure. In addition, ventricular end-diastolic volume and pressure ar higher than normal because of the extra blood that reenters the chamber through the incompetent aortic v during diastole. Turbulent flow of the blood reentering the left ventricle during early diastole produces a characteristic diastolic murmur. Often the aortic valve is altered so that it is both stenotic and insufficient. these instances, both a systolic and a diastolic murmur are present.

Mitral Regurgitation

Typical consequences of mitral regurgitation (insufficiency) are shown in Figure 5–4D. When the mitral val insufficient, some blood regurgitates from the left ventricle into the left atrium during systole. A systolic m may accompany this abnormal flow pattern. Left atrial pressure is raised to abnormally high levels, and lef ventricular end-diastolic volume and pressure increase. Mitral valve *prolapse* is a common form of mitral insufficiency in which the valve leaflets evert into the left atrium during systole.

KEY CONCEPTS

Cardiac arrhythmia can often be detected from a single electrocardiographic lead.

Physiological consequences of abnormal excitation and conduction in the heart depend on whether the electrical abnormality limits the time for adequate cardiac filling or decreases the coordination of myocyte contractions resulting in inadequate pressure development and ejection.

Supraventricular arrhythmias are a result of abnormal action potential initiation at the sinoatrial node altered propagation characteristics through the atrial tissue and the atrioventricular node.

Tachycardias may originate either in the atria or ventricles and are a result of increased pacemaker automaticity or of continuously circling pathways setting up a reentrant circuit.

Abnormal conduction through the atrioventricular node results in conduction blocks.

Abnormal conduction pathways in the Purkinje system or in the ventricular tissue result in significant C alterations.

Ventricular tachycardia and ventricular fibrillation represent severe abnormalities that are incompatibl effective cardiac pumping.

Failure of cardiac valves to open (stenosis) or close (insufficiency, regurgitation) normally result in sys diastolic murmurs, abnormal pressure gradients across valves, impaired ejection of blood, and congestion upstream vascular beds.

STUDY QUESTIONS

5–1. Which of the following arrhythmias might result in a reduced stroke volume?

a. Paroxysmal atrial tachycardia

b. Ventricular tachycardia

c. Atrial fibrillation

d. Ventricular fibrillation

e. Third-degree heart block

5–2. Describe the primary pressure abnormalities associated with

a. Aortic stenosis

b. Mitral stenosis

5–3. You notice an abnormally large pulsation of your patient's jugular vein, which occurs at about the sam as heart sound S_1. What is your diagnosis?

5–4. What alteration in jugular venous pulsations might accompany third-degree heart block?

See answers.

SUGGESTED READINGS

Carmeliet E. Cardiac ionic currents and acute ischemia: from channels to arrhythmias. *Physiol Rev.* 1999;79:917–1017. [PMID: 10390520]

Clancy CE, Kass RS. Inherited and acquired vulnerability to ventricular arrhythmias: cardiac Na^+ and K^+ ch *Physiol Rev*. 2004;85:33–47.

Da Costa D, Brady WJ, Edhouse J. Bradycardias and atrioventricular conduction block. *BMJ.* 2002;324535–

Jalife J. Ventricular fibrillation: mechanisms of initiation and maintenance. *Annu Rev Physiol.* 2000;62:25–5 [PMID: 10845083]

LeClercq C, Hare JM. Ventricular resynchronization: current state of the heart. *Circulation* 2004;109: 296–3 [PMID: 14744953]

Maron BJ. Sudden death in young athletes. *N Engl J Med.* 2003;349:1064–1075. [PMID: 12968091]

Peters NS, Schilling RJ, Kanagaratnam P, Markides V. Atrial fibrillation: strategies to control, combat, and c *Lancet.* 2002;359:593–603. [PMID: 11867130]

Weiss JN, Qu Z, Chen PS, et al. The dynamics of cardiac fibrillation. *Circulation* 2005;112:1232–1240. [PM 16116073]

Zipes DP, Jalife J. *Cardiac Electrophysiology*, 4th ed. Philadelphia, Pa: WB Saunders and Company, 2004.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.
Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.

Mc Graw Hill Medical a silverchair information system The McGraw-Hill Companies

McGraw-Hill's ACCESSMedicine

Print Close Wind

Note: Large images and tables on this page may necessitate printing in landscape mode.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.

OBJECTIVES

The student understands the basic principles of cardiovascular transport and its role in maintaining homeostasis:

- *Defines convective transport and diffusion and lists the factors that determine the rate of each.*
- *Given data, uses the Fick principle to calculate the rate of removal of a solute from blood as it passes through an organ.*
- *Describes how capillary wall permeability to a solute is related to the size and lipid solubility of the solute.*
- *Lists the factors that influence transcapillary fluid movement and, given data, predicts the direction of transcapillary fluid movement.*
- *Describes the lymphatic vessel system and its role in preventing fluid accumulation in the interstitial space.*

The student understands the physical factors that regulate blood flow through the various components of the vasculature:

- *Given data, calculates the vascular resistances of networks of vessels arranged in parallel and in series.*
- *Describes differences in the blood flow velocity in the various segments and how these differences are related to their total cross-sectional area.*
- *Describes laminar and turbulent flow patterns and the origin of flow sounds in the cardiovascular system.*
- *Identifies the approximate percentage of the total blood volume that is contained in the various vascular segments in the systemic circulation.*
- *Defines peripheral venous pool and central venous pool.*
- *Describes the pressure changes that occur as blood flows through a vascular bed and relates them to the vascular resistance of the various vascular segments.*
- *States how the resistance of each consecutive vascular segment contributes to an organ's overall vascular resistance and, given data, calculates the overall resistance.*
- *Defines total peripheral resistance (systemic vascular resistance) and states the relationship between it and the vascular resistance of each systemic organ.*
- *Defines vascular compliance and states how the volume-pressure curves for arteries and veins differ.*
- *Predicts what will happen to venous volume when venous smooth muscle contracts or when venous transmural pressure increases.*
- *Describes the role of arterial compliance in storing energy for blood circulation.*

- *Describes the auscultation technique of determining arterial systolic and diastolic pressures.*
- *Identifies the physical bases of the Korotkoff sounds.*
- *Indicates the relationship between arterial pressure, cardiac output, and total peripheral resistance and predicts how arterial pressure will be altered when cardiac output and/or total peripheral resistance change.*
- *Given arterial systolic and diastolic pressures, estimates mean arterial pressure.*
- *Indicates the relationship between pulse pressure, stroke volume, and arterial compliance and predicts how pulse pressure will be changed by changes in stroke volume, or arterial compliance.*
- *Describes how arterial compliance changes with age and how this affects arterial pulse pressure.*

THE PERIPHERAL VASCULAR SYSTEM: INTRODUCTION

An overview of the vascular system was presented in Chapter 1. Many more details about vascular design and operation are presented in this chapter. Be careful not to let these details detract from understanding the overall picture presented earlier.

CARDIOVASCULAR TRANSPORT

The Fick Principle



Substances are carried between organs within the cardiovascular system by the process of *convective transport,* the simple process of being swept along with the flow of the blood in which they are contained. The rate at which a substance (X) is transported by this process depends solely on the concentration of the substance in the blood and the blood flow rate.

$$\text{Transport rate} = \text{flow rate} \times \text{concentration}$$

or

$$\dot{X} = \dot{Q}[\text{X}]$$

where $\dot{X}$ = rate of transport of X (mass/time)
$\dot{Q}$ = blood flow rate (volume/time)
[X] = concentration of X in blood (mass/volume)

It is evident from the preceding equation that only two methods are available for altering the rate at which a substance is carried to an organ: (1) a change in the blood flow rate through the organ or (2) a change in the arterial blood concentration of the substance. The preceding equation might be used, for example, to calculate how much oxygen is carried to a certain skeletal muscle each minute. Note, however, that this calculation would not indicate whether the muscle actually used the oxygen carried to it.

One can extend the convective transport principle to determine a tissue's rate of utilization (or production) of a substance by simultaneously considering the transport rate of the substance to *and from* the tissue. The relationship that results is referred to as the *Fick principle* (Adolf Fick, a German physician, 1829–1901) and may be formally stated as follows:

$$\dot{X}_{tc} = \dot{Q}([\text{X}]_a - [\text{X}]_v)$$

where $\dot{X}_{tc}$ = transcapillary efflux rate of X (mass/time)
$\dot{Q}$ = blood flow rate (volume/time)
$[\text{X}]a,v$ = arterial and venous concentrations of X

The Fick principle essentially says that the amount of a substance that goes into an organ in a given perioc of time ($\dot{Q}[X]_a$) minus the amount that comes out ($\dot{Q}[X]_v$) must equal the tissue utilization rate of that substance. (If the tissue is producing substance X, then the above equation will yield a negative utilization rate.)

Recall that one method for determining cardiac output described in Chapter 3 used the Fick principle to calculate the blood flow rate through the systemic circulation. In that case, the known variables included the systemic tissue oxygen consumption rate and the concentrations of oxygen in arterial blood and mixed venous blood. The above equation was rearranged to solve for the blood flow rate ($\dot{Q}$).

Transcapillary Solute Diffusion

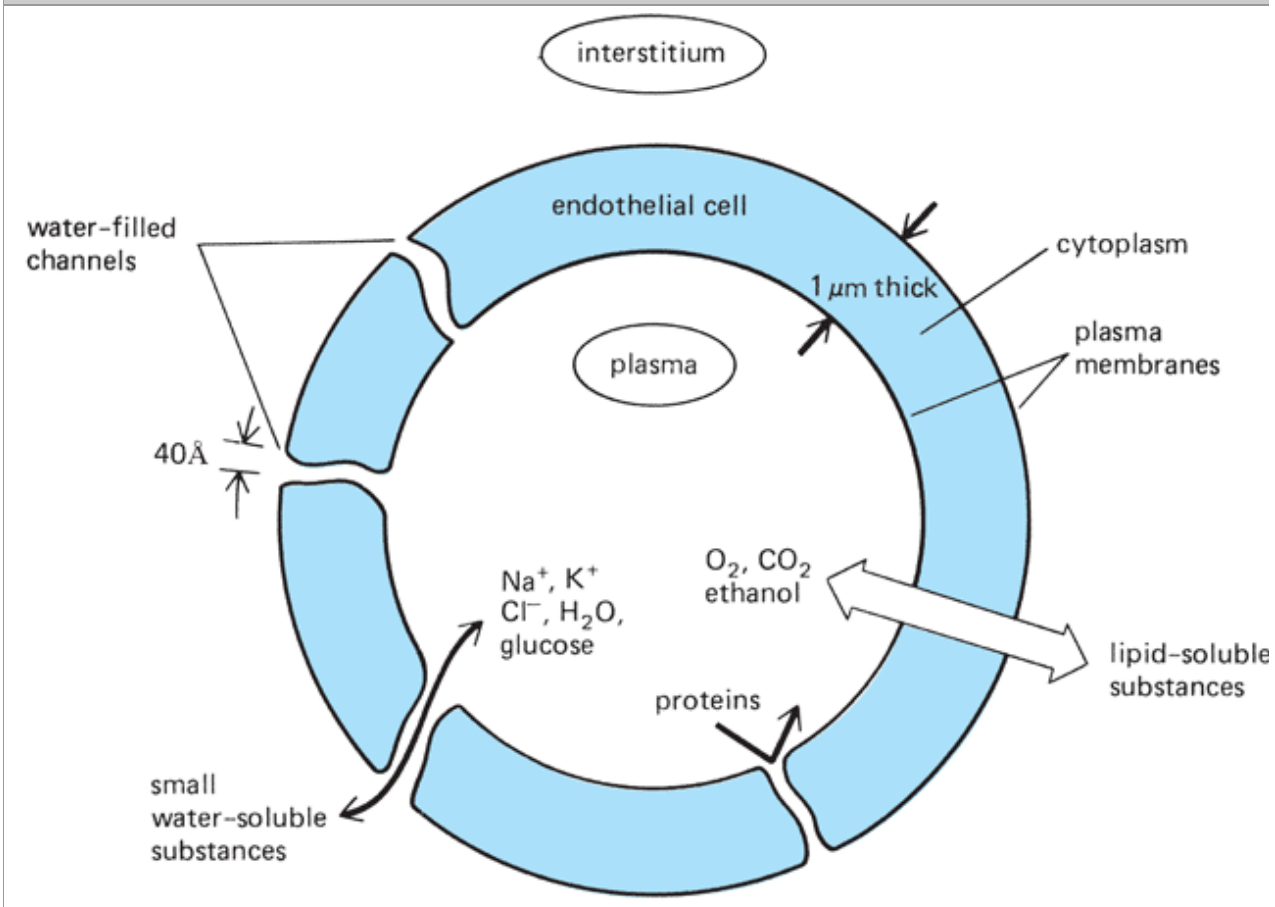


Capillaries act as efficient exchange sites where most substances cross the capillary walls simply by *passively diffusing* from regions of high concentration to regions of low concentration.[1] As in any diffusion situation, there are four factors that determine the diffusion rate of a substance between the blood and the interstitial fluid: (1) the concentration difference, (2) the surface area for exchange, (3) the diffusion distance, and (4) the permeability of the capillary wall to the diffusing substance.[2]

Capillary beds allow huge amounts of materials to enter and leave blood because they maximize the area across which exchange can occur while minimizing the distance over which the diffusing substances must travel. Capillaries are extremely fine vessels with a *lumen* (inside) diameter of about 5 μm, a wall thickness of approximately 1 μm, and an average length of perhaps 0.5 mm. (For comparison, a human hair is roughly 100 μm in diameter.) Capillaries are distributed in incredible numbers in organs and communicate intimately with all regions of the interstitial space. It is estimated that there are about 10^{10} capillaries in the systemic organs with a collective surface area of about 100 square meters. That is roughly the area of one player's side of a singles tennis court. Recall from Chapter 1 that no cell is more than about 10 μm (less than 1/10th the thickness of paper) from a capillary. Diffusion is a tremendously powerful mechanism for material exchange when operating over such a short distance and through such a large area. We are far from being able to duplicate—in an artificial lung or kidney, for example—the favorable geometry for diffusional exchange that exists in our own tissues.

As diagramed in Figure 6–1, the capillary wall itself consists of only a single thickness of endothelial cells joined to form a tube. The ease with which a particular solute crosses the capillary wall is expressed in a parameter called its capillary *permeability.* Permeability takes into account all the factors (diffusion coefficient, diffusion distance, and surface area)—except concentration difference—that affect the rate at which a solute crosses the capillary wall.

Figure 6–1.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Pathways for transcapillary solute diffusion.

Careful experimental studies on how rapidly different substances cross capillary walls indicate that two fundamentally distinct pathways exist for transcapillary exchange. Lipid-soluble substances, such as the gases oxygen and carbon dioxide, cross the capillary wall easily. Because the lipid endothelial cell plasma membranes are not a significant diffusion barrier for lipid-soluble substances, trans-capillary movement of these substances can occur through the entire capillary surface area.

The capillary permeability to small polar particles such as sodium and potassium ions is about 10,000-fold less than that for oxygen. Nevertheless, the capillary permeability to small ions is several orders of magnitude higher than the permeability that would be expected if the ions were forced to move through the lipid plasma membranes. It is therefore postulated that capillaries are somehow perforated at intervals with water-filled channels or *pores.*[3] Calculations from diffusion data indicate that the collective cross-sectional area of the pores relative to the total capillary surface area varies greatly between capillaries in different organs. Brain capillaries appear to be very tight (have few pores), whereas capillaries in the kidney and fluid-producing glands are much more leaky. On the average, however, pores constitute only a very small fraction of total capillary surface area—perhaps 0.01%. This area is, nevertheless, sufficient to allow very rapid equilibration of small water-soluble substances between the plasma and interstitial fluids of most organs. Thus, the concentrations of inorganic ions measured in a plasma sample can be taken to

indicate their concentrations throughout the entire extracellular space.

An effective maximum diameter of about 40 Å has been assigned to individual pores because substances with molecular diameters larger than this essentially do not cross capillary walls.[4] Thus, albumin and other proteins in the plasma are normally confined to the plasma space.[5]

[1] Evidence indicates that the capillary endothelial cells can metabolize or produce certain substances. In these special cases, the capillary wall cannot be considered as a passive barrier between the intravascular and interstitial compartments.

[2] These factors are combined in an equation (Fick's first law of diffusion) which describes the rate of diffusion ($\dot{X}_d$) of a substance X across a barrier: $\dot{X}_d = DA\,\Delta[X]/\Delta L$, where D, A, $\Delta[X]$, and ΔL represent the diffusion coefficient, surface area, concentration difference, and diffusion distance, respectively.

[3] Pores, as such, are not readily apparent in electron micrographs of capillary endothelial cells. Most believe the pores are really clefts in the junctions between endothelial cells.

[4] The precise mechanism responsible for this size-selectivity remains controversial. It may stem from the actual physical dimensions of the "pores," or it may represent the filtering properties of a fiber matrix that either covers or fills the pores.

[5] In reality, macromolecules do cross capillary walls ever so slowly by a pinocytotic mechanism sometimes referred to as the "large pore" system. Even with this special system, the capillary protein permeability is still about 1000-fold less than either sodium or glucose permeability.

Transcapillary Fluid Movement



In addition to providing a diffusion pathway for polar molecules, the water-filled channels that travers capillary walls permit fluid flow through the capillary wall. Net shifts of fluid between the capillary and interstitial compartments are important for a host of physiological functions, including the maintenance of circulating blood volume, intestinal fluid absorption, tissue edema formation, and saliva, sweat, and urine production. Net fluid movement out of capillaries is referred to as *filtration,* and fluid movement into capillaries is called *reabsorption.*

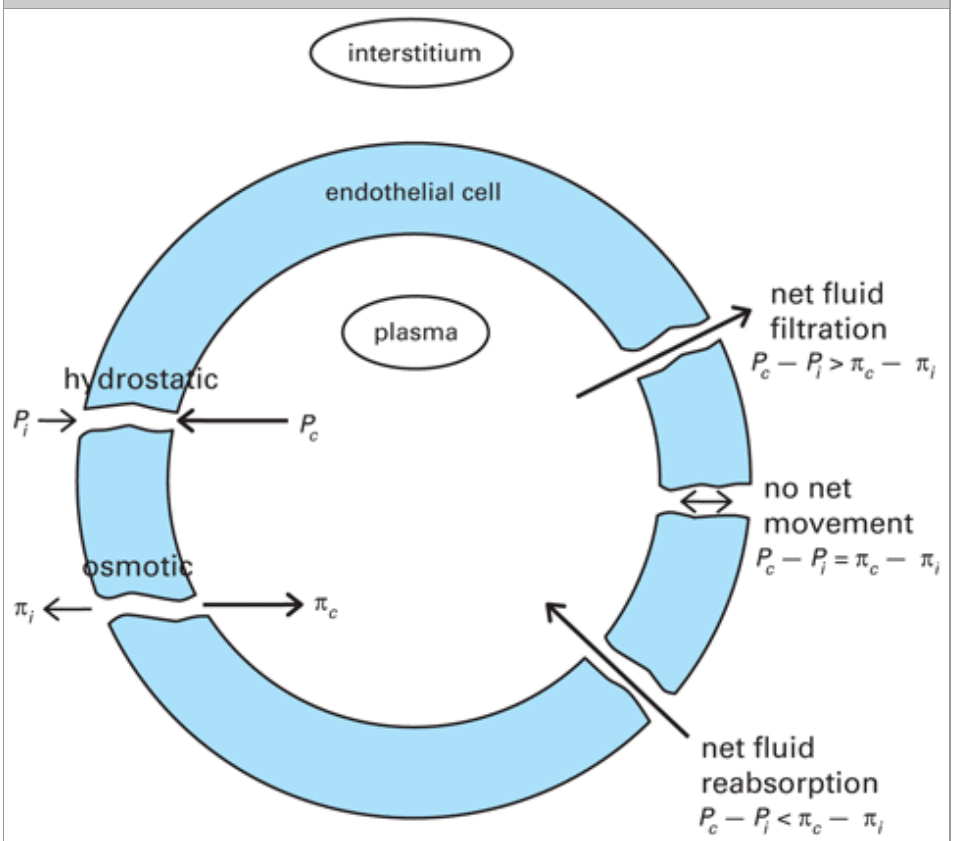
Fluid flows through transcapillary channels in response to pressure differences between the interstitial and intracapillary fluids according to the basic flow equation. However, both *hydrostatic* and *osmotic pressures* influence transcapillary fluid movement. How hydrostatic pressure provides the driving force for causing blood flow along vessels has been discussed previously. The hydrostatic pressure inside capillaries, P_c, is about 25 mmHg and is the driving force that causes blood to return to the right heart from the capillaries of systemic organs. In addition, however, the 25-mmHg hydrostatic intracapillary pressure tends to cause fluid to flow through the transcapillary pores into the interstitium where the hydrostatic pressure (P_i) is near 0 mmHg. Thus, there is normally a large hydrostatic pressure difference favoring fluid filtration across the capillary wall. Our entire plasma volume would soon be in the interstitium if there were not some counteracting force tending to draw fluid into the capillaries. The balancing force is an osmotic pressure that arises from the fact that plasma has a higher protein concentration than does interstitial fluid.



Recall that water always tends to move from regions of low to regions of high total solute concentration in establishing osmotic equilibrium. Also recall that osmotic forces are quantitatively expressed in terms of osmotic pressure. The osmotic pressure of a given solution is defined as the hydrostatic pressure necessary to prevent osmotic water movement into the test solution when it is exposed to pure water across a membrane permeable only to water. The total osmotic pressure of a

solution is proportional to the total number of solute particles in the solution. Plasma, for example, has a total osmotic pressure of about 5000 mmHg—nearly all of which is attributable to dissolved mineral salts such as NaCl and KCl. As discussed, the capillary permeability to small ions is quite high. Their concentrations in plasma and interstitial fluid are very nearly equal and, consequently, they do not affect transcapillary fluid movement. However, there is a small but important difference in the osmotic pressures of plasma and interstitial fluid that is due to the presence of albumin and other proteins in the plasma, which are normally absent from the interstitial fluid. A special term, *oncotic pressure,* is used to denote that portion of a solution's total osmotic pressure that is due to particles that do not move freely across capillaries.[6] Because of the plasma proteins, the oncotic pressure of plasma (π_c) is about 25 mmHg. Due to the absence of proteins, the oncotic pressure of the interstitial fluid (π_i) is near 0 mmHg. Thus, there is normally a large osmotic force for fluid reabsorption into capillaries. The forces that influence transcapillary fluid movement are summarized on the left side of Figure 6–2.

Figure 6–2.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Factors influencing transcapillary fluid movement.

The relationship among the factors that influence transcapillary fluid movement, known as the *Starling hypothesis,*[7] can be expressed by the equation:

$$\text{Net filtration rate} = K[(P_c - P_i) - (\pi_c - \pi_i)]$$

where P_c = the hydrostatic pressure of intracapillary fluid
π_c = the oncotic pressure of intracapillary fluid
P_i and π_i = the same quantities for interstitial fluid
K = a constant expressing how readily fluid can move across capillaries (essentially the reciprocal of the resistance to fluid flow through the capillary wall)

Fluid balance within a tissue (the absence of net transcapillary water movement) occurs when the bracketed term in this equation is zero. This equilibrium may be upset by alterations in any of the four pressure terms. The pressure imbalances that cause capillary filtration and reabsorption are indicated on the right side of Figure 6–2.

In most tissues, rapid net filtration of fluid is abnormal and causes tissue swelling as a result of excess flui in the interstitial space (edema). For example, a substance called histamine is often released in damaged tissue. One of the actions of histamine is to increase capillary permeability to the extent that proteins leak into the interstitium. Net filtration and edema accompany histamine release, in part because the oncotic pressure difference ($\pi_c - \pi_i$) is reduced below normal.

Transcapillary fluid filtration is not always detrimental. Indeed, fluid-producing organs such as salivary glands and kidneys utilize high intracapillary hydrostatic pressure to produce continual net filtration. Moreover, in certain abnormal situations, such as severe loss of blood volume through hemorrhage, the ne fluid reabsorption accompanying diminished intracapillary hydrostatic pressure helps restore the volume of circulating fluid.

[6] This osmotic force is also called "colloid osmotic pressure."

[7] After the British physiologist Ernest Starling (1866–1927).

Lymphatic System

Despite the extremely low capillary permeability to proteins, these molecules as well as other large particles such as long-chain fatty acids and bacteria find their way into the interstitial space. If such particles are allowed to accumulate in the interstitial space, filtration forces will ultimately exceed reabsorption forces and edema will result. The lymphatic system represents a pathway by which large molecules reenter the circulating blood.

The lymphatic system begins in the tissues with blind-end lymphatic capillaries that are roughly equivalent in size to but less numerous than regular capillaries. These capillaries are very porous and easil collect large particles accompanied by interstitial fluid. This fluid, called *lymph,* moves through the converging lymphatic vessels, is filtered through lymph nodes where bacteria and particulate matter are removed, and reenters the circulatory system near the point where the blood enters the right heart.

Flow of lymph from the tissues toward the entry point into the circulatory system is promoted by two factors: (1) increases in tissue interstitial pressure (due to fluid accumulation or to movement of surrounding tissue) and (2) contractions of the lymphatic vessels themselves. Valves located in these vessels also prevent backward flow.

Roughly 2.5 L of lymphatic fluid enters the cardiovascular system each day. In the steady state, this indicates a total body *net* transcapillary fluid filtration rate of 2.5 L per day. When compared with the total amount of blood that circulates each day (about 7000 L), this may seem like an insignificant amount of ne

capillary fluid leakage. However, lymphatic blockage is a very serious problem and is accompanied by severe swelling. Thus, the lymphatics play a critical role in keeping the interstitial protein concentration lov and in removing excess capillary filtrate from the tissues.

BASIC VASCULAR FUNCTION

Resistance & Flow in Networks of Vessels

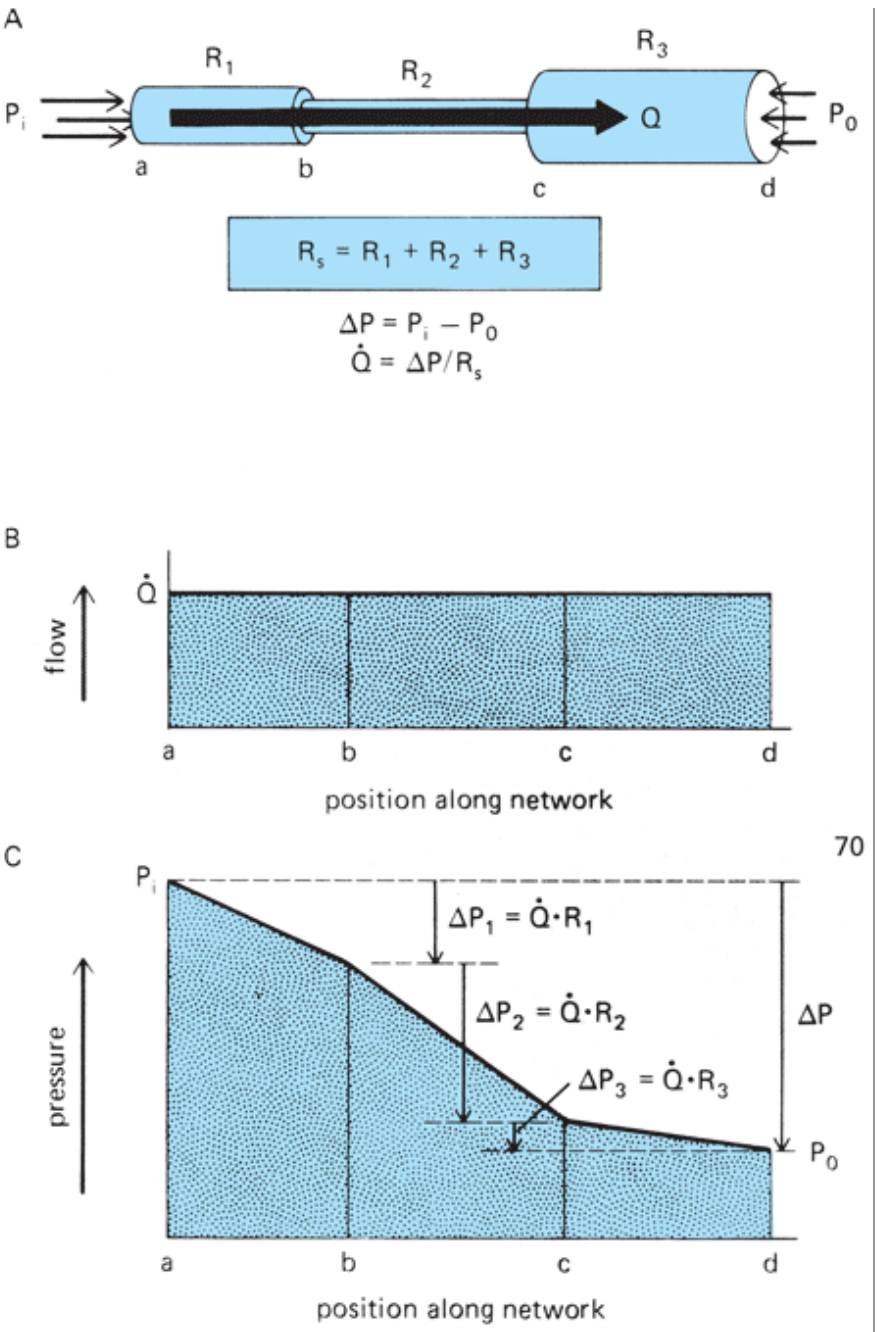
In Chapter 1, it was asserted that the basic flow equation ($\dot{Q} = \Delta P/R$) may be applied to networks of tubes as well as to individual tubes. The reason is that any network of resistances, however complex, can always be reduced to a single "equivalent" resistor that relates the total flow through the network to the pressure difference across the network. Of course one way of finding the overall resistance of a network is to perform an experiment to see how much flow goes through it for a given pressure difference between its inlet and outlet. Another approach to finding the overall resistance of a network is to calculate it from a knowledge of the resistances of the individual elements in the network and how they are connected. To do so, one needs to apply the parallel and series resistance formulas presented below. These formulas may look familiar because they are analogous to those by which networks of electrical resistances are analyzed with Ohm's law (I = V/R).

When vessels with individual resistances R_1, R_2, . . . , R_n are connected in series, the overall resistance of the network is given by the following formula:

$$R_s = R_1 + R_2 + \cdots + R_n$$

Figure 6–3A shows an example of three vessels connected *in series* between some region where the pressure is P_i and another region with a lower pressure P_o, so that the total pressure difference across the network, ΔP, is equal to $P_i - P_o$. By the series resistance equation, the total resistance across this network (R_S) is equal to $R_1 + R_2 + R_3$. By the basic flow equation, the flow through the network ($\dot{Q}$) is equal to $\Delta P/R_S$. It should be intuitively obvious that ($\dot{Q}$) is the flow (volume/time) through each of the elements in the series as indicated in Figure 6–3B. [Fluid particles may move with different velocities (distance/time) in different elements of a series network, but the volume that passes through each element in a minute must be identical.]

Figure 6–3.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

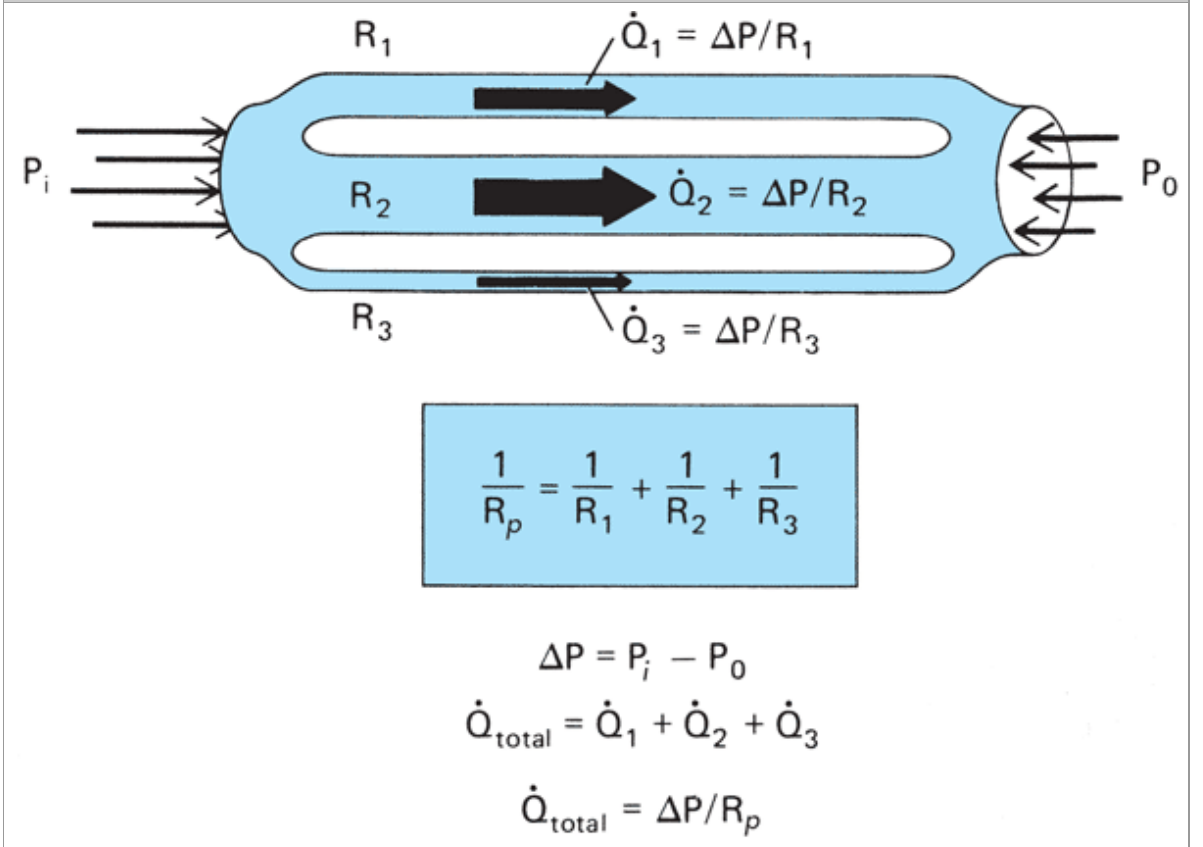
Series resistance network.

As shown in Figure 6–3C, a portion of the total pressure drop across the network occurs within each element of the series. The pressure drop across any element in the series can be calculated by applying th basic flow equation to that element, eg, $\Delta P_1 = \dot{Q}R_1$. Note that the largest portion of the overall pressure drop will occur across the element in the series with the largest resistance to flow (R_2 in Figure 6–3).

As indicated in Figure 6–4, when several tubes with individual resistances R_1, R_2, . . . , R_n are brought together to form a *parallel* network of vessels, one can calculate a single overall resistance for the parallel networkR_p according to the following formula:

$$R_{organ} = R_{arteries} + R_{arterioles} + R_{capillaries} + R_{venules} + R_{veins}$$

Figure 6–4.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Parallel resistance network.

The total flow through a parallel network is determined by $\Delta P/R_p$. As the preceding equation implies, the overall resistance of any parallel network will always be less than that of any of the elements in the network. (In the special case where the individual elements that form the network have identical resistancesR_x, the overall resistance of the network is equal to the resistance of an individual element divided by the number of n of parallel elements in the network: $R_p = R_x/n$.) In general, the more parallel elements that occur in the network, the lower the overall resistance of the network. Thus, for example, a capillary bed that consists of many individual capillary vessels in parallel can have a very low overall resistance to flow even though the resistance of a single capillary is relatively high.

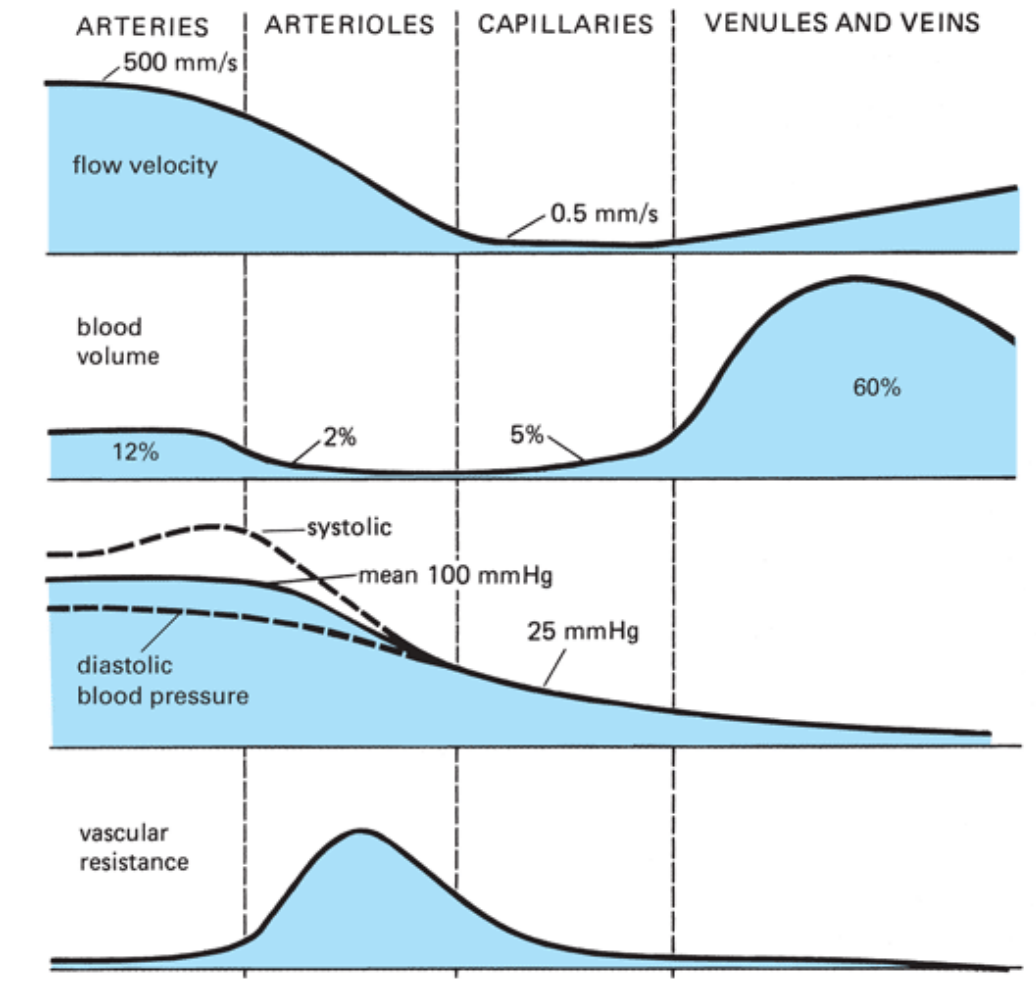
As indicated in Figure 6–4, the basic flow equation may be applied to any single element in the network or to the network as a whole. For example, the flow through only the first element of the network ($\dot{Q}_1$) is given by $\dot{Q}_1 = \Delta P/R_1$, whereas the flow through the entire parallel network is given by $\dot{Q}_p = \Delta P/R_p$.

The series and parallel resistance equations may be used alternately to analyze resistance networks of great complexity. For example, any or all of the series resistances shown in Figure 6–3 could actually represent the calculated overall resistance of many vessels arranged in parallel.

Peripheral Blood Flow Velocities

It is important to make the distinction between blood flow (volume/time) and blood flow velocity (distance/time) in the peripheral vascular system. Consider the analogy of a stream whose water moves with greater velocity through a shallow rapids than it does through an adjacent deep pool. The volume of water passing through the pool in a day (volume/time = flow), however, must equal that passing through the rapids in the same day. In such a series arrangement, the flow is the same at all points along the channel but the flow velocity varies inversely with the local cross-sectional area. The situation is the same in the peripheral vasculature, where blood flows most rapidly in the region with the smallest total cross-sectional area (the aorta) and most slowly in the region with the largest total cross-sectional area (the capillary beds). Regardless of the differences in velocity, when the cardiac output (flow into the aorta) is 5 L/min, the flow through the systemic capillaries (or arterioles, or venules) is also 5 L/min. The changes in flow velocity that occur as blood passes through the peripheral vascular system are shown in the top trace of Figure 6–5. These are a direct consequence of the variations in total cross-sectional area that were indicated in Figure 1–8.

Figure 6–5.

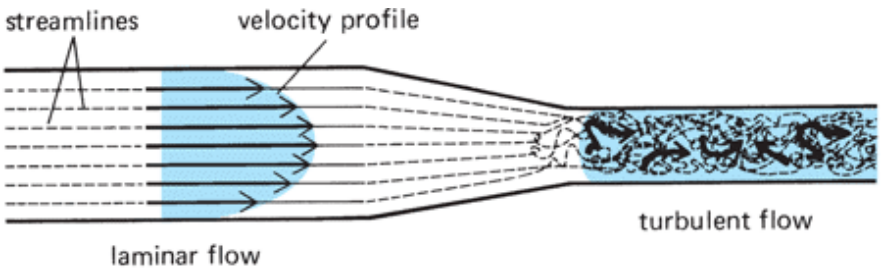


Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Flow velocities, blood volumes, blood pressures, and vascular resistances in the peripheral vasculature from aorta to right atrium.

Blood normally flows through all vessels in the cardiovascular system in an orderly streamlined manner called *laminar flow.* With laminar flow, there is a parabolic velocity profile across the tube as shown on the left side of Figure 6–6. Velocity is fastest along the central axis of the tube and falls to zero at the wall. Th concentric layers of fluid with different velocities slip smoothly over one another. Little mixing occurs between fluid layers so that individual particles move in straight streamlines parallel to the axis of the flow Laminar flow is very efficient because little energy is wasted on anything but producing forward fluid motion.

Figure 6–6.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Laminar and turbulent flow patterns.

Because blood is a viscous fluid, its movement through a vessel exerts a *shear stress* on the walls of the vessel. This is a force that wants to drag the inside surface (the endothelial cell layer) of the vessel along with the flow. With laminar flow, the shear stress on the wall of a vessel is proportional to the rate of flow through it.[8] The endothelial cells that line a vessel are able to sense (and possibly respond to) changes in the rate of blood flow through the vessel by detecting changes in the shear stress on them. Shear stress may also be an important factor in certain pathological situations. For example, atherosclerotic plaques tend to form preferentially near branches off large arteries where, for complex hemodynamic reasons beyond the scope of this text, high shear stresses exist.

When blood is forced to move with too high a velocity through a narrow opening, the normal laminar flow pattern may break down into the *turbulent flow* pattern shown on the right side of Figure 6–6.[9] With turbulent flow, there is much internal mixing and friction. When the flow within a vessel is turbulent, the vessel's resistance to flow is significantly higher than that predicted from the Poiseuille equation given in Chapter 1. Turbulent flow also generates sound, which can be heard with the aid of a stethoscope. Cardiac murmurs, for example, are manifestations of turbulent flow patterns generated by cardiac valve abnormalities. Detection of sounds from peripheral arteries (bruits) is abnormal and usually indicates significant pathological reduction of a large vessel's cross-sectional area.

[8] With pure laminar flow of a homogeneous fluid in a uniform smooth round tube, the shear stress (force/surface area σ_s) on the wall is a function of fluid viscosity (η), flow (volume/time, $\dot{Q}$), and the inside radius of the tube (r_i) as follows: $\sigma_s = 4\eta\dot{Q}/\pi r_i^3$.

[9] Turbulence occurs when a parameter called the Reynolds number (R_e) exceeds a value of 2000. $R_e = 4\rho Q/\pi\eta d_i$, where ρ = fluid density, $\dot{Q}$ = flow (volume-time), η = fluid viscosity, and d_i = inside diameter.

Peripheral Blood Volumes

The second trace in Figure 6–5 shows the approximate percentage of the total circulating blood volume that is contained in the different vascular regions of the systemic organs at any instant of time. (Approximately 20% of the total volume is contained in the pulmonary system and the heart chambers and is not accounted for in this figure.) Note that most of the circulating blood is contained within the veins of the systemic organs. This diffuse but large blood reservoir is often referred to as the *peripheral venous pool.* A second but smaller reservoir of venous blood, called the *central venous pool,* is contained in the great veins of the thorax and the right atrium. When peripheral veins constrict, blood is displaced from the peripheral venous pool and enters the central pool. An increase in the central venous volume, and thus pressure, enhances cardiac filling, which in turn augments stroke volume according to the Frank-Starling law of the heart. This is an extremely important mechanism of cardiovascular regulation and will be discussed in greater detail in Chapter 8.

Peripheral Blood Pressures

Blood pressure decreases in the consecutive segments with the pattern shown in the third trace of Figure 6–5. Recall from Figure 3–1 that aortic pressure fluctuates between a systolic and diastolic value with each heartbeat, and the same is true throughout the arterial system. (For complex hemodynamic reasons, the difference between systolic and diastolic pressure actually increases with the distance from the heart in the large arteries.[10]) The average pressure in the arch of the aorta, however, is about 100 mmHg, and this *mean arterial pressure* falls by only a small amount within the arterial system.

A large pressure drop occurs in the arterioles, where the pulsatile nature of the pressure also nearly disappears. The average capillary pressure is approximately 25 mmHg. Pressure continues to decrease in the venules and veins as blood returns to the right heart. The central venous pressure (which is the filling pressure for the right heart) is normally very close to 0 mmHg.

[10] A rigorous analysis of the dynamics of pulsatile fluid flow in tapered, branching, elastic tubes is required to explain such behavior. Pressure does not increase simultaneously throughout the arterial system with the onset of cardiac ejection. Rather, the pressure increase begins at the root of the aorta and travels outward from there. When this rapidly moving pressure wave encounters obstacles such as vessel bifurcations, reflected waves are generated which travel back toward the heart. These reflected waves can summate with and reinforce the oncoming wave in a manner somewhat analogous to the progressive cresting of surface waves as they impinge on a beach.

Peripheral Vascular Resistances

The bottom trace in Figure 6–5 indicates the relative resistance to flow that exists in each of the consecutive vascular regions. Recall from Chapter 1 that resistance, pressure difference, and flow are related by the basic flow equation $\dot{Q} = \Delta P/R$. Because the flow ($\dot{Q}$) must be the same through each of the consecutive regions indicated in Figure 6–5, the pressure drop that occurs across each of these regions is a direct reflection of the resistance to flow within that region (see Figure 6–3). Thus, the large pressure drop occurring as blood moves through arterioles indicates that arterioles present a large resistance to flow. The mean pressure drops little in arteries because they have little resistance to flow. Similarly, the modest pressure drop that exists across capillaries is a reflection of the fact that the capillary bed has a modest resistance to flow when compared with that of the arteriolar bed. (Recall from Figure 6–4 that the capillary bed can have a low resistance to flow because it is a parallel network of a very large number of individual capillaries.)

Blood flow through many individual organs can vary over a 10-fold or greater range. Because mean arterial

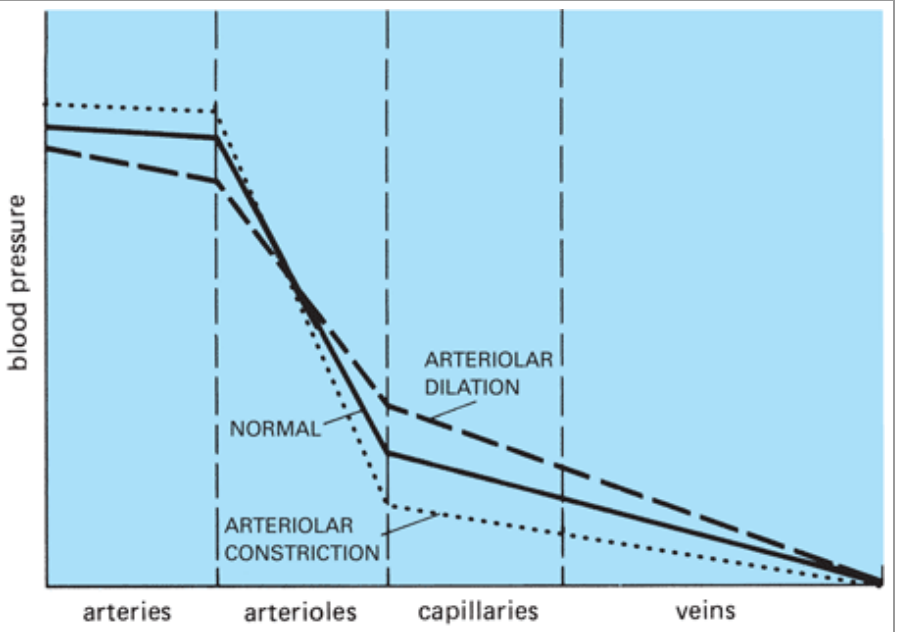
pressure is a relatively stable cardiovascular variable, large changes in an organ's blood flow are achieved by changes in its overall vascular resistance to blood flow. The consecutive vascular segments are arrange in series within an organ, and the overall vascular resistance of the organ must equal the sum of the resistances of its consecutive vascular segments:

$$R_{organ} = R_{arteries} + R_{arterioles} + R_{capillaries} + R_{venules} + R_{veins}$$

Because arterioles have such a large vascular resistance in comparison to the other vascular segments, the overall vascular resistance of any organ is determined to a very large extent by the resistance of its arterioles. Arteriolar resistance is, of course, strongly influenced by arteriolar radius (*R* is proportional to l/r^4). Thus, the blood flow through an organ is primarily regulated by adjustments in the internal diameter of arterioles caused by contraction or relaxation of their muscular arteriolar walls.

When the arterioles of an organ change diameter, not only does the flow to the organ change but the manner in which the pressures drop within the organ is also modified. The effects of arteriolar dilation and constriction on the pressure profile within a vascular bed are illustrated in Figure 6–7. Arteriolar constriction causes a greater pressure drop across the arterioles, and this tends to increase the arterial pressure while it decreases the pressure in capillaries and veins. (The arterioles function somewhat like a dam; closing a dam's gates decreases the flow while increasing the level of the reservoir behind it and decreasing the level of its outflow stream.) Conversely, increased organ blood flow caused by arteriolar dilation is accompanied by decreased arterial pressure and increased capillary pressure. Because of the changes in capillary hydrostatic pressure, arteriolar constriction tends to cause transcapillary fluid reabsorption whereas arteriolar dilation tends to promote transcapillary fluid filtration.

Figure 6–7.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Effect of changes in arteriolar resistance on vascular pressures.

Total Peripheral Resistance

The overall resistance to flow through the entire systemic circulation is called the *total peripheral resistance.* Because the systemic organs are generally arranged in parallel (Figure 1–2), the vascular resistance of each organ contributes to the total peripheral resistance according to the following parallel resistance equation:

$$\frac{1}{TPR} = \frac{1}{R_{organ\ 1}} + \frac{1}{R_{organ\ 2}} + \cdots + \frac{1}{R_{organ\ n}}$$

As will be discussed later in this chapter, the total peripheral resistance is an important determinant of arterial blood pressure.

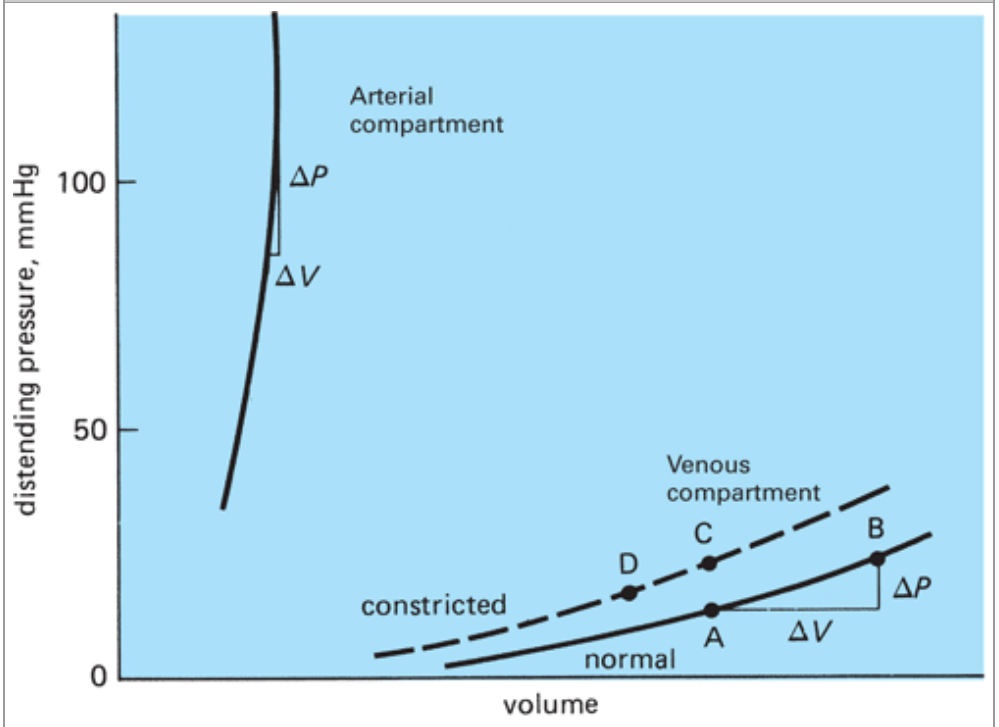
Elastic Properties of Arteries & Veins

As indicated earlier, arteries and veins contribute only a small portion to the overall resistance to flow through a vascular bed. Therefore, changes in their diameters have no significant effect on the blood flow through systemic organs. The elastic behavior of arteries and veins is, however, very important to overall cardiovascular function because they can act as reservoirs and substantial amounts of blood can be stored in them. Arteries or veins behave more like balloons with one pressure throughout rather than as resistive pipes with a flow-related pressure difference from end-to-end. Thus, think of an "arterial compartment" and a "venous compartment," each with an internal pressure that is related to the volume of blood within i at any instant and how elastic (stretchy) its walls are.

The elastic nature of a vascular region is characterized by a parameter called *compliance* (*C*) that describes how much its volume changes (△*V*) in response to a given change in distending pressure (△*P*):*C* = △*V*/△*P*. Distending pressure is the difference between the internal and external pressures on the vascula walls.

The volume-pressure curves for the systemic arterial and venous compartments are shown in Figure 6–8. It is immediately apparent from the disparate slopes of the curves in this figure that the elastic properties of arteries and veins are very different. For the arterial compartment, the △*V*/△*P* measured near a normal operating pressure of 100 mmHg indicates a compliance of about 2 mL/mmHg. By contrast, the venous pool has a compliance of over 100 mL/mmHg near its normal operating pressure of 5 to 10 mmHg.

Figure 6–8.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Volume-pressure curves of arterial and venous compartments.

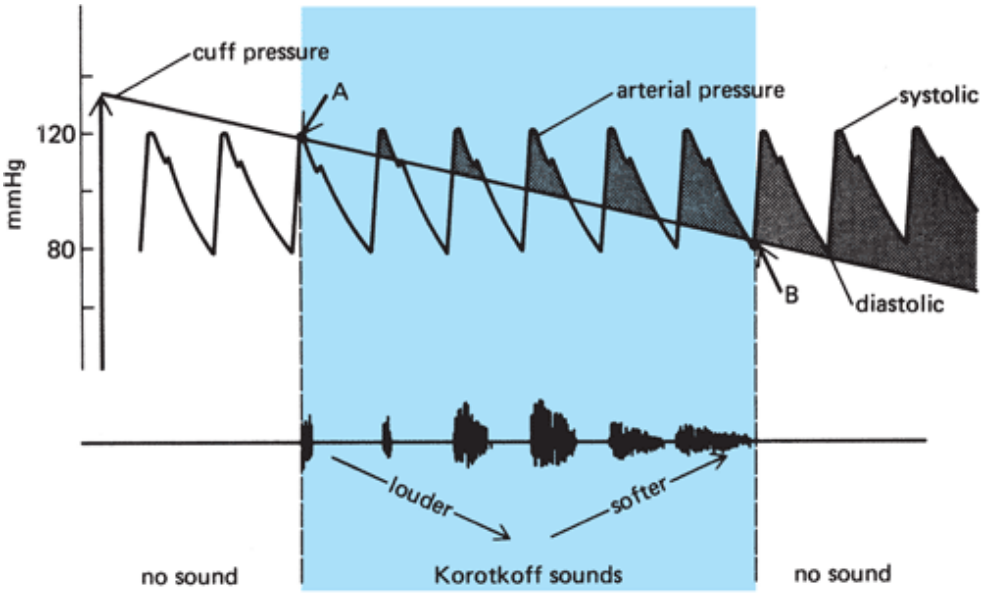
Because veins are so compliant, even small changes in peripheral venous pressure can cause a significant amount of the circulating blood volume to shift into or out of the peripheral venous pool. Standing upright, for example, increases venous pressure in the lower extremities and promotes blood accumulation (pooling) in these vessels as might be represented by a shift from point A to point B in Figure 6–8. Fortunately, this process can be counteracted by active venous constriction. The dashed line in Figure 6–8 shows the venous volume-pressure relationship that exists when veins are constricted by activation of venous smooth muscle. In constricted veins, volume may be normal (point C) or even below normal (point D) despite higher than normal venous pressure. Peripheral venous constriction tends to increase periphera venous pressure and shift blood out of the peripheral venous compartment.

The elasticity of arteries allows them to act as a reservoir on a beat-to-beat basis. Arteries play an important role in converting the pulsatile flow output of the heart into a steady flow through the vascular beds of systemic organs. During the early rapid phase of cardiac ejection, the arterial volume increases because blood is entering the aorta more rapidly than it is passing into systemic arterioles. Thus, part of the work the heart does in ejecting blood goes to stretching the elastic walls of arteries. Toward the end of systole and throughout diastole, arterial volume decreases because the flow out of arteries exceeds flow into the aorta. Previously stretched arterial walls recoil to shorter lengths, and in the process give up their stored potential energy. This reconverted energy is what actually does the work of propelling blood throug the peripheral vascular beds during diastole. If the arteries were rigid tubes that could not store energy by expanding elastically, arterial pressure would fall immediately to zero with the termination of each cardiac ejection.

MEASUREMENT OF ARTERIAL PRESSURE

Recall that the systemic arterial pressure fluctuates with each heart cycle between a diastolic value (P_D) and a higher systolic value (P_S). Obtaining estimates of an individual's systolic and diastolic pressures is one of the most routine diagnostic techniques available to the physician. The basic principles of the *auscultation* technique used to measure blood pressure are described here with the aid of Figure 6–9.

Figure 6–9.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Blood pressure measurement by auscultation. Point A indicates systolic pressure and point B indicates diastolic pressure.

An inflatable cuff is wrapped around the upper arm, and a device, such as a mercury manometer, is attached to monitor the pressure within the cuff. The cuff is initially inflated with air to a pressure (175 to 200 mmHg) that is well above normal systolic values. This pressure is transmitted from the flexible cuff into the upper arm tissues, where it causes all blood vessels to collapse. No blood flows into (or out of) the forearm as long as the cuff pressure is higher than the systolic arterial pressure. After the initial inflation, air is allowed to gradually "bleed" from the cuff so that the pressure within it falls slowly and steadily through the range of arterial pressure fluctuations. The moment the cuff pressure falls below the peak systolic arterial pressure, some blood is able to pass through the arteries beneath the cuff during the systolic phase of the cycle. This flow is intermittent and occurs only over a brief period of each heart cycle. Moreover, because it occurs through partially collapsed vessels beneath the cuff, the flow is turbulent rather than laminar. The intermittent periods of flow beneath the cuff produce tapping sounds, which can be detected with a stethoscope placed over the radial artery at the elbow. As indicated in Figure 6–9, sounds of varying character, known collectively as *Korotkoff sounds,* are heard whenever the cuff pressure is between the systolic and diastolic aortic pressures.

Because there is no blood flow and thus no sound when cuff pressure is higher than systolic arterial pressure,*the highest cuff pressure at which tapping sounds are heard is taken as the systolic arterial pressure.* When the cuff pressure falls below the diastolic pressure, blood flows through the vessels

beneath the cuff without periodic interruption and again no sound is detected over the radial artery. *The cuff pressure at which the sounds become muffled or disappear is taken as the diastolic arterial pressure.* The Korotkoff sounds are more distinct when the cuff pressure is near the systolic arterial pressure than when it is near the diastolic pressure. Thus, consistency in determining diastolic pressure by auscultation requires concentration and experience.

DETERMINANTS OF ARTERIAL PRESSURE

Mean Arterial Pressure



Mean arterial pressure is a critically important cardiovascular variable because it is the average effective pressure that drives blood through the systemic organs. One of the most fundamental equations of cardiovascular physiology is that which indicates how mean arterial pressure ($\bar{P}_A$) is related to cardiac output (CO) and total peripheral resistance (TPR):

$$\bar{P}_A = \mathrm{CO} \times \mathrm{TPR}$$

This equation is simply a rearrangement of the basic flow equation ($\dot{Q} = \Delta P/R$) applied to the entire systemic circulation with the single assumption that central venous pressure is approximately zero so that $\Delta P = \bar{P}_A$. Note that mean arterial pressure is influenced both by the heart (via cardiac output) and by the peripheral vasculature (via total peripheral resistance). *All changes in mean arterial pressure result from changes in either cardiac output or total peripheral resistance.*

Calculating the true value of mean arterial pressure requires mathematically averaging the arterial pressure waveform over one or more complete heart cycles. Most often, however, we know from auscultation only the systolic and diastolic pressures, yet wish to make some estimate of the mean arterial pressure. Mean arterial pressure necessarily falls between the systolic and diastolic pressures. A useful rule of thumb is that mean arterial pressure ($\bar{P}_A$) is approximately equal to diastolic pressure (P_D) plus one third of the difference between systolic and diastolic pressure ($P_S - P_D$):

$$\bar{P}_A \simeq P_D + \frac{1}{3}\left(P_S - P_D\right)$$

Arterial Pulse Pressure

The*arterial pulse pressure* (P_p) is defined simply as systolic pressure minus diastolic pressure:

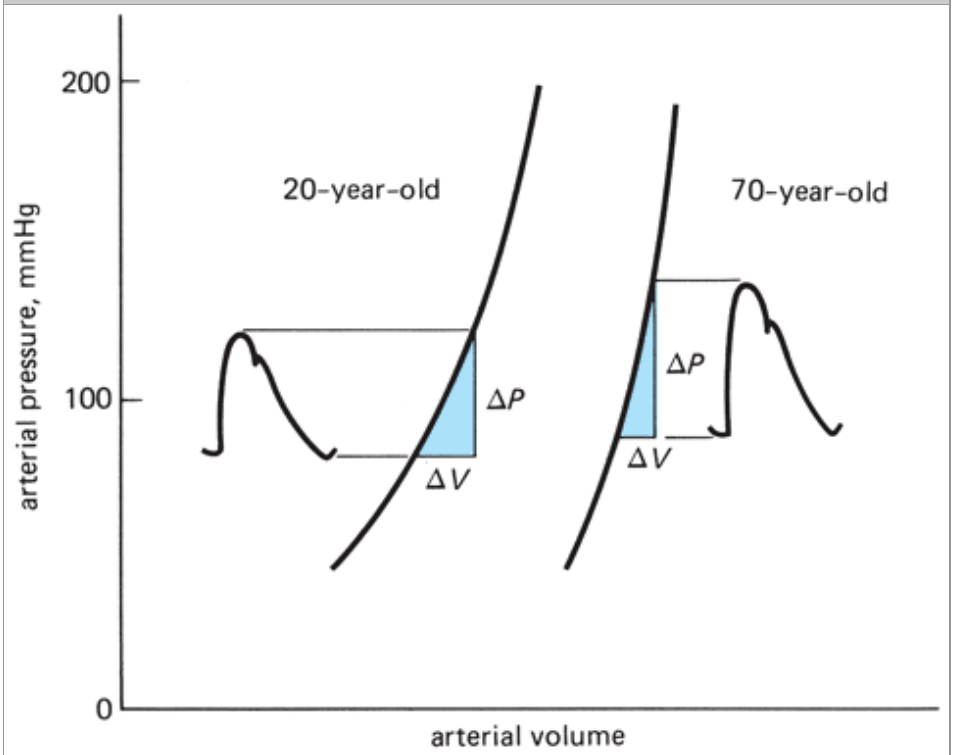
$$P_p = P_S - P_D$$

To be able to use pulse pressure to deduce something about how the cardiovascular system is operating, one must do more than just define it. It is important to understand what *determines* pulse pressure; ie, what causes it to be what it is and what can cause it to change. In a previous section of this chapter there was a brief discussion about how, as a consequence of the compliance of the arterial vessels, arterial pressure increases as arterial blood volume is expanded during cardiac ejection. The magnitude of the pressure increase (ΔP) caused by an increase in arterial volume depends on how large the volume change ΔV) is and on how compliant (C_A) the arterial compartment is: $\Delta P = \Delta V/C_A$. If, for the moment, the fact that some blood leaves the arterial compartment *during* cardiac ejection is neglected, then the increase in arterial volume during each heartbeat is equal to the stroke volume (SV). Thus, pulse pressure is, to a first approximation, equal to stroke volume divided by arterial compliance:

$$P_p \simeq \frac{SV}{C_A}$$

Arterial pulse pressure is about 40 mmHg in a normal resting young adult because stroke volume is about 80 mL and arterial compliance is about 2 mL/mmHg. Pulse pressure tends to increase with age in adults because of a decrease in arterial compliance ("hardening of the arteries"). Arterial volume-pressure curves for a 20-year-old and a 70-year-old are shown in Figure 6–10. The decrease in arterial compliance with ag is indicated by the steeper curve for the 70-year-old (more ΔP for a given ΔV) than for the 20-year-old. Thus, a 70-year-old will necessarily have a larger pulse pressure for a given stroke volume than a 20-year old. As indicated in Figure 6–10, the decrease in arterial compliance is sufficient to cause increased pulse pressure even though stroke volume tends to decrease with age.

Figure 6–10.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Effect of age on the systemic arterial volume-pressure relationship.

Figure 6–10 also illustrates the fact that arterial blood volume and mean arterial pressure tend to increase with age. The increase in mean arterial pressure is *not* caused by the decreased arterial compliance, however, because compliance changes do not directly influence cardiac output or total peripheral resistance, which are the *sole determinants* of $\bar{P}_A$. Mean arterial pressure tends to increase with age because of an age-dependent increase in total peripheral resistance which is controlled primarily by arterioles, not arteries.

Arterial compliance also decreases with increasing mean arterial pressure as evidenced by the curvature o the volume-pressure relationships shown in Figure 6–10. Otherwise, arterial compliance is a relatively

stable parameter. Thus, most acute changes in arterial pulse pressure are the result of changes in stroke volume.

The preceding equation for pulse pressure is a much simplified description of some very complex hemodynamic processes. It correctly identifies stroke volume and arterial compliance as the major determinants of arterial pulse pressure but is based on the assumption that no blood leaves the aorta during systolic ejection. Obviously this is not strictly correct. Furthermore, close examination of Figure 3–1 will reveal that peak systolic pressure is reached even before cardiac ejection is complete. It is therefore not surprising that several factors other than arterial compliance and stroke volume have minor influences on pulse pressure. For example, faster cardiac ejection caused by increased myocardial contractility tends to increase pulse pressure somewhat even if stroke volume remains constant. Changes in total peripheral resistance, however, have *little or no effect on pulse pressure*, because a change in total peripheral resistance causes parallel changes in both systolic and diastolic pressure.

A common misconception in cardiovascular physiology is that the systolic pressure alone or the diastolic pressure alone indicates the status of a specific cardiovascular variable. For example, high diastolic pressure is often taken to indicate high total peripheral resistance. This is not necessarily so since high diastolic pressure can exist with normal (or even reduced) total peripheral resistance if heart rate and cardiac output are high. Both systolic pressure and diastolic pressure are influenced by heart rate, stroke volume, total peripheral resistance, and C_A.[11] The student should not attempt to interpret systolic and diastolic pressure values independently. Interpretation is much more straightforward when the focus is on mean arterial pressure ($\bar{P}_A$ = CO x TPR) and arterial pulse pressure (P_p SV/C_A). (See study question 14.)

[11] The equations presented in this and preceding chapters can be solved simultaneously to show that

$$P_S \simeq \mathrm{SV} \times \mathrm{HR} \times \mathrm{TPR} + \frac{2}{3}\frac{\mathrm{SV}}{C_A}$$

$$P_D \simeq \mathrm{SV} \times \mathrm{HR} \times \mathrm{TPR} - \frac{1}{3}\frac{\mathrm{SV}}{C_A}$$

KEY CONCEPTS

1. Within the cardiovascular system, convection is used to transport substances between capillary beds and diffusion is used to transport substances between blood and tissue.

2. Water may move out of (filtration) or into (reabsorption) capillaries depending on the net balance of hydrostatic and osmotic forces across capillary walls.

3. Plasma proteins are responsible for the major osmotic force across capillary walls.

4. Lymphatic vessels serve to remove excess filtrate from tissues and keep interstitial protein concentration low.

5. Turbulent blood flow is abnormal and makes noise (murmurs and bruits).

6. Veins contain most of the total blood volume.

7. Arterioles contribute most to the resistance to flow through organs.

8. Arteriolar constriction tends to reduce flow through an organ and promote transcapillary fluid reabsorption within the organ.

9. Venous constriction is important for cardiac filling and the ability to cope with blood loss.

10. Because arteries are elastic, the intermittent flow from the heart is converted to continuous flow through capillaries.

11. Mean systemic arterial pressure is determined by the product of cardiac output and total peripheral resistance.

12. Changes in arterial pulse pressure reflect changes in stroke volume and/or the compliance of the arterial space.

STUDY QUESTIONS

6–1. Determine the rate of glucose uptake by an exercising skeletal muscle ($\dot{G}_m$) from the following data:

Arterial blood glucose concentration, $[G]_a$ = 50 mg per 100 mL

Muscle venous blood glucose concentration, $[G]_v$ = 30 mg per 100 mL

Blood flow, $\dot{Q}$ = 60 mL/min

6–2. Determine the direction of transcapillary fluid movement ($\dot{F}$) within a tissue, given the following data:

Capillary hydrostatic pressure, P_c = 28 mmHg

Plasma oncotic pressure, π_c = 24 mmHg

Tissue hydrostatic pressure, P_i = –4 mmHg

Tissue oncotic pressure, π_i = 0 mmHg

6–3. Which of the following conditions favor edema formation?

a. Lymphatic blockage

b. Thrombophlebitis (venous clot)

c. Decreased plasma protein concentration

d. Greatly increased capillary pore size

6–4. Assume that three vessels with identical dimensions are combined into a network of one vessel followed by a parallel combination of the other two and that a pressure (P_i) is applied to the inlet of the first vessel while a lower pressure (P_o) exists at the outlet of the parallel pair.

a. Find the overall resistance of the network (R_n) if the resistance of each vessel is equal to R_e.

b. Is the pressure (P_j) at the central junction of the network closer to P_i or P_o?

c. Use the basic flow equation to derive an equation that relates the pressure drop across the input vessel ($P_i - P_j$) to the total pressure drop across the network ($P_i - P_o$).

6–5. Given the following data, calculate an individual's total peripheral resistance (TPR):

Mean arterial pressure, $\bar{P}_A$ = 100 mmHg

Central venous pressure, P_{CV} = 0 mmHg

Cardiac output, CO = 6 L/min

6–6. The TPR to blood flow is greater than the resistance to flow through any of the systemic organs. True or false?

6–7. Other factors being equal, a decrease in the renal vascular resistance will increase TPR. True or false?

6–8. Constriction of arterioles in an organ promotes reabsorption of interstitial fluid from that organ. True or false?

6–9. Chronic elevation of arterial pressure requires that either cardiac output or TPR (or both) be chronically elevated. True or false?

6–10. Whenever cardiac output is increased, mean arterial pressure must also be increased. True or false?

6–11. Acute increases in arterial pulse pressure usually result from increases in stroke volume. True or false?

6–12. An increase in TPR increases diastolic pressure (P_D) more than systolic pressure (P_S). True or false?

6–13. Estimate the mean arterial pressure when the measured arterial pressure is 110/70 mmHg.

6–14. At rest the patient has a pulse rate of 70 beats per minute and an arterial blood pressure of 119/80 mmHg. During exercise on a treadmill, pulse rate is 140 beats per minute and blood pressure is 135/90 mmHg. Use this information to estimate the exercise-related changes in the following variables:

a. Stroke volume

b. Cardiac output

c. Total peripheral resistance (TPR)

See answers.

SUGGESTED READINGS

Aukland K, Reed RK. Interstitial-lymphatic mechanisms in the control of extracellular volume. *Physiol Rev.* 1993;73:1–78. [PMID: 8419962]

Bazzoni G, Dejana E. Endothelial cell-to-cell junctions: molecular organization and role in vascular homeostasis.*Physiol Rev*. 2004;84:869–901. [PMID: 15269339]

Clough G. Relationship between microvascular permeability and ultrastructure. *Prog Biophys Mol Biol.* 1991;55:47–69. [PMID: 2057577]

deWit C. Connexins pave the way for vascular communication. *News Physiol Sci.* 2004;19:148–153.

Figueroa XF, Isakson BE, Duling BR. Connexins: gaps in our knowledge of vascular function. *Physiology* 2004;19:277–284. [PMID: 15381756]

Harris NR. Arteriovenous pairing: a determinant of capillary exchange. *News Physiol Sci.* 2003;18:83–87. [PMID: 12644625]

McCarron JG, Bradley KN, MacMillan D, et al. The sarcoplasmic reticulum, Ca^{2+} trapping and wave mechanisms in smooth muscle. *News Physiol Sci*. 2004;19:138–147. [PMID: 15143210]

Michel CC. Starling: The formulation of his hypothesis of microvascular fluid exchange and its significance after 100 years. *Exp Physiol.* 1997;82:1–30. [PMID: 9023503]

Michel CC, Curry FE. Microvascular permeability. *Physiol Rev.* 1999;79:763–854.

Mulvany MJ, Aalkjaer C. Structure and function of small arteries. *Physiol Rev.* 1990;70:921–961. [PMID: 2217559]

Perloff D, Grim C, Flack J, et al. Human blood pressure determination by sphygmomanometry. *Circulation.* 1993;88:2460–2470. [PMID: 8222141]

Rippe B, Haraldsson B. Transport of macromolecules across microvascular walls: The two-pore theory. *Physiol Rev.* 1994;74:163–219. [PMID: 8295933]

Starling EH. On the absorption of fluids from the connective tissue spaces. *J Physiol* (London). 1896;19:312.

Tsai, AG, Johnson PC, Intaglietta M. Oxygen gradients in the microcirculation. *Physiol Rev.* 2003; 83:933–963.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.
Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.

Medical a silverchair information system The McGraw-Hill Companies

Note: Large images and tables on this page may necessitate printing in landscape mode.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.

OBJECTIVES

The student understands the general mechanisms involved in local vascular control:

- *Identifies the major ways in which smooth muscle differs anatomically and functionally from striated muscle.*
- *Lists the steps leading to cross-bridge cycling in smooth muscle.*
- *Lists the major ion channels involved in the regulation of membrane potential in smooth muscle.*
- *Describes the processes of electromechanical and pharmacomechanical coupling in smooth muscle.*
- *Defines basal tone.*
- *Lists several substances potentially involved in local metabolic control.*
- *States the local metabolic vasodilator hypothesis.*
- *Describes how vascular tone is influenced by prostaglandins, histamine, and bradykinin.*
- *Describes the myogenic response of blood vessels.*
- *Defines active and reactive hyperemia and indicates a possible mechanism for each.*
- *Defines autoregulation of blood flow and briefly describes the metabolic, myogenic, and tissue pressu theories of autoregulation.*
- *Defines neurogenic tone and describes how sympathetic (and parasympathetic) neural influences can alter it.*
- *Describes how vascular tone is influenced by circulating catecholamines, vasopressin, and angiotensin*
- *Lists the major influences on venous diameters.*
- *Describes in general how control of flow differs between organs with strong local metabolic control of arteriolar tone and organs with strong neurogenic control of arteriolar tone.*

The student knows the dominant mechanisms of flow and blood volume control in the major body organs:

- *States the relative importance of local metabolic and neural control of coronary blood flow.*
- *Defines systolic compression and indicates its relative importance to blood flow in the endocardial and epicardial regions of the right and left ventricular walls.*
- *Describes the major mechanisms of flow and blood volume control in each of the following specific systemic organs: skeletal muscle, brain, splanchnic organs, skin, and kidney.*
- *States why mean pulmonary arterial pressure is lower than mean systemic arterial pressure.*
- *Describes how pulmonary vascular control differs from that in systemic organs.*

VASCULAR SMOOTH MUSCLE

Because the body's metabolic needs are continually changing, the cardiovascular system must continually make adjustments in the diameter of its blood vessels. The purposes of these vascular changes to (1) control the rate of blood flow through particular tissues (the job of arterioles) and (2) regulate the distribution of blood volume and cardiac filling (the job of veins). These diameter adjustments are made by regulating the contractile activity of vascular smooth muscle cells, which are present in the walls of all vess except capillaries. The task of vascular smooth muscle is unique because to maintain a certain vessel diam in the face of the continual distending pressure of the blood within it, vascular smooth muscle must be abl sustain active tension for prolonged periods.

There are many functional characteristics that distinguish smooth muscle from either skeletal or cardiac m For example, when compared with these other muscle types, smooth muscle cells:

1. Contract and relax much more slowly.

2. Develop active tension over a greater range of muscle lengths.

3. Can change their contractile activity as the result of action potentials or changes in resting membrane potential.

4. May change their contractile activity in the absence of changes in membrane potential.

5. Maintain tension for prolonged periods at low energy cost.

6. Can be activated by stretch.

Contractile Machinery

Vascular smooth muscle cells are small (about 5 mm x 50 mm) spindle-shaped cells usually arranged circumferentially or at small helical angles in blood vessel walls. In many but not all vessels, adjacent smo muscle cells are electrically connected by gap junctions similar to those found in the myocardium.

Just as in other muscle types, smooth muscle force development and shortening are the result of cross-bri interaction between thick and thin contractile filaments composed of myosin and actin, respectively. In sm muscle, however, these filaments are not arranged in regular, repeating sarcomere units. As a consequenc "smooth" muscle cells lack the microscopically visible striations characteristic of skeletal and cardiac muscl cells. The actin filaments in smooth muscle are much longer than those in striated muscle. Many of these a filaments attach to the inner surface of the cell at structures called *dense bands.* In the interior of the cell, filaments do not attach to Z-lines but rather anchor to small transverse structures called *dense bodies* tha themselves tethered to the surface membrane by cable-like *intermediate filaments.* Myosin filaments are interspersed between the smooth muscle actin filaments but in a more haphazard fashion than the regular interweaving pattern of striated muscle. In striated muscle, the contractile filaments are invariably aligned the long axis of the cell whereas in smooth muscle many contractile filaments travel obliquely or even transversely to the long axis of the cell. Despite the absence of organized sarcomeres, changes in smooth muscle length affect its ability to actively develop tension. Perhaps because of the long actin filaments and lack of sarcomere arrangement, smooth muscle can develop tension over a greater range of length change than either skeletal or cardiac muscle.

As in striated muscle, the strength of the cross-bridge interaction between thick and thin filaments in smoo muscle is controlled primarily by changes in the intracellular free Ca^{2+} level, which range from about $10^{-7}M$ relaxed muscle to $10^{-6}M$ during maximal contraction. However, the sequence of steps linking an increased Ca^{2+} level to contractile filament interaction is different in smooth muscle than in striated muscle. In smoo muscle:

1. Ca^{2+} first forms a complex with the calcium binding protein *calmodulin.*

2. The Ca^{2+}-calmodulin complex then activates a phosphorylating enzyme called *myosin light chain kinase*.

3. This enzyme causes phosphorylation by adenosine triphosphate (ATP) of the light chain protein that is a portion of the cross-bridge head of myosin.

4. Myosin light chain phosphorylation enables cross-bridge formation and cycling during which energy from is utilized for tension development and shortening.

Smooth muscle is also unique in that once tension is developed, it can be maintained at very low ener costs, ie, without the need to continually split ATP in cross-bridge cycling. The mechanisms responsible are somewhat unclear but presumably involve very slowly cycling or even noncycling cross-bridges. This is ofte referred to as the *latch state* and may involve light chain dephosphorylation of attached cross-bridges. Alsc mechanisms that are yet incompletely understood, it is apparent that vascular smooth muscle contractile activity is regulated not only by changes in intracellular free Ca^{2+} levels but also by changes in the Ca^{2+}*sensitivity* of the contractile machinery. Thus the contractile state of vascular smooth muscle may sometimes change in the absence of changes in intracellular free Ca^{2+} levels.

Membrane Potentials

Smooth muscle cells have resting membrane potentials ranging from –40 to –65 mV and thus are generall lower than those in striated muscle. As in all cells, the resting membrane potential of smooth muscle is determined largely by the cell permeability to potassium. Many types of K^+ channels have been identified i smooth muscle. The one that seems to be predominantly responsible for determining the resting membrar potential is termed an *inward rectifying* type K^+ channel. (*Inward rectifying* signifies that K^+ ions move into through this channel slightly more easily than they move out through it.) There are also *ATP-dependent* K^+ channels that are closed when cellular ATP levels are normal but open if ATP levels fall. Such channels have been proposed to be important in matching organ blood flow to the metabolic state of the tissue.

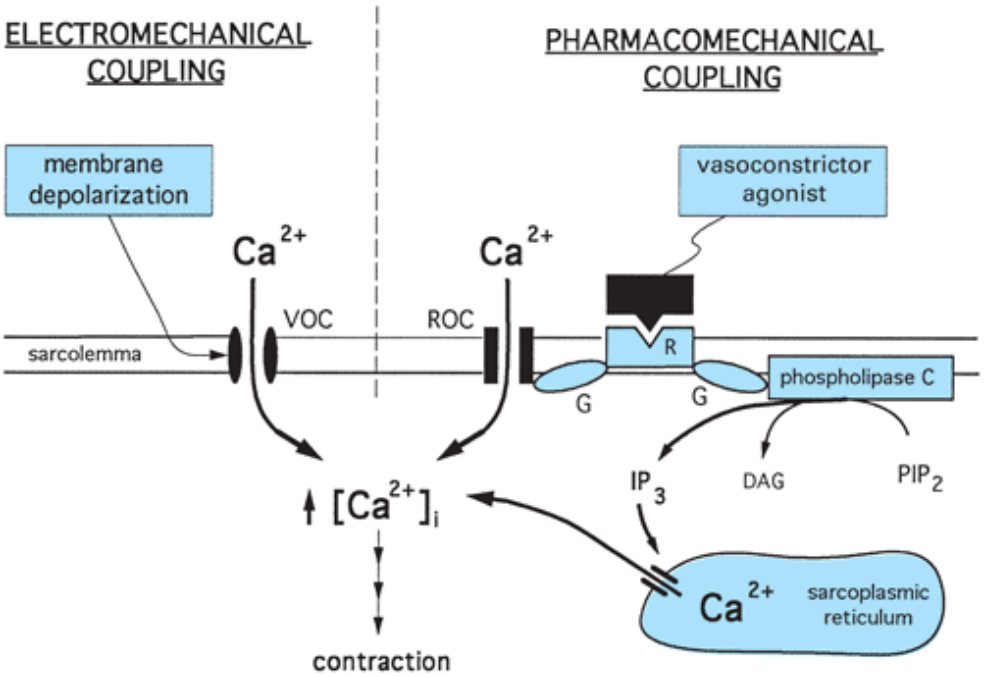
Smooth muscle cells regularly have action potentials only in certain vessels. When they do occur, smooth muscle action potentials are initiated primarily by inward Ca^{2+} current and are developed slowly like the "s type" cardiac action potentials (see Figure 2–2). As in the heart, this inward (depolarizing) Ca^{2+} current flo through a *voltage-operated calcium channel* (VOC); this type of channel is one of several types of calcium channels present in smooth muscle. The repolarization phase of the action potential occurs primarily by an outward flux of potassium ions through both *delayed* K^+ channels and *calcium-activated* K^+ channels.

Many types of ion channels in addition to those mentioned have been identified in vascular smooth muscle in most cases their exact role in cardiovascular function remains obscure. For example, there appear to be nonselective, stretch-sensitive cation channels that may be involved in the response of smooth muscle to stretch. The reader should note, however, that many of the important ion channels in vascular smooth mu are also important in heart muscle (see Table 2–1).

Electromechanical versus Pharmacomechanical Coupling

In smooth muscle, changes in intracellular free Ca^{2+} levels can occur both with *and* without changes in membrane potential. The processes involved are called *electromechanical coupling* and *pharmacomechanic coupling,* respectively, and are illustrated in Figure 7–1.

Figure 7–1.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

General mechanisms for activation of vascular smooth muscle. VOC, voltage-operated Ca^{2+} channel; ROC receptor-operated Ca^{2+} channel; R, agonist specific receptor; G, GTP-binding protein; PIP_2, phosphatidyl inositol biphosphate; IP_3, inositol triphosphate; DAG, diacylglycerol.

Electromechanical coupling, shown in the left half of Figure 7–1, occurs because the smooth muscle surfac membrane contains voltage-operated channels for calcium (the same VOCs that are involved in action pot generation). Membrane depolarization increases the open-state probability of these channels and thus lea smooth muscle cell contraction and vessel constriction. Conversely, membrane hyperpolarization leads to smooth muscle relaxation and vessel dilation. Because the VOCs for Ca^{2+} are partially activated by the low resting membrane potential of vascular smooth muscle, changes in resting potential can alter the resting calcium influx rate and therefore the basal contractile state.

With pharmacomechanical coupling, chemical agents (eg, released neurotransmitters) can induce smooth muscle contraction without the need for a change in membrane potential. As illustrated in the right side of Figure 7–1, the combination of a vasoconstrictor agonist (such as norepinephrine) with a specific membra bound receptor (such as an α_1-adrenergic receptor) initiates events that cause intracellular free Ca^{2+} level increase for two reasons. One, the activated receptor may open surface membrane *receptor-operated cha* (ROCs) for Ca^{2+} that allow Ca^{2+} influx from the extracellular fluid. Two, the activated receptor may induce formation of an intracellular "second messenger," inositol trisphosphate (IP_3), that opens specific channels release Ca^{2+} from the intracellular sarcoplasmic reticulum stores. In both processes, the activated recepto stimulates specific guanosine triphosphate binding proteins (GTP-binding proteins or "*G proteins*"). Such receptor-associated G proteins seem to represent a general first step through which most membrane rece operate to initiate their particular cascade of events that ultimately lead to specific cellular responses.

The reader should *not* conclude from Figure 7–1 that all vasoactive chemical agents (chemical agents that vascular effects) produce their actions on smooth muscle without changing membrane potential. In fact, m

vasoactive chemical agents do cause changes in membrane potential because their receptors can be linkec G proteins or other means, to ion channels of many kinds.

Not shown in Figure 7–1 are the processes that remove Ca^{2+} from the cytoplasm of vascular smooth musc although they are important as well in determining the free cytosolic Ca^{2+} levels. As in cardiac cells (see Fi 2–7), smooth muscle cells actively pump calcium into the sarcoplasmic reticulum and outward across the sarcolemma. Calcium is also countertransported out of the cell in exchange for sodium.

Mechanisms for Relaxation

Hyperpolarization of the cell membrane is one mechanism for causing smooth muscle relaxation and vesse dilation. In addition, however, there are at least two general mechanisms by which certain chemical vasod agents can cause smooth muscle relaxation by pharmacomechanical means. In Figure 7–1, the specific rec for a chemical vasoconstrictor agent is shown linked by a specific G protein to phospholipase C. In an anal manner, other specific receptors may be linked by other specific G proteins to other enzymes that produce second messengers other than IP_3. An example is the β_2-adrenergic receptor[1] that is present in arterioles skeletal muscle and liver. β_2-receptors are not innervated but can sometimes be activated by abnormally elevated levels of circulating *epinephrine.* The β_2-receptor is linked by a particular G protein (G_s) to adenyl cyclase. Adenylate cyclase catalyzes the conversion of ATP to cyclic adenosine monophosphate (cAMP). Increased intracellular levels of cAMP cause the activation of protein kinase A, a phosphorylating enzyme t turn causes phosphorylation of proteins at many sites. The overall result is stimulation of Ca^{2+} efflux, membrane hyperpolarization, and decreased contractile machinery sensitivity to Ca^{2+}—all of which act synergistically to cause vasodilation. In addition to epinephrine, histamine and vasoactive intestinal peptid vasodilator substances that act through the cAMP pathway.

In addition to cAMP, cyclic guanosine monophosphate (cGMP) is an important intracellular second messeng that causes vascular smooth muscle relaxation by mechanisms that are not yet clear. Nitric oxide is an important vasodilator substance that operates via the cGMP pathway. Nitric oxide can be produced by endothelial cells and also by nitrates—a clinically important class of vasodilator drugs. Nitric oxide is gaseo and easily diffuses into smooth muscle cells, where it activates the enzyme guanylyl cyclase that in turn ca cGMP formation from GTP.

[1] Vascular β-receptors are designated β_2-receptors and are pharmacologically distinct from the β_1-recepto found on cardiac cells.

Vascular Tone

Vascular tone is a term commonly used to characterize the general contractile state of a vessel or a vascul region. The "vascular tone" of a region can be taken as an indication of the "level of activation" of the indiv smooth muscle cells in that region. Actually, this association is a statistical one because rarely do all the ce a vessel or all the vessels in a vascular region act in precise unison.

CONTROL OF ARTERIOLAR TONE

As described in Chapter 6, the blood flow through any organ is determined largely by its vascular resistanc which is dependent primarily on the diameter of its arterioles. Consequently, an organ's flow is controlled l factors that influence the arteriolar smooth muscle tone.

Basal Tone

Arterioles remain in a state of partial constriction even when all external influences on them are removed; hence they are said to have a degree of *basal tone.* The understanding of the mechanism is incomplete, bu basal arteriolar tone may be a reflection of the fact that smooth muscle cells inherently and actively resist stretched as they continually are in pressurized arterioles. In any case, this basal tone establishes a baseli

partial arteriolar constriction from which the external influences on arterioles exert their dilating or constri effects. These influences can be separated into three categories: local influences, neural influences, and hormonal influences.

Local Influences on Arterioles

LOCAL METABOLIC INFLUENCES

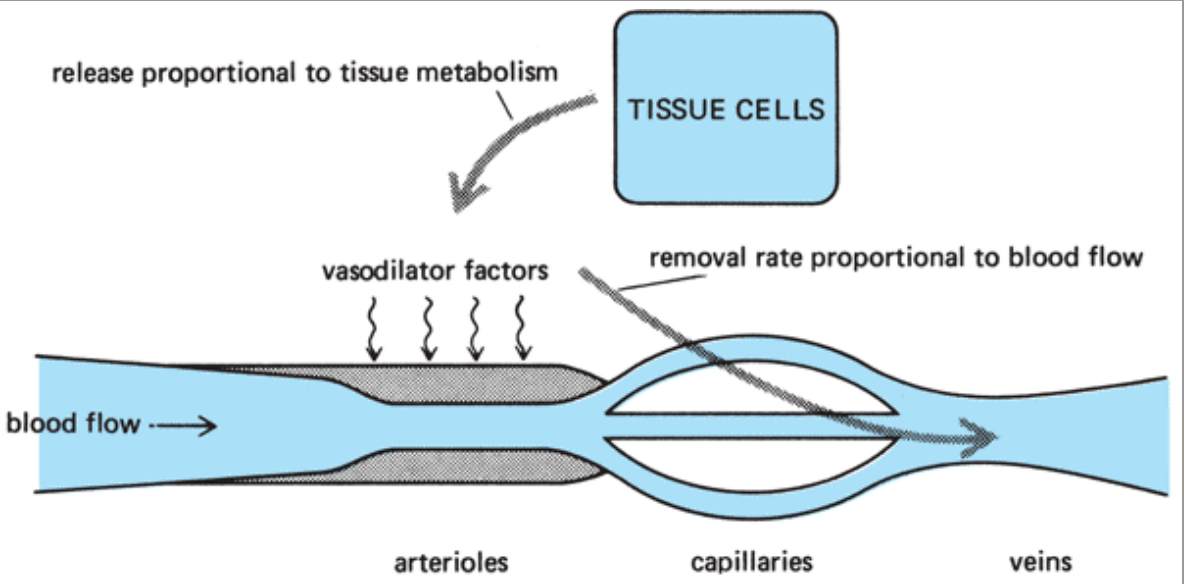
The arterioles that control flow through a given organ lie within the organ tissue itself. Thus, arterioles the smooth muscle in their walls are exposed to the chemical composition of the interstitial fluid of the org they serve. The interstitial concentrations of many substances reflect the balance between the metabolic a of the tissue and its blood supply. Interstitial oxygen levels, for example, fall whenever the tissue cells are oxygen faster than it is being supplied to the tissue by blood flow. Conversely, interstitial oxygen levels ris whenever excess oxygen is being delivered to a tissue from the blood. In nearly all vascular beds, exposur low oxygen reduces arteriolar tone and causes vasodilation, whereas high oxygen levels cause arteriolar vasoconstriction.[2] Thus, a local feedback mechanism exists that automatically operates on arterioles to reg a tissue's blood flow in accordance with its metabolic needs. Whenever blood flow and oxygen delivery fall below a tissue's oxygen demands, the oxygen levels around arterioles fall, the arterioles dilate, and the blo flow through the organ appropriately increases.

Many substances in addition to oxygen are present within tissues and can affect the tone of vascular smoo muscle. When the metabolic rate of skeletal muscle is increased by exercise, for example, not only do tissu levels of oxygen decrease, but those of carbon dioxide, H^+, and K^+ increase. Muscle tissue osmolarity also increases during exercise. All of these chemical alterations cause arteriolar dilation. In addition, with increa metabolic activity or oxygen deprivation, cells in many tissues may release *adenosine,* which is an extreme potent vasodilator agent.

At present, it is not known which of these (or possibly other) metabolically related chemical alterations wit tissues are most important in the local metabolic control of blood flow. It appears likely that arteriolar tone depends on the combined action of many factors.

For conceptual purposes, Figure 7–2 summarizes current understanding of local metabolic control. Vasodila factors enter the interstitial space from the tissue cells at a rate proportional to tissue metabolism. These vasodilator factors are removed from the tissue at a rate proportional to blood flow. Whenever tissue metabolism is proceeding at a rate for which the blood flow is inadequate, the interstitial vasodilator factor concentrations automatically build up and cause the arterioles to dilate. This, of course, causes blood flow increase. The process continues until blood flow has risen sufficiently to appropriately match the tissue metabolic rate and prevent further accumulation of vasodilator factors. The same system also operates to reduce blood flow when it is higher than required by the tissue's metabolic activity, because this situation causes a reduction in the interstitial concentrations of metabolic vasodilator factors.

Figure 7–2.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Local metabolic vasodilator hypothesis.

Local metabolic mechanisms represent by far the most important means of local flow control . By these mechanisms, individual organs are able to regulate their own flow in accordance with their metabolic need indicated below, several other types of local influences on blood vessels have been identified. However, ma these represent fine-tuning mechanisms and many are important only in certain, usually pathological, situations.

[2] An important exception to this rule occurs in the pulmonary circulation and will be discussed later in this chapter.

LOCAL INFLUENCES FROM ENDOTHELIAL CELLS

Endothelial cells cover the entire inner surface of the cardiovascular system. A large number of studies hav shown that blood vessels respond very differently to certain vascular influences when their endothelial linir missing. Acetylcholine, for example, causes vasodilation of intact vessels but causes vasoconstriction of ve stripped of their endothelial lining. This and other similar results have led to the realization that endothelia respond to various stimuli by producing a local factor that can decrease the tone of the overlying smooth muscle layers. Originally called EDRF (endothelial derived relaxing factor), this substance has now been identified as nitric oxide. It is produced within endothelial cells from the amino acid, L-arginine, by the acti an enzyme, nitric oxide synthase. Nitric oxide synthase is activated by a rise in the intracellular level of the Ca^{2+}. Nitric oxide is a small lipid-soluble molecule that, once formed, easily diffuses into adjacent smooth muscle cells where it causes relaxation by stimulating cGMP production as mentioned previously.

Acetylcholine and several other agents (including bradykinin, vasoactive intestinal peptide, and substance stimulate endothelial cell nitric oxide production because their receptors on endothelial cells are linked to receptor-operated Ca^{2+} channels. Probably more importantly from a physiological standpoint, flow-related stresses on endothelial cells stimulates their nitric oxide production presumably because stretch-sensitive channels for Ca^{2+} are activated. Such flow-related endothelial cell nitric oxide production probably explains for example, exercise and increased blood flow through muscles of the lower leg can cause dilation of the l

supplying femoral artery at points far upstream of the exercising muscle itself.

Agents that block nitric oxide production by inhibiting nitric oxide synthase cause significant increases in th vascular resistances of most resting organs. For this reason, it is believed that endothelial cells are normal always producing some nitric oxide that is importantly involved, along with other factors, in reducing the n net resting tone of arterioles throughout the body.

Endothelial cells have also been shown to produce several other locally acting vasoactive agents including vasodilators "endothelial-derived hyperpolarizing factor" (EDHF) and prostacyclin (PGI_2) and the vasoconst *endothelin.* The roles of these agents in the overall scheme of normal checks and balances on local flow co is speculative at present.

OTHER LOCAL CHEMICAL INFLUENCES

In addition to the local metabolic influences on vascular tone, many specific locally produced and loca acting chemical substances have been identified that have vascular effects and therefore could be importa local vascular regulation in certain instances. In most cases, however, definite information about the relati importance of these substances in cardiovascular regulation is lacking.

Prostaglandins and thromboxane are a group of several chemically related products of the cyclooxygenase pathway of arachidonic acid metabolism. Certain prostaglandins are potent vasodilators while others are p vasoconstrictors. Despite the vasoactive potency of the prostaglandins and the fact that most tissues (inclu endothelial cells and vascular smooth muscle cells) are capable of synthesizing prostaglandins, it has not b demonstrated convincingly that prostaglandins play a crucial role in *normal* vascular control. It is clear, however, that vasodilator prostaglandins are involved in inflammatory responses. Consequently, inhibitors prostaglandin synthesis, such as aspirin, are effective anti-inflammatory drugs. Prostaglandins produced b platelets and endothelial cells are important in the hemostatic (flow stopping, antibleeding) vasoconstricto platelet-aggregating responses to vascular injury. Hence, aspirin is often prescribed to reduce the tendenc blood clotting—especially in patients with potential coronary flow limitations. Arachidonic acid metabolites produced via the lipoxygenase system (eg, *leukotrienes*) also have vasoactive properties and may influenc blood flow and vascular permeability during inflammatory processes.

Histamine is synthesized and stored in high concentrations in secretory granules of tissue mast cells and circulating basophils. When released, histamine produces arteriolar vasodilation (via the cAMP pathway) ar increases vascular permeability, which leads to edema formation and local tissue swelling. Histamine incre vascular permeability by causing separations in the junctions between the endothelial cells that line the va system. Histamine release is classically associated with *antigen-antibody reactions* in various allergic and immune responses. Many drugs and physical or chemical insults that damage tissue also cause histamine release. Histamine can stimulate sensory nerve endings to cause itching and pain sensations. While clearly important in many pathological situations, it seems unlikely that histamine participates in normal cardiova regulation.

Bradykinin is a small polypeptide that has about 10 times the vasodilator potency of histamine on a molar It also acts to increase capillary permeability by opening the junctions between endothelial cells. Bradykini formed from certain plasma globulin substrates by the action of an enzyme, *kallikrein,* and is subsequently rapidly degraded into inactive fragments by various tissue kinases. Like histamine, bradykinin is thought to involved in the vascular responses associated with tissue injury and immune reactions. It also stimulates nocioceptive nerves and may thus be involved in the pain associated with tissue injury.

TRANSMURAL PRESSURE

The passive elastic mechanical properties of arteries and veins and how changes in transmural pressure af

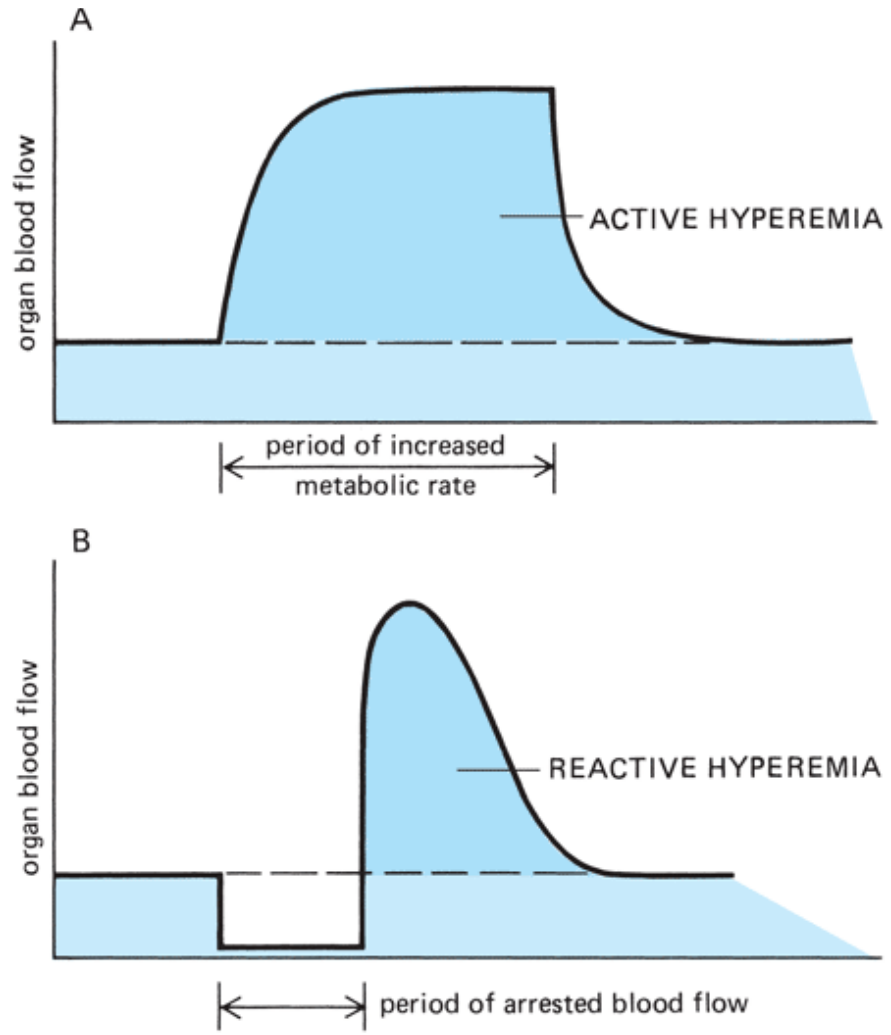
their diameters were discussed in Chapter 6. The effect of transmural pressure on arteriolar diameter is m complex because arterioles respond both passively *and actively* to changes in transmural pressure. For example, a sudden increase in the internal pressure within an arteriole produces (1) first an initial slight pa mechanical distention (slight because arterioles are relatively thick-walled and muscular), and (2) then an active constriction that, within seconds, may completely reverse the initial distention. A sudden decrease i transmural pressure elicits essentially the opposite response, ie, an immediate passive decrease in diamet followed shortly by a decrease in active tone which returns the arteriolar diameter to near that which exist before the pressure change. The active phase of such behavior is referred to as a *myogenic response,* beca it seems to originate within the smooth muscle itself. The mechanism of the myogenic response is not kno for certain, but stretch-sensitive ion channels on arteriolar vascular smooth muscle cells are likely candida for involvement.

All arterioles have some normal distending pressure to which they probably are actively responding. There the myogenic mechanism is likely to be a fundamentally important factor in determining the basal tone of arterioles everywhere. Also, for obvious reasons and as will be soon discussed, the myogenic response is potentially involved in the vascular reaction to any cardiovascular disturbance that involves a change in arteriolar transmural pressure.

FLOW RESPONSES CAUSED BY LOCAL MECHANISMS

In organs with a highly variable metabolic rate, such as skeletal and cardiac muscle, the blood flow closely follows the tissue's metabolic rate. For example, skeletal muscle blood flow increases within seconds of the onset of muscle exercise and returns to control values shortly after exercise ceases. This phenomenon, wh illustrated in Figure 7–3A, is known as *exercise* or *active hyperemia* (*hyperemia* means high flow). It shoul clear how active hyperemia could result from the local metabolic vasodilator feedback on arteriolar smooth muscle. As alluded to previously, once initiated by local metabolic influences on small resistance vessels, endothelial flow-dependent mechanisms may assist in propagating the vasodilation to larger vessels upstre which helps promote the delivery of blood to the exercising muscle.

Figure 7–3.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

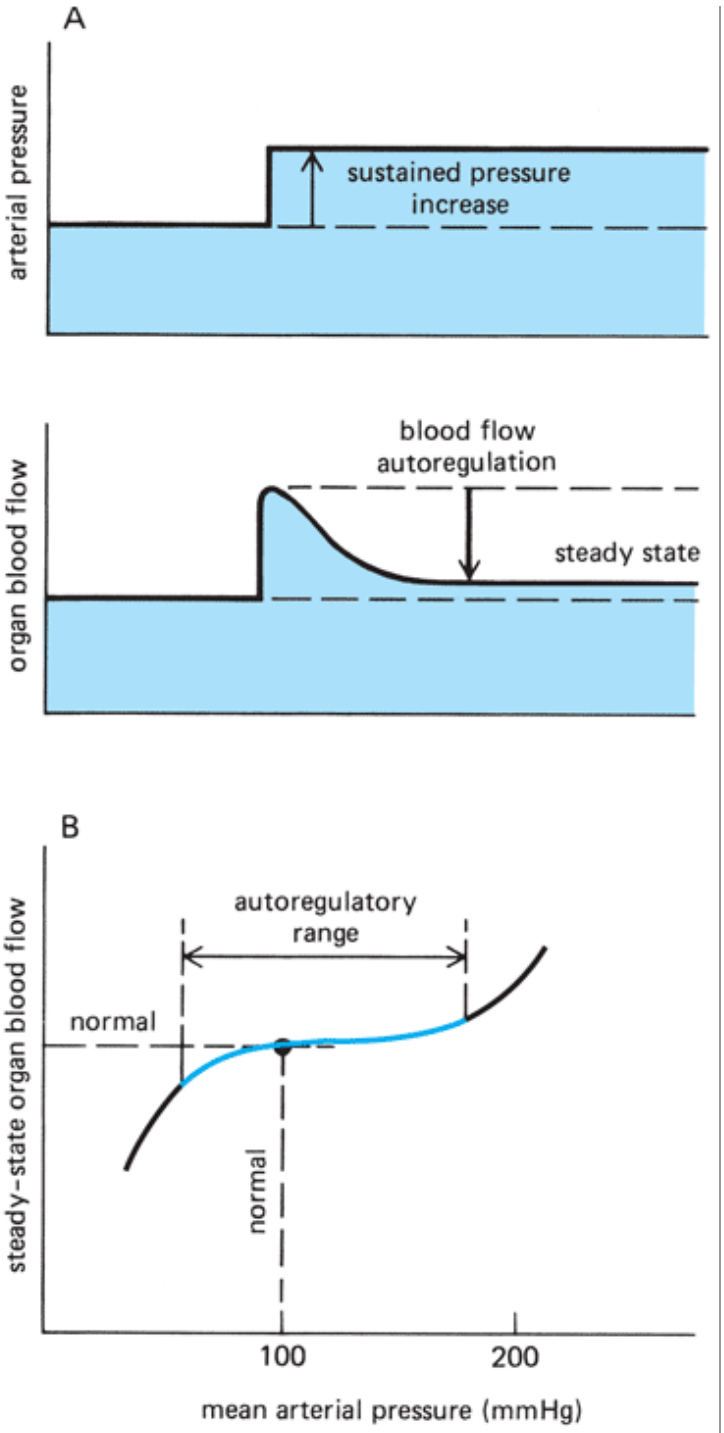
Organ blood flow responses caused by local mechanisms: active and reactive hyperemia.

Reactive or postocclusion hyperemia is a higher than normal blood flow that occurs transiently after the re of any restriction that has caused a period of lower than normal blood flow. The phenomenon is illustrated Figure 7–3B. For example, flow through an extremity is higher than normal for a period after a tourniquet removed from the extremity. Both local metabolic and myogenic mechanisms may be involved in producin reactive hyperemia. The magnitude and duration of reactive hyperemia depend on the duration and severi the occlusion as well as the metabolic rate of the tissue. These findings are best explained by an interstitia accumulation of metabolic vasodilator substances during the period of flow restriction. However, unexpecte large flow increases can follow arterial occlusions lasting only 1 or 2 seconds. These may be explained bes myogenic dilation response to the reduced intravascular pressure and decreased stretch of the arteriolar w that exists during the period of occlusion.

Except when displaying active and reactive hyperemia, nearly all organs tend to keep their blood flow cons despite variations in arterial pressure—ie, they *autoregulate* blood flow. As shown in Figure 7–4A, an abru increase in arterial pressure is normally accompanied by an initial abrupt increase in organ blood flow that gradually returns toward normal despite the sustained elevation in arterial pressure. The initial rise in flow

increased pressure is expected from the basic flow equation ($\dot{Q} = \Delta P/R$). The subsequent return of flow tow
the normal level is caused by a gradual increase in active arteriolar tone and resistance to blood flow.
Ultimately, a new steady state is reached with only slightly elevated blood flow because the increased drivi
pressure is counteracted by a higher than normal vascular resistance. As with the phenomenon of reactive
hyperemia, blood flow autoregulation may be caused by both local metabolic feedback mechanisms and
myogenic mechanisms. The arteriolar vasoconstriction responsible for the autoregulatory response shown
Figure 7–4A, for example, may be partially due to (1) a "washout" of metabolic vasodilator factors from th
interstitium by the excessive initial blood flow and (2) a myogenic increase in arteriolar tone stimulated by
increase in stretching forces that the increase in pressure imposes on the vessel walls. There is also a *tissu
pressure hypothesis* of blood flow autoregulation for which it is assumed that an abrupt increase in arterial
pressure causes transcapillary fluid filtration and thus leads to a gradual increase in interstitial fluid volume
pressure. Presumably the increase in extravascular pressure would cause a decrease in vessel diameter by
simple compression. This mechanism might be especially important in organs such as the kidney and brain
whose volumes are constrained by external structures.

Figure 7–4.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Autoregulation of organ blood flow.

Although not illustrated in Figure 7–4A, autoregulatory mechanisms operate in the opposite direction in response to a decrease in arterial pressure below the normal value. One important general consequence o autoregulatory mechanisms is that the steady state blood flow in many organs tends to remain near the n value over quite a wide range of arterial pressure. This is illustrated in the graph of Figure 7–4B. As will be discussed later, the inherent ability of certain organs to maintain adequate blood flow despite lower than n

arterial pressure is of considerable importance in situations such as shock from blood loss.

Neural Influences on Arterioles

SYMPATHETIC VASOCONSTRICTOR FIBERS

These neural fibers innervate arterioles in all systemic organs and provide by far the most important r of*reflex* control of the vasculature. Sympathetic vasoconstrictor nerves are the backbone of the system for controlling total peripheral resistance and thus are essential participants in global cardiovascular tasks suc regulating arterial blood pressure.

Sympathetic vasoconstrictor nerves release norepinephrine from their terminal structures in amounts generally proportional to their electrical activity.[3,4] Norepinephrine causes an increase in the tone of arteri after combining with an a_1-*adrenergic receptor* on smooth muscle cells. Norepinephrine appears to increas vascular tone primarily by pharmacomechanical means. The mechanism involves G protein linkage of a-adrenergic receptors to phospholipase C and subsequent Ca^{2+} release from intracellular stores by the actic the second messenger IP_3, as was illustrated in the pharmacomechanical section of Figure 7–1.

Sympathetic vasoconstrictor nerves normally have a continual or *tonic firing activity.* This tonic activity of sympathetic vasoconstrictor nerves makes the normal contractile tone of arterioles considerably greater th their basal tone. The additional component of vascular tone is called *neurogenic tone.* When the firing rate sympathetic vasoconstrictor nerves is increased above normal, arterioles constrict and cause organ blood f to fall below normal. Conversely, vasodilation and increased organ blood flow can be caused by sympathet vasoconstrictor nerves if their normal tonic activity level is reduced. Thus, an organ's blood flow can either reduced below normal or be increased above normal by changes in the sympathetic vasoconstrictor fiber fi rate.

[3] Pharmacological studies indicate that the amount of norepinephrine released from sympathetic nerves at given level of electrical activity can be modulated by presynaptic influences from a variety of agents. Norepinephrine release from sympathetic nerves is inhibited by high extracellular K^+, adenosine, certain prostaglandins, acetylcholine, and by norepinephrine itself. The latter effect is mediated by α_2-adrenergic receptors located on the sympathetic nerves. These receptors are pharmacologically distinct from the α_1-adrenergic receptors on smooth muscle cells. Angiotensin can enhance norepinephrine release from sympa nerves. Whether such effects are important in physiological situations is unclear at present.

[4] In addition to norepinephrine, sympathetic vasoconstrictor nerves to some tissues are now thought to als release some ATP and neuropeptide Y as "cotransmitters." Like norepinephrine, these agents promote ves constriction.

OTHER NEURAL INFLUENCES

Blood vessels, as a general rule, do not receive innervation from the parasympathetic division of the auton nervous system. However, *parasympathetic vasodilator nerves,* which release *acetylcholine,* are present in vessels of the brain and the heart but their influence on arteriolar tone in these organs appears to be inconsequential. Parasympathetic vasodilator nerves are also present in the vessels of the salivary glands, pancreas, gastric mucosa, and external genitalia. In the latter, they are responsible for the vasodilation of inflow vessels responsible for erection.

Hormonal Influences on Arterioles

Under normal circumstances hormonal influences on blood vessels are generally thought to be of mino consequence in comparison to the local metabolic and neural influences. However, it should be emphasized

the understanding of how the cardiovascular system operates in many situations is incomplete. Thus, the hormones discussed below may play more important roles in cardiovascular regulation than is now appreci

CIRCULATING CATECHOLAMINES

During activation of the sympathetic nervous system, the adrenal glands release the catecholamines *epinephrine* and *norepinephrine* into the bloodstream. Under normal circumstances, the blood levels of the agents are probably not high enough to cause significant cardiovascular effects. However, circulating catecholamines may have cardiovascular effects in situations (such as vigorous exercise or hemorrhagic sh that involve high activity of the sympathetic nervous system. In general, the cardiovascular effects of high levels of circulating catecholamines parallel the direct effects of sympathetic activation which have already discussed; both epinephrine and norepinephrine can activate cardiac β_1-adrenergic receptors to increase h rate and myocardial contractility and can activate vascular α-receptors to cause vasoconstriction. Recall th addition to the α_1-receptors that mediate vasoconstriction, arterioles in a few organs also possess β_2-adre receptors that mediate vasodilation. Because vascular β_2-receptors are more sensitive to epinephrine than vascular α_1-receptors, moderately elevated levels of circulating epinephrine can cause vasodilation—where higher levels cause α_1-receptor-mediated vasoconstriction. Vascular β_2-receptors are not innervated and therefore are *not* activated by norepinephrine released from sympathetic vasoconstrictor nerves. The physiological importance of these vascular β_2-receptors is unclear because adrenal epinephrine release oc during periods of increased sympathetic activity when arterioles would simultaneously be undergoing direc neurogenic vasoconstriction. Again, under normal circumstances, circulating catecholamines are not an important factor in cardiovascular regulation.

VASOPRESSIN



This polypeptide hormone, also known as antidiuretic hormone (ADH), plays an important role in extracellular fluid homeostasis and is released into the bloodstream from the posterior pituitary gland in response to low blood volume and/or high extracellular fluid osmolarity. Vasopressin acts on collecting duc the kidneys to decrease renal excretion of water. Its role in body fluid balance has some very important in influences on cardiovascular function, which will be discussed in more detail in Chapter 9. Vasopressin, hov is also a potent arteriolar vasoconstrictor. While it is not thought to be significantly involved in normal vas control, direct vascular constriction from abnormally high levels of vasopressin may be important in the response to certain disturbances such as severe blood loss through hemorrhage.

ANGIOTENSIN II



Angiotensin II is a circulating polypeptide that regulates aldosterone release from the adrenal cortex a part of the system for controlling body sodium balance. This system, to be discussed in greater detail in Ch 9, is very important in blood volume regulation. Angiotensin II is also a very potent vasoconstrictor agent. Although it should not be viewed as a normal regulator of arteriolar tone, direct vasoconstriction from angiotensin II seems to be an important component of the general cardiovascular response to severe bloo loss. There is also strong evidence suggesting that direct vascular actions of angiotensin II may be involve intrarenal mechanisms for controlling kidney function. In addition, angiotensin II may be partially responsi for the abnormal vasoconstriction that accompanies many forms of hypertension. Again, it should be emphasized that knowledge of many pathological situations—including hypertension—is incomplete. These situations may well involve vascular influences that are not yet recognized.

CONTROL OF VENOUS TONE

Before considering the details of the control of venous tone, recall that venules and veins play a much diffe role in the cardiovascular system than do arterioles. Arterioles are the inflow valves that control the rate o nutritive blood flow through organs and individual regions within them. Appropriately, arterioles are usuall strongly influenced by the current local metabolic needs of the region in which they reside, whereas veins not. Veins do, however, collectively regulate the distribution of available blood volume between the periph and central venous compartments. Recall that central blood volume (and therefore pressure) has a marke influence on stroke volume and cardiac output. Consequently, when one considers what *peripheral* veins a doing, one should be thinking primarily about what the effects will be on *central* venous pressure and cardi output.



Veins contain vascular smooth muscle that is influenced by many of the things that influence vas smooth muscle of arterioles. Constriction of the veins (venoconstriction) is largely mediated through activi the sympathetic nerves that innervate them. As in arterioles, these sympathetic nerves release norepineph which interacts with α_1-receptors and produces an increase in venous tone and a decrease in vessel diame There are, however, several functionally important differences between veins and arterioles. Compared wit arterioles, veins normally have little basal tone. Thus, veins are normally in a dilated state. One important consequence of the lack of basal venous tone is that vasodilator metabolites that may accumulate in the ti have little effect on veins.

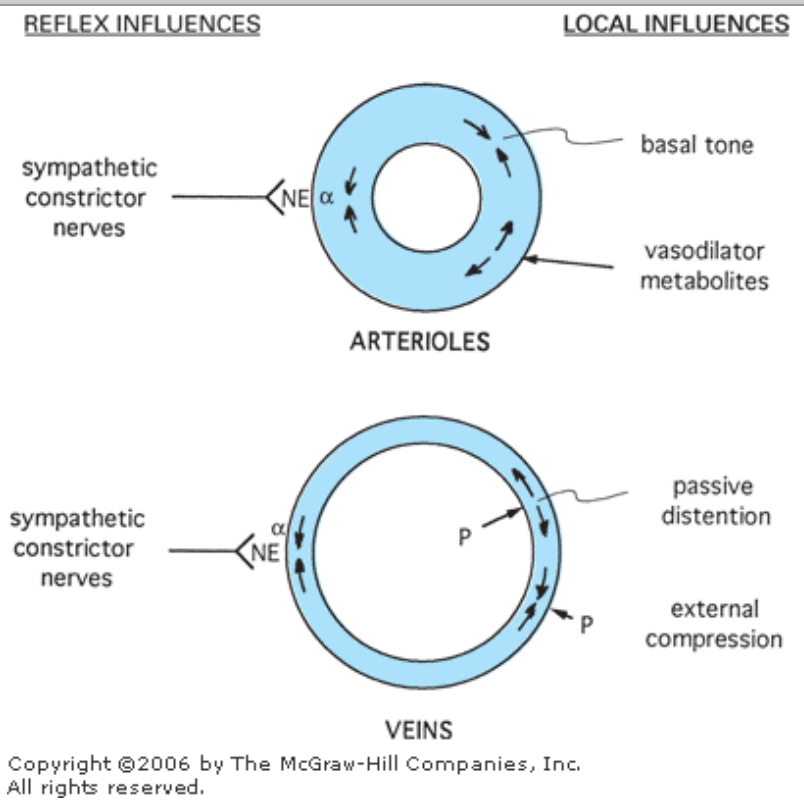
Because of their thin walls, veins are much more susceptible to physical influences than are arterioles. The effect of internal venous pressure on venous diameter was discussed in Chapter 6 and is evident in the poo of blood in the veins of the lower extremities that occurs during prolonged standing (as will be discussed fu in Chapter 10).

Often external compressional forces are an important determinant of venous volume. This is especially tru veins in skeletal muscle. Very high pressures are developed inside skeletal muscle tissue during contractio cause venous vessels to collapse. Because veins and venules have one-way valves, the blood displaced fro veins during skeletal muscle contraction is forced in the forward direction toward the right heart. In fact, rhythmic skeletal muscle contractions can produce a considerable pumping action, often called the *skeletal muscle pump,* which helps return blood to the heart during exercise.

SUMMARY OF PRIMARY VASCULAR CONTROL MECHANISMS

Vessels are subject to a wide variety of influences, and special influences often apply to particular organs. Certain general factors, however, dominate the control of the peripheral vasculature when it is viewed fron standpoint of overall cardiovascular system function; these influences are summarized in Figure 7–5. Basa tone, local metabolic vasodilator factors, and sympathetic vasoconstrictor nerves acting through α_1-recept are the major factors controlling arteriolar tone and therefore the blood flow rate through peripheral organ Sympathetic vasoconstrictor nerves, internal pressure, and external compressional forces are the most important influences on venous diameter and therefore on peripheral-central distribution of blood volume.

Figure 7–5.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Primary influences on arterioles and veins. NE, norepinephrine; α, alpha-adrenergic receptor; P, pressure.

VASCULAR CONTROL IN SPECIFIC ORGANS

As will become evident in the remaining sections of this chapter, many details of vascular co vary from organ to organ. However, with regard to flow control, most organs can be placed somewhere in spectrum that ranges from almost total dominance by local metabolic mechanisms to almost total dominar sympathetic vasoconstrictor nerves.

The flow in organs like the brain, heart muscle, and skeletal muscle is very strongly controlled by local metabolic control whereas the flow in the kidneys, skin, and splanchnic organs is very strongly controlled b sympathetic nerve activity. Consequently, some organs are automatically forced to participate in overall cardiovascular reflex responses to a greater extent than are other organs. The overall plan seems to be th cardiovascular emergency, flow to the brain and heart will be preserved at the expense of everything else need be.

Coronary Blood Flow

The major right and left coronary arteries that serve the heart tissue are the first vessels to branch off the aorta. Thus the driving force for myocardial blood flow is the systemic arterial pressure, just as it is for oth systemic organs. Most of the blood that flows through the myocardial tissue returns to the right atrium by of a large cardiac vein called the coronary sinus.

LOCAL METABOLIC CONTROL

As emphasized before, coronary blood flow is controlled primarily by local metabolic mechanisms and

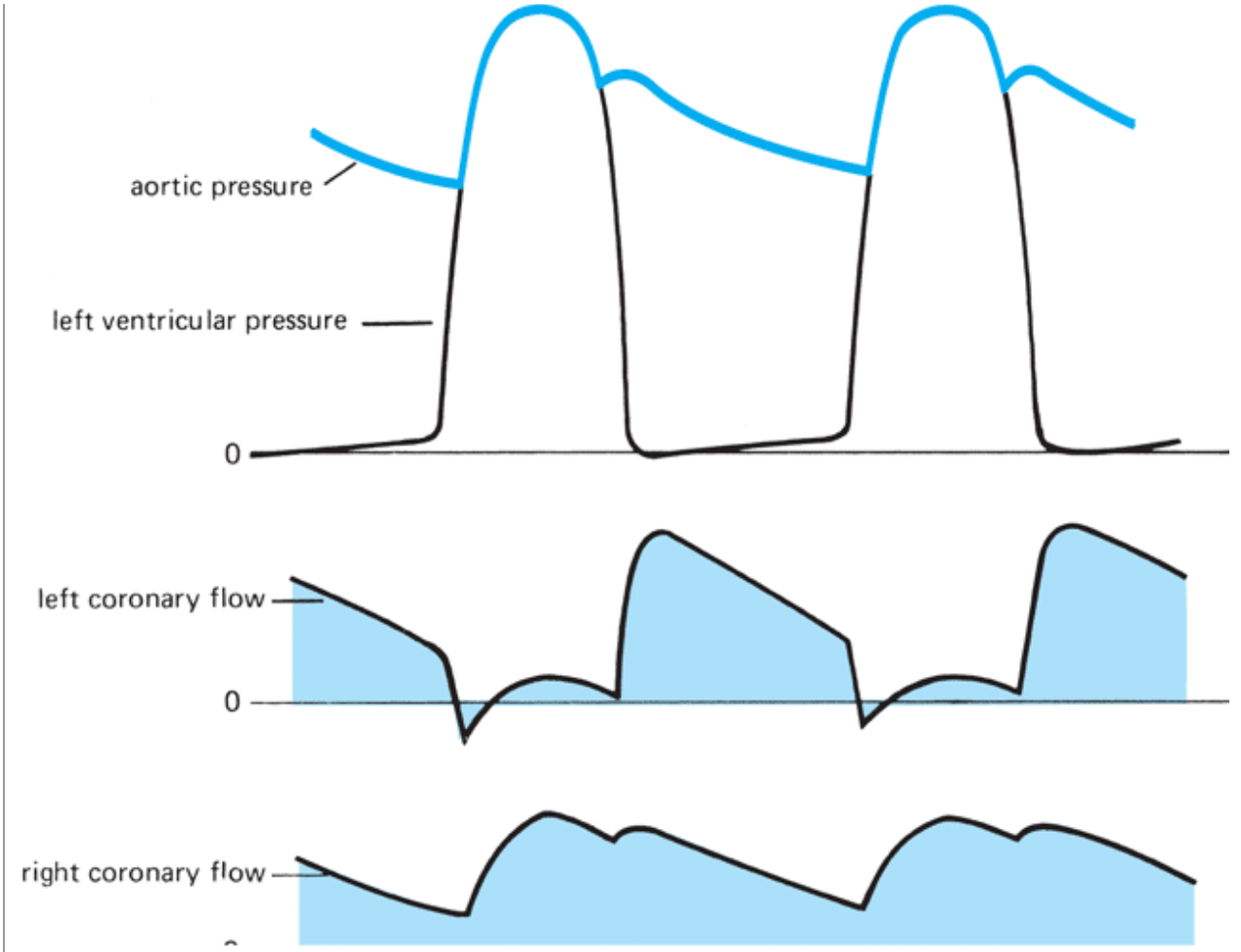
it responds rapidly and accurately to changes in myocardial oxygen consumption. In a resting individual, tl myocardium extracts 70–75% of the oxygen in the blood that passes through it. Coronary sinus blood nor has a lower oxygen content than blood at any other place in the cardiovascular system. Myocardial oxygen extraction cannot increase significantly from its resting value. Consequently, increases in myocardial oxyge consumption must be accompanied by appropriate increases in coronary blood flow.

The issue of which metabolic vasodilator factors play the dominant role in modulating the tone of coronary arterioles is unresolved at present. Many believe that adenosine, released from myocardial muscle cells in response to increased metabolic rate, may be an important local coronary metabolic vasodilator influence. Regardless of the specific details, myocardial oxygen consumption is the most important influence on coro blood flow.

SYSTOLIC COMPRESSION

Large forces and/or pressures are generated *within* the myocardial tissue during cardiac muscle contractio Such intramyocardial forces press on the outside of coronary vessels and cause them to collapse during sy Because of this *systolic compression* and the associated collapse of coronary vessels, coronary vascular resistance is greatly increased during systole. The result, at least for much of the left ventricular myocardi that coronary flow is lower during systole than during diastole, even though systemic arterial pressure (ie, coronary perfusion pressure) is highest during systole. This is illustrated in the left coronary artery flow tra shown in Figure 7–6. Systolic compression has much less effect on flow through the right ventricular myocardium, as is evident from the right coronary artery flow trace in Figure 7–6. This is because the peal systolic intraventricular pressure is much lower for the right heart than for the left, and the systolic compressional forces in the right ventricular wall are correspondingly less than those in the left ventricular

Figure 7–6.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Phasic flows in the left and right coronary arteries in relation to aortic and left ventricular pressures.

Systolic compressional forces on coronary vessels are greater in the endocardial (inside) layers of the left ventricular wall than in the epicardial layers.[5] Thus, the flow to the endocardial layers of the left ventricle i impeded more than the flow to epicardial layers by systolic compression. Normally, the endocardial region the myocardium can make up for the lack of flow during systole by a high flow in the diastolic interval. However, when coronary blood flow is limited—for example, by coronary disease and stenosis—the endoca layers of the left ventricle are often the first regions of the heart to have difficulty maintaining a flow suffic for their metabolic needs. *Myocardial infarcts* (areas of tissue killed by lack of blood flow) occur most frequ in the endocardial layers of the left ventricle.

[5] Consider that the endocardial surface of the left ventricle is exposed to intraventricular pressure (12 mmHg during systole), while the epicardial surface is exposed only to intrathoracic pressure (0 mmHg

NEURAL INFLUENCES ON CORONARY FLOW

Coronary arterioles are densely innervated with sympathetic vasoconstrictor fibers, yet when the activity o sympathetic nervous system increases, the coronary arterioles normally vasodilate rather than vasoconstri This is because an increase in sympathetic tone increases myocardial oxygen consumption by increasing h rate and contractility. The increased local metabolic vasodilator influence apparently outweighs the concur

vasoconstrictor influence due to an increase in the activity of sympathetic vasoconstrictor fibers that termi on coronary arterioles. It has been experimentally demonstrated that a given increase in cardiac sympathe nerve activity causes a greater increase in coronary blood flow after the direct vasoconstrictor influence of sympathetic nerves on coronary vessels has been eliminated with α-receptor blocking agents. However, sympathetic vasoconstrictor nerves do not appear to influence coronary flow enough to affect the mechani performance of normal hearts. Whether these coronary vasoconstrictor fibers might be functionally import certain pathological situations is an open question.

Skeletal Muscle Blood Flow

Collectively, the skeletal muscles constitute 40–45% of body weight—more than any other single body org Even at rest, about 15% of the cardiac output goes to skeletal muscle, and during strenuous exercise skel muscle may receive more than 80% of the cardiac output. Thus, skeletal muscle blood flow is an importan factor in overall cardiovascular hemodynamics.

Because of a high level of intrinsic tone of the resistance vessels in resting skeletal muscles, the blood flow gram of tissue is quite low when compared with that of other organs such as the kidneys. However, resting skeletal muscle blood flow is still substantially above that required to sustain its metabolic needs. Resting skeletal muscles normally extract only 25–30% of the oxygen delivered to them in arterial blood. Changes the activity of sympathetic vasoconstrictor fibers do alter resting muscle blood flow. For example, maximu sympathetic discharge rates can decrease blood flow in a resting muscle to less than one fourth its normal value, and conversely, if all neurogenic tone is removed, resting skeletal muscle blood flow may double. Th a modest increase in flow compared with the 20-fold increase in flow that can occur in an exercising skelet muscle. Nonetheless, because of the large mass of tissue involved, changes in the vascular resistance of re skeletal muscle brought about by changes in sympathetic activity are very important in the overall reflex regulation of arterial pressure.


A particularly important characteristic of skeletal muscle is its very wide range of metabolic rates. Dur heavy exercise, the oxygen consumption rate of and oxygen extraction by skeletal muscle tissue can reach high values typical of the myocardium. In most respects, the factors that control blood flow to exercising m are similar to those that control coronary blood flow. Local metabolic control of arteriolar tone is very stron exercising skeletal muscle, and muscle oxygen consumption is the most important determinant of blood flo exercising skeletal muscle.

As will be discussed in Chapter 10, the cardiovascular response to muscle exercise involves a general incre in sympathetic activity. This of course reduces flow to susceptible organs, which include non-exercising mu In exercising muscles, the increased sympathetic vasoconstrictor nerve activity is not evident as outright vasoconstriction but does limit the degree of metabolic vasodilation. One important function that this seem counterproductive process may serve is that of preventing an excessive reduction in total peripheral resist (TPR) during exercise. Indeed, if arterioles in most of the skeletal muscles in the body were allowed to dila their maximum capacity simultaneously, TPR would be so low that the heart could not possibly supply enou cardiac output to maintain arterial pressure.

As in the heart, muscle contraction produces large compressional forces within the tissue, which can collap vessels and impede blood flow. Strong, sustained (tetanic) skeletal muscle contractions may actually stop muscle blood flow. About 10% of the total blood volume is normally contained within the veins of skeletal muscle, and during rhythmic exercise the "skeletal muscle pump" is very effective in displacing blood from skeletal muscle veins. Blood displaced from skeletal muscle into the central venous pool is an important fa in the hemodynamics of strenuous whole body exercise.

The veins in skeletal muscle are rather sparsely innervated with sympathetic vasoconstrictor fibers, and th

rather small volume of blood that can be mobilized from skeletal muscle by sympathetic nerve activation is probably not of much significance to total body hemodynamics. This is in sharp contrast to the large displacement of blood from exercising muscle by the muscle pump mechanism.

Cerebral Blood Flow

Adequate cerebral blood flow is of paramount importance for survival because unconsciousness occurs very rapidly after an interruption in flow. One rule of overall cardiovascular system function is that, in *all* situati measures are taken that are appropriate to preserve adequate blood flow to the brain.

The brain as a whole has a nearly constant rate of metabolism that, on a per gram basis, is nearly as high that of myocardial tissue. Cerebral blood flow appears to be regulated almost entirely by local mechanisms Flow through the cerebrum is autoregulated very strongly and is little affected by changes in arterial press unless it falls below about 60 mmHg. When arterial pressure decreases below 60 mmHg, brain blood flow decreases proportionately. It is presently unresolved whether metabolic mechanisms or myogenic mechan or both are involved in the phenomenon of cerebral autoregulation.


Presumably because the overall average metabolic rate of brain tissue shows little variation, total brai blood flow is remarkably constant over nearly all situations. The cerebral activity in discrete locations withi brain, however, changes from situation to situation. As a result, blood flow to discrete regions is not consta but closely follows the local neuronal activity. The mechanisms responsible for this strong local control of cerebral blood flow are as yet undefined, but H^+, K^+, oxygen, and adenosine seem most likely to be involv

Cerebral blood flow does increase whenever the partial pressure of carbon dioxide (P_{CO_2}) is raised above n in the arterial blood. Conversely, cerebral blood flow decreases whenever arterial blood P_{CO_2} falls below no It appears that cerebral arterioles respond not to changes in P_{CO_2} but to changes in the extracellular H^+ concentration (ie, pH) caused by changes in P_{CO_2}. Cerebral arterioles also vasodilate whenever the partial pressure of oxygen (P_{O_2}) in arterial blood falls significantly below normal values. Higher than normal arteri blood P_{O_2}, such as that caused by oxygen inhalation, produces little decrease in cerebral blood flow.

Although cerebral vessels receive both sympathetic vasoconstrictor and parasympathetic vasodilator fiber innervation, cerebral blood flow is influenced very little by changes in the activity of either under normal circumstances. Sympathetic vasoconstrictor responses may, however, be important in protecting cerebral vessels from excessive passive distention following large, abrupt increases in arterial pressure.

Brain capillaries are unique in that they are considerably less porous than those in other organs, and they greatly restrict the transcapillary movement of all polar particles. The diffusional restriction and other spec metabolic mechanisms associated with the endothelial cells of brain capillaries constitute what is known as *blood-brain barrier.*[6] Because of the blood-brain barrier, the extracellular space of the brain represents a s fluid compartment in which the chemical composition is regulated separately from that in the plasma and general body extracellular fluid compartment. The extracellular compartment of the brain encompasses bo interstitial fluid and *cerebrospinal fluid* (CSF) which surrounds the brain and spinal cord and fills the brain ventricles. The CSF is formed from plasma by selective secretion (not simple filtration) by specialized tissu the*choroid plexes,* located within the ventricles. These processes regulate the chemical composition of the The interstitial fluid of the brain takes on the chemical composition of CSF through free diffusional exchang

The blood-brain barrier serves to protect the cerebral cells from ionic disturbances in the plasma. Also, by exclusion and/or endothelial cell metabolism, it prevents many circulating hormones (and drugs) from influencing the parenchymal cells of the brain and the vascular smooth muscle cells in brain vessels.

[6] Brain capillaries have a special carrier system for glucose and present no barrier to oxygen and carbon di diffusion. Thus, the blood-brain barrier does not restrict nutrient supply to the brain tissue.

Splanchnic Blood Flow

A number of abdominal organs, including the gastrointestinal tract, spleen, pancreas, and liver, are collect supplied with what is called the *splanchnic blood flow.* Splanchnic blood flow is supplied to these abdomina organs through many arteries, but it all ultimately passes through the liver and returns to the inferior vena through the hepatic veins.

The organs of the splanchnic region receive about 25% of the resting cardiac output and moreover contain more than 20% of the circulating blood volume. Thus adjustments in either the blood flow or the blood vol of this region have extremely important effects on the cardiovascular system.

There is a great diversity of function among individual organs and even regions within organs in the splanchnic region. Blood flow is required to support secretory and absorptive processes as well as muscula contractions of the gastrointestinal tract. The mechanisms of vascular control in specific areas of the splan region are not well understood but are likely to be quite varied. Nonetheless, since most of the splanchnic organs are involved in the digestion and absorption of food from the gastrointestinal tract, splanchnic bloo increases after food ingestion. A large meal can elicit a 30–100% increase in splanchnic flow, but individua organs in the splanchnic region probably have higher percentage increases in flow at certain times because are involved sequentially in the digestion-absorption process.

Collectively, the splanchnic organs have a relatively high blood flow and extract only 15–20% of the oxygen delivered to them in the arterial blood. In general, sympathetic nerves play a major role in vascula control. The arteries and veins of all the organs involved in the splanchnic circulation are richly innervated sympathetic vasoconstrictor nerves. Maximal activation of sym-

pathetic vasoconstrictor nerves can produce an 80% reduction in flow to the splanchnic region and also ca large shift of blood from the splanchnic organs to the central venous pool. In humans, a large fraction of th blood mobilized from the splanchnic circulation during periods of sympathetic activation comes from the constriction of veins in the liver. In many other species, the spleen acts as a major reservoir from which bl mobilized by sympathetically mediated contraction of smooth muscle located in the outer capsule of the or

Renal Blood Flow

The kidneys normally receive approximately 20% of the cardiac output of a resting individual, and sin this can be reduced to practically zero during strong sympathetic activation, the control of renal blood *flow* important to overall cardiovascular function. However, because the kidneys are such small organs, change renal blood *volume* are inconsequential to overall cardiovascular hemodynamics.

Increases in sympathetic vasoconstrictor activity can markedly reduce total renal blood flow by increasing neurogenic tone of renal resistance vessels. In fact, extreme situations involving intense and prolonged sympathetic vasoconstrictor activity can lead to renal failure.

It has long been known that experimentally *isolated* kidneys (ie, kidneys deprived of their normal sympath input) autoregulate their flow quite strongly. The mechanism responsible for this phenomenon has not bee definitely established but myogenic, tissue pressure, and metabolic hypotheses have been advanced. The question is what purpose such a strong local mechanism plays in the intact organism where it seems to be largely overridden by reflex mechanisms. In an intact individual, renal blood flow is not constant but is hig variable, depending on the prevailing level of sympathetic vasoconstrictor nerve activity. In extreme situat such as severe blood loss, highly elevated sympathetic nerve activity can reduce renal blood flow to such a value that permanent kidney damage can occur.

The mechanisms responsible for the intrinsic regulation of renal blood flow and kidney function have not be established. While studies suggest that prostaglandins and some intrarenal renin-angiotensin system may involved, the whole issue of local renal vascular control remains quite obscure. Renal function is itself of paramount importance to overall cardiovascular function, as will be described in Chapter 9.

Cutaneous Blood Flow

The metabolic activity of body cells produces heat, which must be lost in order for the body temperature to remain constant. The skin is the primary site of exchange of body heat with the external environment. Alterations in cutaneous blood flow in response to various metabolic states and environmental conditions provide the primary mechanism responsible for temperature homeostasis. (Other mechanisms such as shivering, sweating, and panting also participate in body temperature regulation under more extreme conditions.)

Cutaneous blood flow, which is about 6% of the resting cardiac output, can decrease to about one twentiet its normal value when heat is to be retained (eg, in a cold environment, during the development stages of fever). In contrast, cutaneous blood flow can increase up to seven times its normal value when heat is to b (eg, in a hot environment, accompanying a high metabolic rate, after a fever breaks).

The anatomic interconnections between microvessels in the skin are highly specialized and extremely comp An extensive system of interconnected veins called the *venous plexus* normally contains the largest fractio cutaneous blood volume, which, in individuals with lightly pigmented skin, gives the skin a reddish hue. To large extent, heat transfer from the blood takes place across the large surface area of the venous plexus. T venous plexus is richly innervated with sympathetic vasoconstrictor nerves. When these fibers are activate blood is displaced from the venous plexus, and this helps reduce heat loss and also lightens the skin color. the skin is one of the largest body organs, venous constriction can shift a considerable amount of blood int central venous pool.


Cutaneous resistance vessels are also richly innervated with sympathetic vasoconstrictor nerves, and these fibers have a normal tonic activity, cutaneous resistance vessels normally have a high degree of neurogenic tone. When body temperature rises above normal, skin blood flow is increased by reflex mechanisms. In certain areas (such as the hands, ears, and nose) vasodilation appears to result entirely fr the withdrawal of sympathetic vasoconstrictor tone. In other areas (such as the forearm, forehead, chin, n and chest) the cutaneous vasodilation that occurs with body heating greatly exceeds that which occurs wit the removal of sympathetic vasoconstrictor tone. This "active" vasodilation is closely linked to the onset of sweating in these areas. The sweat glands in human cutaneous tissue are innervated by *cholinergic sympa fibers* that release acetylcholine. Activation of these nerves elicit sweating *and* an associated marked cutar vasodilation. The exact mechanism for this sweating-related cutaneous vasodilation remains unclear becau is not abolished by agents that block acetylcholine's vascular effects. It has long been thought that it was caused by local bradykinin formation secondary to the process of sweat gland activation. Newer evidence suggests that instead the cholinergic sympathetic nerves to sweat glands may release not only acetylcholi also other vasodilator cotransmitters. While these special sympathetic nerves are very important to temperature regulation, they do not participate in the normal, moment-to-moment, regulation of the cardiovascular system.

In addition to responding reflexly to changes in body temperature, cutaneous vessels also respond to local temperature. In general, local cooling leads to local vasoconstriction and local heating causes local vasodil The mechanisms for this are unknown. If the hand is placed in ice water, there is initially a nearly complete cessation of hand blood flow accompanied by intense pain. After some minutes, hand blood flow begins to to reach values greatly in excess of the normal value, hand temperature increases, and the pain disappear

This phenomenon is referred to as *cold-induced vasodilation.* With continued immersion, hand blood flow c every few minutes between periods of essentially no flow and periods of hyperemia. The mechanism respo for cold vasodilation is unknown, but it has been suggested that norepinephrine may lose its ability to cons vessels when their temperature approaches 0°C. Whatever the mechanism, cold-induced vasodilation apparently serves to protect exposed tissues from cold damage.

Tissue damage from burns, ultraviolet radiation, cold injury, caustic chemicals, and mechanical trauma pro reactions in skin blood flow. A classical reaction called the *triple response* is evoked after vigorously stroki skin with a blunt point. The first component of the triple response is a *red line* that develops along the dire path of the abrasion in about 15 seconds. Shortly thereafter, an irregular *red flare* appears that extends ab cm on either side of the red line. Finally, after a minute or two, a *wheal* appears along the line of the injury mechanisms involved in the triple response are unknown, but it seems likely that histamine release from damaged cells is at least partially responsible for the dilation evidenced by the red line and the subsequen edema formation of the wheal. The red flare seems to involve nerves in some sort of a local *axon reflex* be it can be evoked immediately after cutaneous nerves are sectioned but not after the peripheral portions of sectioned nerves degenerate.

Pulmonary Blood Flow

The rate of blood flow through the lungs is necessarily equal to cardiac output in all circumstances. When cardiac output increases 3-fold during exercise, for example, pulmonary blood flow must also increase 3-fo Whereas the flow through a systemic organ is determined by its vascular resistance ($\dot{Q} = \triangle P/R$), the blood rate through the lungs is determined simply by the cardiac output ($\dot{Q} = CO$). Pulmonary vessels do, howev offer some vascular resistance. Although the level of pulmonary vascular resistance does not usually influe the pulmonary flow rate, it is important because it is one of the determinants of pulmonary arterial pressu $= \dot{Q}_x R$). Recall that mean *pulmonary* arterial pressure is about 13 mmHg, whereas mean *systemic* arterial pressure is about 100 mmHg. The reason for the difference in pulmonary and systemic arterial pressures is that the right heart is weaker than the left heart but rather that pulmonary vascular resistance is inherentl much lower than systemic total peripheral resistance. The pulmonary bed has a low resistance because it h relatively large vessels throughout.

A very important distinction between the systemic and pulmonary arteries and arterioles is that the pulmo vessels are less muscular and more compliant. When pulmonary arterial pressure increases, the pulmonary arteries and arterioles become larger in diameter. Thus an increase in pulmonary arterial pressure *decreas* pulmonary vascular resistance. This phenomenon is important because it tends to limit the increase in pulmonary arterial pressure that occurs with increases in cardiac output.

The most important active response in the pulmonary vasculature is the *hypoxic vasoconstriction* of pulmo arterioles. Recall that systemic arterioles dilate in response to low P_{O_2}. The mechanisms that cause the opp response in pulmonary vessels are unclear. Current evidence suggests that local prostaglandin synthesis m involved in pulmonary hypoxic vasoconstriction. Whatever the mechanism, hypoxic vasoconstriction is esse to efficient lung gas exchange because it diverts blood flow away from areas of the lung that are underventilated. Consequently, the best-ventilated areas of the lung also receive the most blood flow. Presumably as a consequence of hypoxic arteriolar vasoconstriction, general hypoxia (such as that encoun at high altitude) causes an increase in pulmonary vascular resistance and pulmonary arterial hypertension.

Both pulmonary arteries and veins receive sympathetic vasoconstrictor fiber innervation, but reflex influen on pulmonary vessels appear to be much less important than the physical and local hypoxic influences. Pulmonary veins serve a blood reservoir function for the cardiovascular system, and sympathetic vasoconstriction of pulmonary veins may be important in mobilizing this blood during periods of general cardiovascular stress.

A consequence of the low mean pulmonary arterial pressure is the low pulmonary capillary hydrostatic pre of about 8 mmHg (compared with about 25 mmHg in systemic capillaries). Because the plasma oncotic pre in lung capillaries is near 25 mmHg, as it is in all capillaries, it is likely that the transcapillary forces in the strongly favor continual fluid reabsorption. This cannot be the complete story, however, since the lungs, lik other tissues, continually produce some lymph and some net capillary filtration is required to produce lymp fluid. This filtration is possible despite the unusually low pulmonary capillary hydrostatic pressure because pulmonary interstitial fluid has an unusually high protein concentration and thus oncotic pressure.

KEY CONCEPTS


Continual adjustments of vascular diameter are required to properly distribute the cardiac output to th various systemic tissues (the role of arterioles) and maintain adequate cardiac filling (the role of veins).


Vascular adjustments are made by changes in the tone of vascular smooth muscle.


Vascular smooth muscle has many unique properties that make it sensitive to a wide array of local an reflex stimuli and capable of maintaining tone for long periods of time.


The tone of arterioles, but not veins, can be strongly influenced by local vasodilator factors produced l local tissue metabolism.


In abnormal situations (like tissue injury or severe blood volume depletion), certain local factors like histamine and bradykinin, and hormonal factors like vasopressin and angiotensin have significant vascular influences.


Sympathetic vasoconstrictor nerves provide the primary reflex mechanisms for regulating both arterio and venous tone.


Sympathetic vasoconstrictor nerves release norepinephrine, which interacts with α_1-adrenergic recept on vascular smooth muscle to induce vasoconstriction.


The relative importance of local metabolic versus reflex sympathetic control of arteriolar tone (and therefore blood flow) varies from organ to organ.


In many organs (such as brain, heart muscle, and exercising skeletal muscle), blood flow normally clo follows metabolic rate because of local metabolic influences on arterioles.


In other organs (such as skin and kidneys) blood flow is normally regulated more by sympathetic nerv than by local metabolic conditions.

STUDY QUESTIONS

7–1. Which of the following would increase blood flow through a skeletal muscle?

a. An increase in tissue P_{CO_2}

b. An increase in tissue adenosine

c. The presence of α-receptor blocking drugs

d. Sympathetic activation

7–2. Autoregulation of blood flow implies that arterial pressure is adjusted by local mechanisms to ensure constant flow through an organ. True or false?

7–3. Coronary blood flow will normally increase when

a. Arterial pressure increases

b. Heart rate increases

c. Sympathetic activity increases

d. The heart is dilated

7–4. The arterioles of skeletal muscle would have little or no tone in the absence of normal sympathetic vasoconstrictor fiber activity. True or false?

7–5. A person who hyperventilates (breathes rapidly and deeply) gets dizzy. Why?

7–6. A patient complains of severe leg pains after walking a short distance. The pains disappear after the patient rests (this symptom is called intermittent claudication). What might be the problem?

7–7. How would a stenotic aortic valve influence coronary blood flow?

See answers.

SUGGESTED READINGS

Archer S, Michelakis E. The mechanism(s) of hypoxic pulmonary vasoconstriction: potassium channels, red sensors and controversies. *News Physiol Sci.* 2002;17:162–166.

Bolton TB, Tomita T, eds. *Smooth Muscle Excitation.* London: Academic Press; 1996.

Born GVR, Schwartz CJ. *Vascular Endothelium, Physiology, Pathology and Therapeutic Opportunities.* Schattauer, Stuttgart, 1997.

Bradbury MWB. The blood-brain barrier. *Exp Physiol.* 1993;78:453–472. [PMID: 8398100]

Brown MD. Metabolic control of blood flow with reference to the heart, skeletal muscle, and brain. In: Jorda Marshall J, eds. *Cardiovascular Regulation.* London: Portland Press; 1995.

Charkoudian N. Skin blood flow in adult human thermoregulation: how it works, when it does not, and why *Mayo Clin Proc.* 2003;78:603–612. [PMID: 12744548]

Davies PF. Flow-mediated endothelial mechanotransduction. *Physiol Rev.* 1995;75:519–560. [PMID: 7624

Davis MJ, Hill MA. Signaling mechanisms underlying the vascular myogenic response. *Physiol Rev.* 1999;79:387–423. [PMID: 10221985]

Faranci FM, Heistad DD. Regulation of the cerebral circulation: role of endothelium and potassium channels *Physiol Rev.* 1998;78:53–97.

Grossman JD, Morgan JP. Cardiovascular effects of endothelin. *News Physiol Sci.* 1997;12:113–117.

Harder DR, Zhang C, Gebremedhin D. Astrocytes function in matching blood flow to metabolic activity. *New Physiol Sci.* 2002;17:27–31. [PMID: 11821533]

Hill MA, Zou H, Potocnik SJ, et al. Invited review: arteriolar smooth muscle mechanotransduction: Ca^{2+} signaling pathways underlying myogenic reactivity. *J Appl Physiol.* 2001;91:973–983. [PMID: 11457816]

Hirst GD, Edwards FR. Sympathetic neuroeffector transmission in arteries and arterioles. *Physiol Rev.* 1989;69:546–604. [PMID: 2467318]

Horowitz A, Menice CB, Laporte R, Morgan KG. Mechanisms of smooth muscle contraction. *Physiol Rev.* 1997;76:967–1003.

Johnson PC. Autoregulation of blood flow. *Circ Res.* 1986;59:483–495. [PMID: 3542277]

Konidala S, Gutterman DD. Coronary vasospasm and the regulation of coronary blood flow. *Prog Cardiovas* 2004;46:349–373. [PMID: 14961457]

Matheson PJ, Wilson MA, Garrion RN. Regulation of intestinal blood flow. *J Surg Res.* 2000;93:182–196. [P 10945962]

Monos E, Berczi V, Nadasy G. Local control of veins: biomechanical, metabolic, and hormonal aspects. *Phys Rev.* 1995;75:611–666. [PMID: 7624396]

O'Donnell ME, Owen NE. Regulation of ion pumps and carriers in vascular smooth muscle. *Physiol Rev.* 1994;74:683–721. [PMID: 8036250]

Quayle JM, Nelson MT, Standen NB. ATP-sensitive and inward rectifying potassium channels in vascular sm muscle.*Physiol Rev.* 1997;77:1165–1216. [PMID: 9354814]

Roman RJ. P-450 metabolites of arachidonic acid in the control of cardiovascular function. *Physiol Rev.* 2002;82:131–185. [PMID: 11773611]

Shaul PW. Regulation of endothelial nitric oxide synthase: Location, location, location. *Annu Rev Physiol.* 2002;64:749–774. [PMID: 11826287]

Smiesko V, Johnson PC. The arterial lumen is controlled by flow-related shear stress. *News Physiol Sci.* 1993;8:34–38.

Somlyo AP, Wu X, Walker L, Somlyo AV. Pharmacomechanical coupling: the role of calcium, G-proteins, kir
and phosphates. *Rev Physiol, Biochem Pharmacol.* 1998;134:203–236.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.
Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.

Medical a silverchair information system The McGraw-Hill Companies

McGraw-Hill's ACCESSMedicine

Print Close Window

Note: Large images and tables on this page may necessitate printing in landscape mode.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.

OBJECTIVES

The student understands how central venous pressure can be used to assess circulatory states and how venous return, cardiac output, and central venous pressure are interrelated:

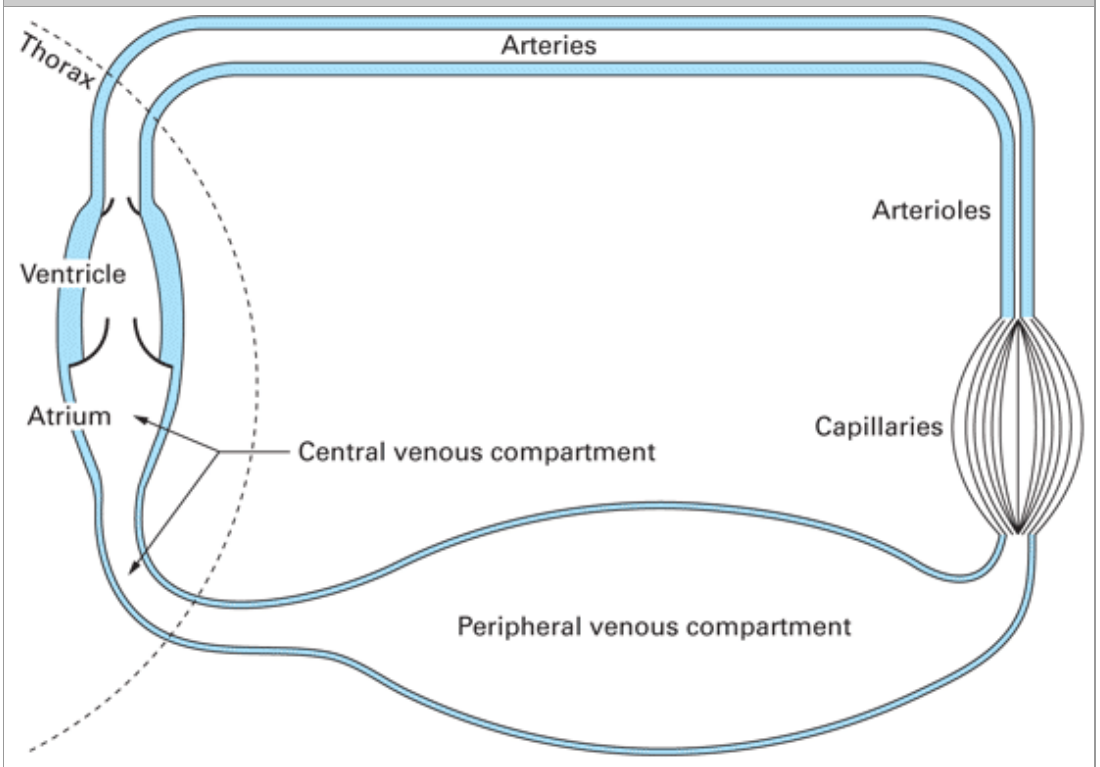
- *Describes the overall arrangement of the systemic circulation and identifies the primary functional properties of each of its major components.*
- *Defines mean circulatory filling pressure and states the primary factors that determine it.*
- *Defines venous return and explains how it is distinguished from cardiac output.*
- *States the reason why cardiac output and venous return must be equal in the steady state.*
- *Lists the factors that control venous return.*
- *Describes the relationship between central venous pressure and venous return and draws the normal venous return curve.*
- *Defines peripheral venous pressure.*
- *Lists the factors that determine peripheral venous pressure.*
- *Predicts the shifts in the venous return curve that occur with altered blood volume and altered venous tone.*
- *Describes how the output of the left heart pump is matched to that of the right heart pump.*
- *Draws the normal venous return and cardiac output curves on a graph and describes the significance of the point of curve intersection.*
- *Predicts how normal venous return, cardiac output, and central venous pressure will be altered with any given combination of changes in cardiac sympathetic tone, peripheral venous sympathetic tone, or circulating blood volume.*
- *Identifies possible conditions that result in abnormally high or low central venous pressure.*

INTERACTION OF SYSTEM COMPONENTS

Once one has learned the basic facts concerning the individual pieces of the cardiovascular system, it is important to step back, take a broad view, and see how those pieces interact in the operation of the intact system.

As illustrated in Figure 8–1, the cardiovascular system is a closed hydraulic circuit that includes the heart, arteries, arterioles, capillaries, and veins.[1] The venous side of this system is often conceptually separated into two different compartments: (1) a large and diverse peripheral section (the peripheral venous compartment) and (2) a smaller intrathoracic section that includes the vena cavae and the right atrium (the central venous compartment). Each of the segments of this circuit has a distinctly different role to play in the overall operation of the system because of inherent differences in anatomical volume, resistance to flow, and compliance that are summarized in Table 8–1.

Figure 8–1.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Major functionally distinct components of the systemic cardiovascular circuit.

Table 8–1. Typical Properties of the Major Components of the Systemic Cardiovascular Circuit.*

Compartment	V_0 mL	C mL/mmHg	R mmHg/(L/min)
Ventricle in diastole	30	24	0
Arteries	600	2	1
Arterioles	100	0	13
Capillaries	250	0	5
Peripheral venous compartment	2500	110	1
Central venous compartment	80	4	0
Entire circuit	3560	140	20

*Values are for a normal, young, resting 70-kg adult. V_0, anatomical volume of compartment at zero pressure: C, compliance of compartment; R, resistance to flow through compartment.

Note especially the high ventricular diastolic compliance of 24 mL/mmHg in Table 8–1. This value indicates how exquisitely sensitive the ventricular end-diastolic volume (and therefore stroke volume and cardiac output) is to small changes in cardiac filling pressure (ie, central venous pressure). In all

physiological and pathological situations, cardiac filling pressure is a crucial factor that determines how well the cardiovascular system will be operating.

[1] The pulmonary circuit is not included in Figure 8–1 because it does not influence the major points to be made in this chapter. The primary leap of faith in this omission is that because of Starling's law of the heart, changes in the end-diastolic volume of the *right* ventricle cause equal changes in the end-diastolic volume of the *left* ventricle.

Mean Circulatory Filling Pressure

Imagine the heart arrested in diastole with no flow around the circuit shown in Figure 8–1. It will take a certain amount of blood just to fill the anatomical space contained by the systemic system without stretching any of its walls or developing any internal pressure. This amount is 3.5 L, as indicated by the total systemic circuit volume (V_0) in Table 8–1. Normally, however, the systemic circuit contains about 4.5 L of blood and thus is somewhat inflated. From the total systemic circuit compliance (C) given in Table 8–1, one can see that an extra 1000 mL of blood would result in an internal pressure of about 7 mmHg (ie, 1000 mL/140 mL/mmHg). This theoretical pressure is called the *mean circulatory filling pressure* and is the actual pressure that would exist throughout the system in the absence of flow.


The two major variables that affect mean circulatory filling pressure are the circulating blood volume and the state of the peripheral venous vessel tone. In the latter case, look at Figure 8–1 and imagine how squeezing on the large venous compartment (increasing venous tone) will have a significant positive influence on pressure throughout the system. In contrast, squeezing on arterioles (increasing arteriolar tone) will have a negligible effect on mean circulatory filling pressure because arterioles contain so little blood in any state. The other major components of the system (arteries and capillaries) essentially do not actively change their contained volume.

Flow-Induced Distribution of Blood Volume and Pressure

The presence of flow around the circuit does not change the total volume of blood in the system or the mean circulatory filling pressure. The flow caused by cardiac pumping action does, however, tend to shift some of the blood volume from the venous side of the circuit to the arterial side. This causes pressures on the arterial side to rise above the mean circulatory pressure while pressures on the venous side fall below it. Because veins are about 50 times more compliant than arteries (Table 8-1), the flow-induced decrease in venous pressure is only about 1/50th as large as the accompanying increase in arterial pressure. Thus, flow or no flow, pressure in the peripheral venous compartment is normally quite close to the mean circulatory filling pressure.

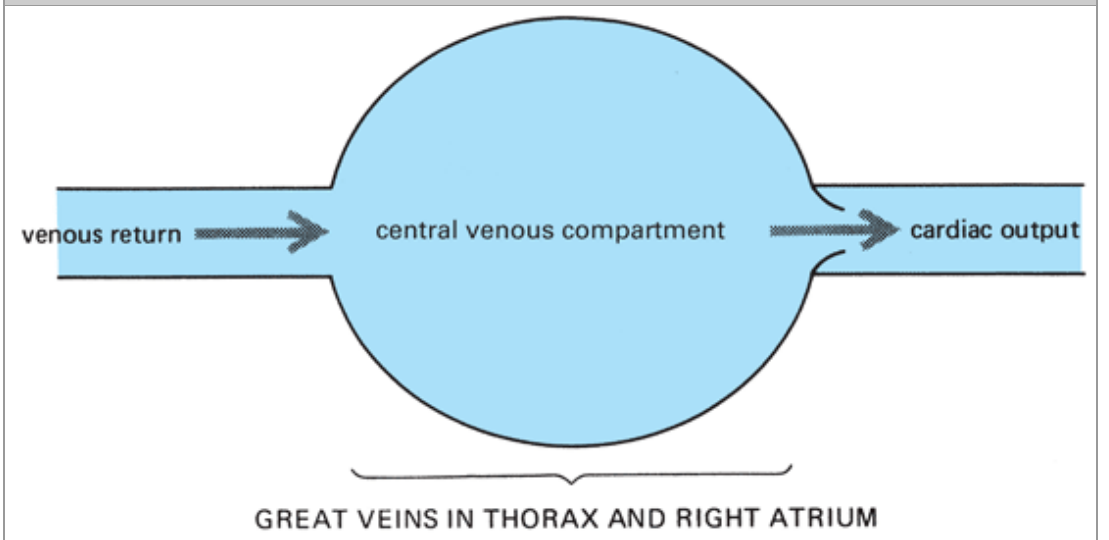
CENTRAL VENOUS PRESSURE: AN INDICATOR OF CIRCULATORY STATUS

The cardiovascular system must adjust its operation continually to meet changing metabolic demands of the body. Because the cardiovascular system is a closed hydraulic loop, adjustments in any one part of the circuit will have pressure, flow, and volume effects throughout the circuit. Because of the critical influence of cardiac filling on cardiovascular function, the remainder of this chapter will focus on the factors that determine the pressure in the central venous compartment. In addition, the way in which measures of central venous pressure can provide clinically useful information about the state of the circulatory system will be discussed.

The central venous compartment corresponds roughly to the volume enclosed by the right atrium and the great veins in the thorax. Blood *leaves* the central venous compartment by entering the right

ventricle at a rate that is equal to the cardiac output. *Venous return,* in contrast, is by definition the rate at which blood returns to the thorax from the peripheral vascular beds and thus is the rate at which blood *enters* the central venous compartment. The important distinction between venous return *to* the central venous compartment and cardiac output *from* the central venous compartment is illustrated in Figure 8–2.

Figure 8–2.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Distinction between cardiac output and venous return.

In any stable situation, venous return must equal cardiac output or blood would gradually accumulate in either the central venous compartment or the peripheral vasculature. However, there often are temporary differences between cardiac output and venous return. Whenever such differences exist, the volume of the central venous compartment must be changing. Because the central venous compartment is enclosed by elastic tissues, any change in central venous volume produces a corresponding change in central venous pressure.

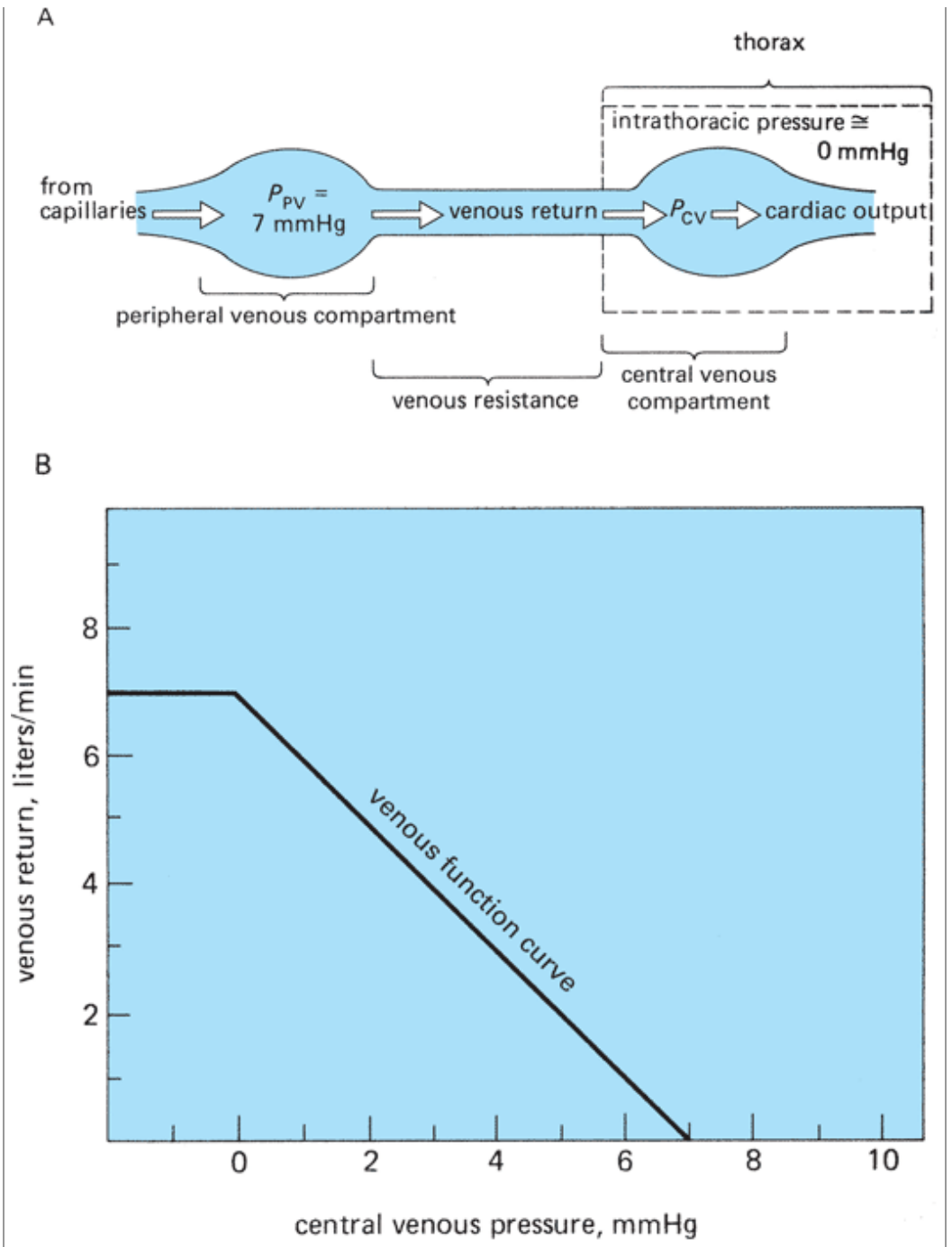
As discussed in Chapter 3, the central venous pressure (ie, cardiac filling pressure) has an extremely important *positive* influence on cardiac output (Starling's law of the heart). As argued below, central venous pressure has an equally important *negative* effect on venous return. Thus, central venous pressure is always automatically driven to a value that makes cardiac output equal to venous return. The factors that determine central venous pressure in any given situation are discussed below.

INFLUENCE OF CENTRAL VENOUS PRESSURE ON VENOUS RETURN

The important factors involved in the process of venous return can be summarized as shown in Figure 8–3A. Basically, venous return is blood flow from the peripheral venous compartment to the central venous compartment through converging vessels. Anatomically the peripheral venous compartment is scattered throughout the systemic organs, but functionally it can be viewed as a single vascular space that has a particular pressure (P_{PV}) at any instant of time. The normal operating pressure in the peripheral venous compartment is usually very close to mean circulatory filling pressure. Moreover, the

same factors that influence mean circulatory filling pressure have essentially equal influences on peripheral venous pressure. Thus "peripheral venous pressure" can be viewed as essentially equivalent to "mean circulatory filling pressure." The blood flow rate between the peripheral venous compartment and the central venous compartment is governed by the basic flow equation ($\dot{Q} = \Delta P/R$), where ΔP is the pressure drop between the peripheral and central venous compartments and R is the small resistance associated with the peripheral veins. In the example of Figure 8–3, peripheral venous pressure is assumed to be 7 mmHg. Thus, there will be no venous return when the central venous pressure (P_{CV}) is also 7 mmHg as shown in Figure 8–3B.

Figure 8–3.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

A: Factors influencing venous return. B: The venous function curve.

If the peripheral venous pressure remains at 7 mmHg, decreasing central venous pressure will increase the pressure drop across the venous resistance and consequently cause an elevation in venous return. This relationship is summarized by the *venous function curve*, which shows how venous return increases as central venous pressure drops.[2] If central venous pressure reaches very low values and falls below the intrathoracic pressure, the veins in the thorax collapse and tend to limit venous return. In the example of Figure 8–3, intrathoracic pressure is taken to be 0 mmHg and the flat portion

of the venous function curve indicates that lowering central venous pressure below 0 mmHg produces no additional increase in venous return.

Just as a cardiac function curve shows how central venous pressure influences cardiac output, *a venous function curve shows how central venous pressure influences venous return.* [3]

[2] The slope of the venous function curve is determined by the value of the venous vascular resistance. Lowering the venous vascular resistance would tend to raise the venous function curve and make it steeper because more venous return would result for a given difference between P_{PV} and P_{CV}. However, if P_{PV} is 7 mmHg, venous return will be 0 L/min when P_{CV} = 7 mmHg at any level of venous vascular resistance ($\dot{Q} = \Delta P/R$). We have chosen to ignore the complicating issue of changes in venous vascular resistance because they do not affect the general conclusions to be drawn from the discussion of venous function curves.

[3] Graphic relationships are almost invariably plotted with the *independent* variable on the horizontal axis (abscissa) and the *dependent* variable on the vertical axis (ordinate) and they MUST be read in that sense. For example, Figure 8–3B says that increasing central venous pressure tends to cause decreased venous return. Figure 8–3B DOES NOT imply that increasing venous return will tend to lower central venous pressure.

INFLUENCE OF PERIPHERAL VENOUS PRESSURE ON VENOUS RETURN

As can be deduced from Figure 8–3A, it is the pressure difference between the peripheral and central venous compartments that determines venous return. Therefore, an increase in peripheral venous pressure can be just as effective in increasing venous return as a drop in central venous pressure.

The two ways in which peripheral venous pressure can change were discussed in Chapter 6. First, because veins are elastic vessels, changes in the *volume* of blood contained within the peripheral veins alter the peripheral venous pressure. Moreover, because the veins are much more compliant than any other vascular segment, changes in circulating blood volume produce larger changes in the volume of blood in the veins than in any other vascular segment. For example, blood loss by hemorrhage or loss of body fluids through severe sweating, vomiting, or diarrhea will decrease circulating blood volume and significantly reduce the volume of blood contained in the veins and thus decrease the peripheral venous pressure. Conversely, transfusion, fluid retention by the kidney, or transcapillary fluid reabsorption will increase circulating blood volume and venous blood volume. Whenever circulating blood volume increases, so does peripheral venous pressure.

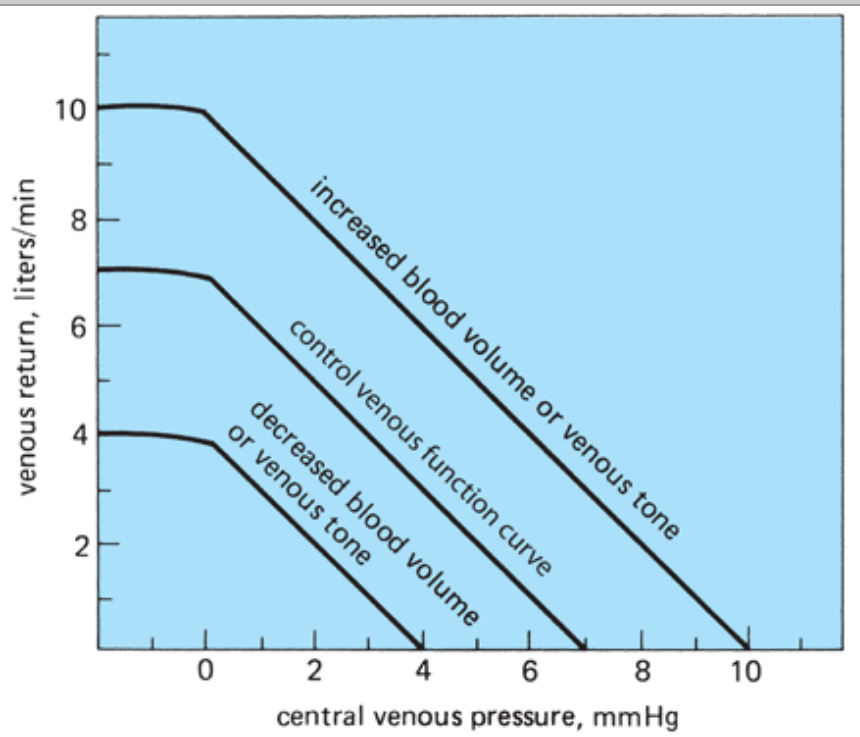
Recall from Chapter 7 that the second way that peripheral venous pressure can be altered is through changes in venous tone produced by increasing or decreasing the activity of sympathetic vasoconstrictor nerves supplying the venous smooth muscle.

Peripheral venous pressure increases whenever the activity of sympathetic vasoconstrictor fibers to veins increases. In addition, an increase in any force compressing veins from the outside has the same effect on the pressure inside veins as an increase in venous tone. Thus, such things as muscle exercise and wearing elastic stockings tend to elevate peripheral venous pressure.

Whenever peripheral venous pressure is altered, the relationship between central venous pressure and venous return is also altered. For example, whenever peripheral venous pressure is elevated by increases in blood volume or by sympathetic stimulation, the venous function curve shifts upward and to the right (Figure 8–4). This phenomenon can be most easily understood by focusing first on the central venous pressure at which there will be no venous return. When peripheral venous pressure is 7

mmHg, venous return is 0 L/min when central venous pressure is 7 mmHg. When peripheral venous pressure is increased to 10 mmHg, considerable venous return occurs with a central venous pressure of 7 mmHg, and venous return stops only when central venous pressure is raised to 10 mmHg. Thus, increasing peripheral venous pressure shifts the whole venous function curve to the right. By similar logic, decreased peripheral venous pressure caused by blood loss or decreased sympathetic vasoconstriction of peripheral veins shifts the venous function curve to the left (Figure 8–4).

Figure 8–4.



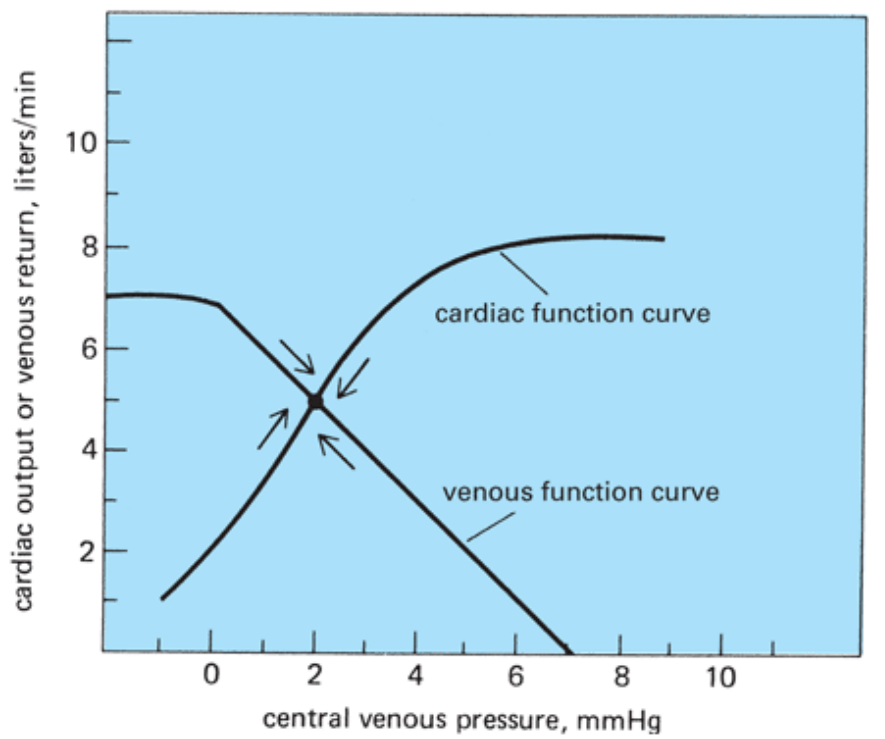
Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Effect of changes in blood volume and venous tone on venous function curves.

DETERMINATION OF CARDIAC OUTPUT & VENOUS RETURN BY CENTRAL VENOUS PRESSURE

The significance of the fact that central venous pressure simultaneously affects both cardiac output and venous return can be best seen by plotting the cardiac function curve (the Starling curve) and the venous function curve on the same graph, as in Figure 8–5.

Figure 8–5.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Interaction of cardiac output and venous return through central venous pressure.

Central venous pressure, as defined earlier, is the filling pressure of the right heart. Strictly speaking, this pressure directly affects only the stroke volume and output of the *right* heart pump. In most contexts, however, "cardiac output" implies the output of the *left* heart pump. How is it then, as has often been previously implied, that central venous pressure (the filling pressure of the right heart) profoundly affects cardiac output (the output of the left heart)? The short answer is that in the steady state, the right and left hearts have equal outputs. (Since the right and left hearts always beat with identical rates, this implies that their stroke volumes must be equal in the steady state.) The proper answer is that changes in central venous pressure automatically cause essentially parallel changes in the filling pressure of the left heart (ie, in left atrial pressure). Consider, for example, the following sequence of consequences that a small step-wise increase in central venous pressure has on a heart that previously was in a steady state:

1. Increased central venous pressure.

2. Increased right ventricular stroke volume via Starling's law.

3. Increased output of right heart.

4. Right heart output temporarily exceeds that of the left heart.

5. As long as this imbalance exists, blood accumulates in the pulmonary vasculature and raises pulmonary venous and left atrial pressure.

6. Increased left atrial pressure increases left ventricular stroke volume via Starling's law.

7. Very quickly, a new steady state will be reached when left atrial pressure has risen sufficiently to make left ventricular stroke volume exactly equal to the increased right ventricular stroke volume.

The major conclusion here is that left atrial pressure will automatically change in the correct direction to match left ventricular stroke volume to the current right ventricular stroke volume. Consequently, it is usually an acceptable simplification to say that central venous pressure affects cardiac output as if the heart consisted only of a single pump.

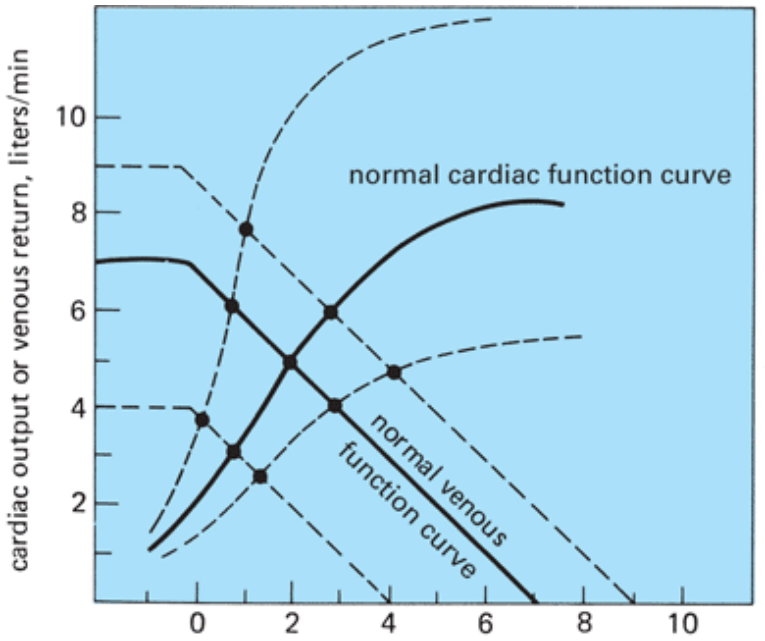
Note that in Figure 8–5, cardiac output and venous return are equal (at 5 L/min) *only* when the central venous pressure is 2 mmHg. If central venous pressure were to decrease to 0 mmHg for any reason, cardiac output would fall (to 2 L/min) and venous return would increase (to 7 L/min). With a venous return of 7 L/min and a cardiac output of 2 L/min, the volume of the central venous compartment would necessarily be increasing and this would produce a progressively increasing central venous pressure. In this manner, central venous pressure would return to the original level (2 mmHg) in a very short time. Moreover, if central venous pressure were to increase from 2 mmHg to 4 mmHg for any reason, venous return would decrease (to 3 L/min) and cardiac output would increase (to 7 L/min). This would quickly reduce the volume of blood in the central venous pool, and the central venous pressure would soon fall back to the original level. The cardiovascular system automatically adjusts to operate at the point where the cardiac and venous function curves intersect.



Central venous pressure is always inherently driven to the value that makes cardiac output and venous return equal. Cardiac output and venous return always stabilize at the level where the cardiac function and venous function curves intersect.

In order to fulfill its homeostatic role in the body, the cardiovascular system must be able to alter its cardiac output. Recall from Chapter 3 that cardiac output is affected by more than just cardiac filling pressure and that at any moment the heart may be operating on any one of a number of cardiac function curves, depending on the existing level of cardiac sympathetic tone (Figure 3–9). The family of possible cardiac function curves may be plotted along with the family of possible venous function curves, as shown in Figure 8–6. At a particular moment, the existing influences on the heart dictate the particular cardiac function curve on which it is operating, and similarly, the existing influences on peripheral venous pressure dictate the particular venous function curve that applies. Thus, the influences on the heart and on the peripheral vasculature determine where the cardiac and venous function curves intersect and thus what the central venous pressure and cardiac output (and venous return) are in the steady state. In the intact cardiovascular system, cardiac output can rise only when the point of intersection of the cardiac and venous function curves is raised. *All changes in cardiac output are caused by a shift in the cardiac function curve, a shift in the venous function curve, or both.*

Figure 8–6.

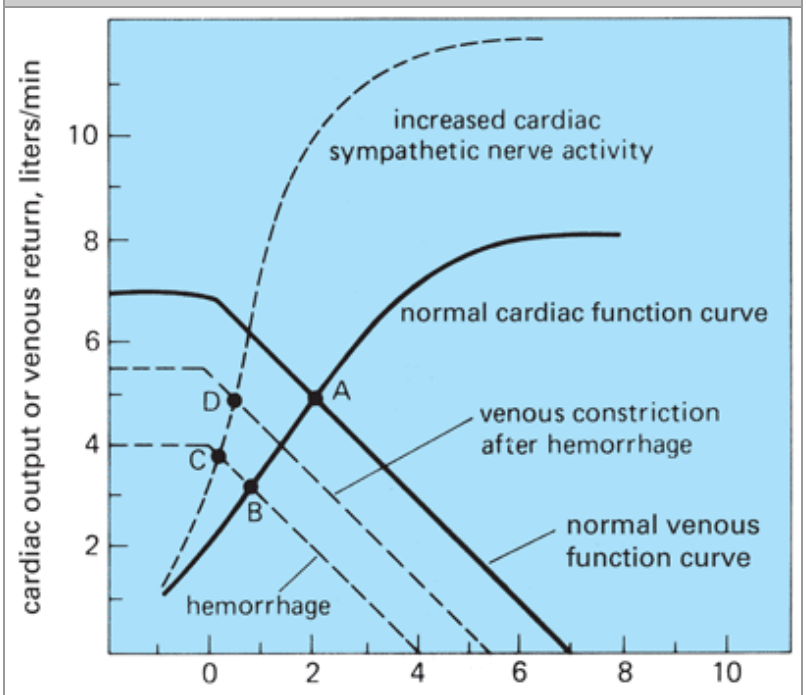


Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Families of cardiac function and venous function curves. Intersection points indicate equilibrium values for cardiac output, venous return, and central venous pressure.

The cardiac function and venous function curves are useful for understanding the complex interactions that occur in the intact cardiovascular system. With the help of Figure 8–7, let us consider, for example, what happens to the cardiovascular system when there is a significant loss of blood (hemorrhage). Assume that before the hemorrhage, sympathetic activity to the heart and peripheral vessels is normal, as is the blood volume. Therefore, cardiac output is related to central venous pressure as indicated by the "normal" cardiac function curve in Figure 8–7. In addition, venous return is determined by central venous pressure as indicated by the "normal" venous function curve shown. The normal cardiac and venous function curves intersect at point A, so cardiac output is 5 L/min and central venous pressure is 2 mmHg in the normal state. When blood volume decreases due to hemorrhage, the peripheral venous pressure falls and the venous function curve is shifted to the left. In the absence of any cardiovascular responses, the cardiovascular system must switch its operation to point B because this is now the point at which the cardiac function curve and the new venous function curve intersect. This automatically occurs because at the moment of blood loss, the venous function curve is shifted to the left and venous return falls below cardiac output at the central venous pressure of 2 mmHg. This is what leads to the fall in the central venous compartment's volume and pressure that causes the shift in operation from point A to point B. Note by comparing points A and B in Figure 8–7 that blood loss itself lowers cardiac output and central venous pressure by shifting the venous function curve. In going from point A to point B, cardiac output falls solely because of decreased filling pressure and Starling's law of the heart.

Figure 8–7.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Cardiovascular adjustments to hemorrhage.

Subnormal cardiac output evokes a number of cardiovascular compensatory mechanisms to bring cardiac output back to more normal levels. One of these compensatory mechanisms is an increase in the activity of cardiac sympathetic nerves which, as discussed in Chapter 3, shifts the heart's operation to a cardiac function curve that is higher than normal. The effect of increasing cardiac sympathetic activity is illustrated by a shift in cardiovascular operation from point B to point C. In itself, the increased cardiac sympathetic nerve activity increases cardiac output (from 3 to 4 L/min) but causes a further decrease in central venous pressure. This drop in central venous pressure occurs because points B and C lie on the same venous function curve. *Cardiac* sympathetic nerves do not affect the venous function curve.[4]

An additional compensatory mechanism evoked by blood loss is increased activity of the sympathetic nerves leading to veins. Recall that this raises peripheral venous pressure and causes a rightward shift of the venous function curve. Therefore, increased sympathetic activity to veins tends to shift the venous function curve, originally lowered by blood loss, back toward normal. As a consequence of the increased peripheral venous tone and the shift to a more normal venous function curve, the cardiovascular operation shifts from point C to point D in Figure 8–7. Thus, peripheral venous constriction increases cardiac output by raising central venous pressure and moving the heart's operation upward along a fixed cardiac function curve. It must be pointed out that separating the response to hemorrhage into distinct, progressive steps (ie, A to B to C to D) is only a conceptualization for appreciating the individual effects of the different processes involved. In reality, the reflex venous and cardiac responses occur simultaneously and so quickly that they will easily keep up with the blood loss as it occurs. Thus, the actual course of a patient's net response to hemorrhage would follow nearly a straight line from point A to point D.

In summary, point D illustrates that normal cardiac output can be sustained in the face of blood loss by the combined effect of peripheral and cardiac adjustments. Hemorrhage is only one of an almost infinite variety of disturbances to the cardiovascular system. Plots such as those shown in Figure 8–7 are very useful for understanding the many disturbances to the cardiovascular system and the ways in which they may be compensated.

[4]Venous return is higher at point C than at point B, but the venous function curve has not shifted.

CLINICAL IMPLICATIONS OF ABNORMAL CENTRAL VENOUS PRESSURES

Although, in the clinical situation, there is no way to actually determine the position of either cardiac function or venous function curves, important information about the patient's circulatory status can be obtained from measures of central venous pressure. From what has been presented in this chapter, it is possible to conclude that a patient with *abnormally high* central venous pressure must have either a depressed cardiac function curve, a right-shifted venous function curve, or both. As will be discussed in Chapter 11, very high central venous pressures are a hallmark of patients with congestive heart failure because they have the combination of dysfunctional heart muscle (depressed cardiac function curve) *and* excessive fluid volume (right-shifted venous function curve). *Abnormally low* central venous pressures, on the other hand, could theoretically be caused either an elevated cardiac function curve or a left-shifted venous function curve. The clinical reality is that abnormally low central venous pressures are invariably the result of a left shift of the venous function curve caused either by low blood volume or lack of venous tone.

Rough estimates of a patient's central venous pressure can be obtained quite easily by observing the external jugular veins. Because the force of gravity tends to keep veins in the head and neck collapsed when an individual is in an upright position, there should be no distention (or retrograde pulsations from atrial contractions) observed in these neck veins. Conversely, when an individual is fully recumbent, the neck veins should be full and pulsations should be easily detected. Because normal central venous pressure is about 2 mmHg (7 cm H_2O), the veins normally will be filled about 7 cm above the right atrium. If a normal individual is placed in a semirecumbent position so that the external jugular veins are positioned at 7 cm above the right atrium, the point between the collapsed venous segment and the filled segment can be visualized. Abnormally high central venous pressures will be associated with neck vein distention at a higher level (perhaps even when the patient is upright).

Because of its diagnostic value in critical care situations, central venous pressure is often monitored continuously via a catheter that is inserted in a peripheral vein and advanced centrally until its tip is in the central venous compartment (ie, near or in the right atrium). In some situations, it is desirable to assess*left atrial* pressure, which is the filling pressure for the left side of the heart. This is commonly done with a specialized flow-directed venous catheter that uses a small inflatable balloon at its tip to drag it with the blood flow through the right ventricle and pulmonic valve into the pulmonary artery. The balloon is then deflated and the cannula is advanced further until it wedges into a terminal branch of the pulmonary vasculature. The *pulmonary wedge pressure* recorded at this junction provides a useful estimate of left atrial pressure.

KEY CONCEPTS


Mean circulatory filling pressure is a theoretical measure of pressure in the systemic circuit when flow is stopped and is influenced primarily by blood volume and peripheral venous tone.


Central venous pressure has a negative influence on venous return that can be illustrated graphically as a venous function curve.


Peripheral venous pressure has a positive influence on venous return and can be elevated by increased blood volume and/or increased venous tone.


Because of its opposing influences on cardiac output and venous return, central venous pressure automatically assumes a value that makes cardiac output and venous return equal.


Central venous pressure gives clinically relevant information about circulatory status.


Central venous pressure can be estimated noninvasively by noting the fullness of a patient's jugular veins.

STUDY QUESTIONS

8–1. Which of the following will decrease the mean circulatory filling pressure?

a. Increased circulating blood volume

b. Decreased arteriolar tone

c. Increased venous tone

8–2. What determines central venous pressure?

8–3. According to the Starling's law, cardiac output always decreases when central venous pressure decreases. True or false?

8–4. In a steady state, venous return will be greater than cardiac output when

a. Peripheral venous pressure is higher than normal

b. Blood volume is higher than normal

c. Cardiac sympathetic nerve activity is lower than normal

8–5. What approaches might a physician logically pursue in an attempt to lower a patient's cardiac preload?

See answers.

SUGGESTED READINGS

Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves.*Physiol Rev.* 1955;35:123. [PMID: 14356924]

Hainsworth R. The importance of vascular capacitance in cardiovascular control. *News Physiol Sci.* 1990;5:250–254.

Rothe CF. Mean circulatory filling pressure: its meaning and measurement. *J Appl Physiol.* 1993;74:499–509. [PMID: 8458763]

Rowell LB. The venous system. *Human Circulation: Regulation During Physical Stress.* New York, NY: Oxford University Press; 1986:44–77.

Sarnoff SJ. Myocardial contractility as described by cardiac function curves. *Physiol Rev.* 1955;35:107. [PMID: 14356923]

Shoukas AA, Bohlen HG. Rat venular pressure-diameter relationships are regulated by sympathetic activity.*Am J Physiol.* 1990;259:H674–H680.

Tyberg JV. How changes in venous capacitance modulate cardic output. *Pflugers Arch.* 2002;445:10–17. [PMID: 12397381]

Ursino M, Antonucci M, Belardinelli E. Role of active changes in venous capacity by the carotid baroreflex: analysis with a mathematical method. *Am J Physiol.* 1994;267:H2531–H2546.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.
Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.

Medical a silverchair information system The McGraw-Hill Companies

McGraw-Hill's ACCESSMedicine

Print Close Wind

Note: Large images and tables on this page may necessitate printing in landscape mode.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.

OBJECTIVES

The student understands the mechanisms involved in the short-term regulation of arterial pressure:

- *Identifies the sensory receptors, afferent pathways, central integrating centers, efferent pathways, and effector organs that participate in the arterial baroreceptor reflex.*
- *States the location of the arterial baroreceptors and describes their operation.*
- *Describes how changes in the afferent input from arterial baroreceptors influence the activity of the sympathetic and parasympathetic preganglionic fibers.*
- *Describes how the sympathetic and parasympathetic outputs from the medullary cardiovascular centers change in response to changes in arterial pressure.*
- *Diagrams the chain of events that are initiated by the arterial baroreceptor reflex to compensate for a change in arterial pressure.*
- *Describes how inputs to the medullary cardiovascular centers from cardiopulmonary baroreceptors, arterial and central chemoreceptors, receptors in skeletal muscle, the cerebral cortex, and the hypothalamus influence sympathetic activity, parasympathetic activity, and mean arterial pressure.*
- *Describes and indicates the mechanisms involved in the Bezold-Jarisch reflex, the cerebral ischemic response, the Cushing reflex, the alerting reaction, blushing, vasovagal syncope, the dive reflex, and the cardiovascular responses to emotion and pain.*
- *Graphs the relationships between mean arterial pressure and sympathetic nerve activity that describe the overall operation of (1) the heart and peripheral vessels and (2) the arterial baroreceptors plus the medullary cardiovascular centers. Uses the graphs to do the following:*
  - *State what determines the normal mean arterial pressure and the normal level of sympathetic nerve activity.*
  - *Indicate how the relationship between sympathetic nerve activity and arterial pressure is shifted by a disturbance on the heart or vessels and how this alters the operating point within the arterial baroreceptor reflex control system.*
  - *Indicate how the relationship between mean arterial pressure and sympathetic nerve activity is altered by inputs to the medullary cardiovascular centers not from arterial baroreceptors and how these shift the operating point within the arterial baroreceptor reflex control system.*

The student understands the mechanisms involved in the long-term regulation of arterial pressure:

- *Describes baroreceptor adaptation.*
- *Describes the influence of changes in body fluid volume on arterial pressure and diagrams the steps involved in this process.*
- *Indicates the mechanisms whereby altered arterial pressure alters glomerular filtration rate and renal tubular function to influence urinary output.*

- *Describes how mean arterial pressure is adjusted in the long term to that which causes fluid output rate to equal fluid intake rate.*

REGULATION OF ARTERIAL PRESSURE: INTRODUCTION

Appropriate systemic arterial pressure is perhaps the single most important requirement for proper operation of the cardiovascular system. Without sufficient arterial pressure, the brain and the heart do not receive adequate blood flow no matter what adjustments are made in their vascular resistance by local control mechanisms. In contrast, unnecessary demands are placed on the heart by excessive arterial pressure. The elaborate mechanisms that have evolved for regulating this critical cardiovascular variable will be discussed in this chapter.

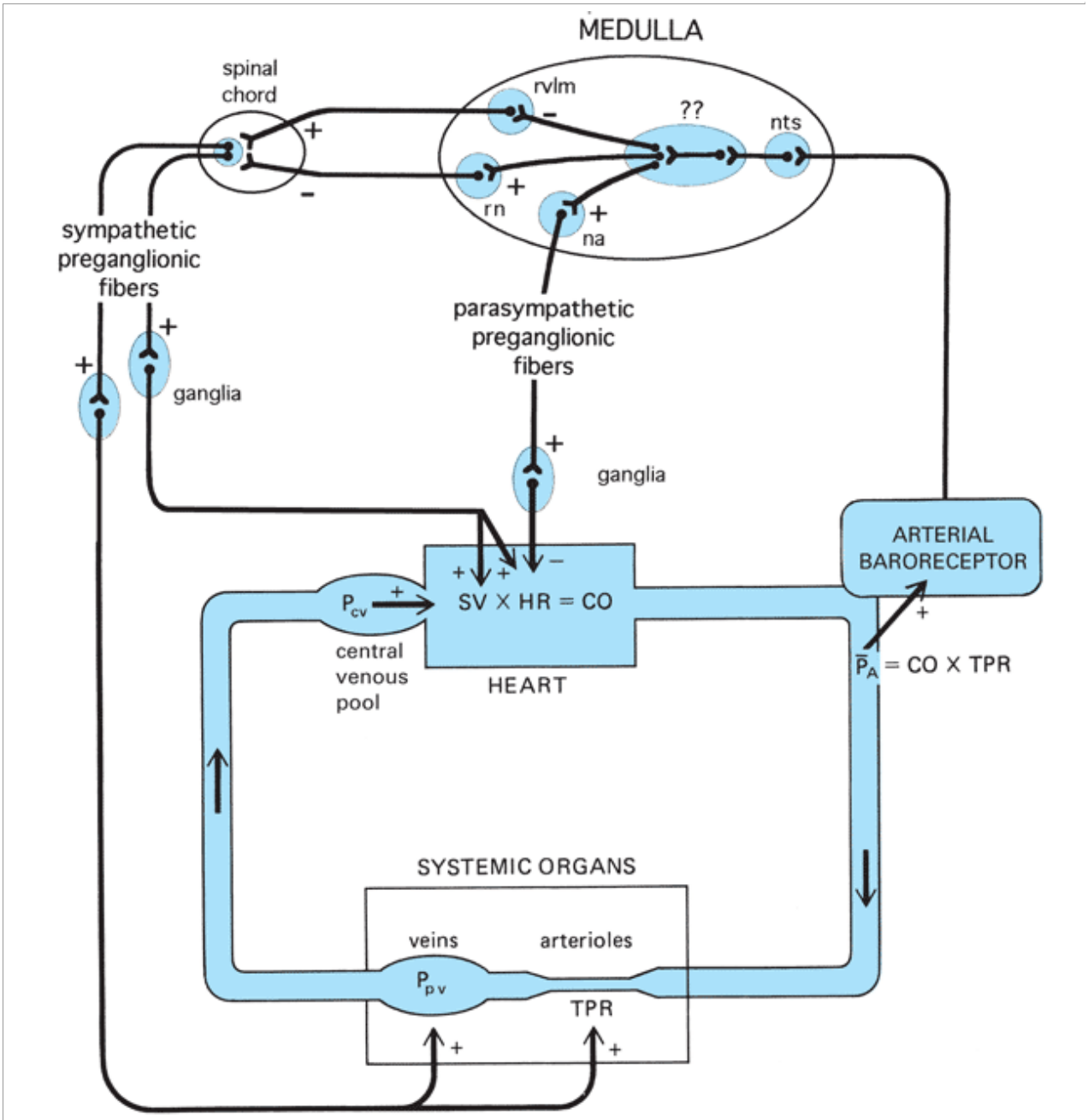
Arterial pressure is continuously monitored by various sensors located within the body. Whenever arterial pressure varies from normal, multiple reflex responses are initiated which cause the adjustments in cardiac output and total peripheral resistance needed to return arterial pressure to its normal value. In the short term (seconds), these adjustments are brought about by changes in the activity of the autonomic nerves leading to the heart and peripheral vessels. In the long term (minutes to days), other mechanisms such as changes in cardiac output brought about by changes in blood volume play an increasingly important role in the control of arterial pressure. The short- and long-term regulation of arterial pressure will be discussed in order in this chapter.

SHORT-TERM REGULATION OF ARTERIAL PRESSURE

Arterial Baroreceptor Reflex

The *arterial baroreceptor reflex* is the single most important mechanism providing short-term regulation of arterial pressure. Recall that the usual components of a reflex pathway include sensory receptors, afferent pathways, integrating centers in the central nervous system, efferent pathways, and effector organs. As shown in Figure 9–1, the efferent pathways of the arterial baroreceptor reflex are the cardiovascular sympathetic and cardiac parasympathetic nerves. The effector organs are the heart and peripheral blood vessels.

Figure 9–1.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Components of the arterial baroreceptor reflex pathway. nts, nucleus tractus solitarius; rvlm, rostral ventrolateral medullary group; rn, raphé nucleus; na, nucleus ambiguus; ??, incompletely mapped integration pathways that may also involve structures outside the medulla.

EFFERENT PATHWAYS

Previous chapters have discussed the many actions of the sympathetic and parasympathetic nerves leadin to the heart and blood vessels. For both systems, *postganglionic fibers,* whose cell bodies are in ganglia outside the central nervous system, form the terminal link to the heart and vessels. The influences of thes postganglionic fibers on key cardiovascular variables are summarized in Figure 9–1.

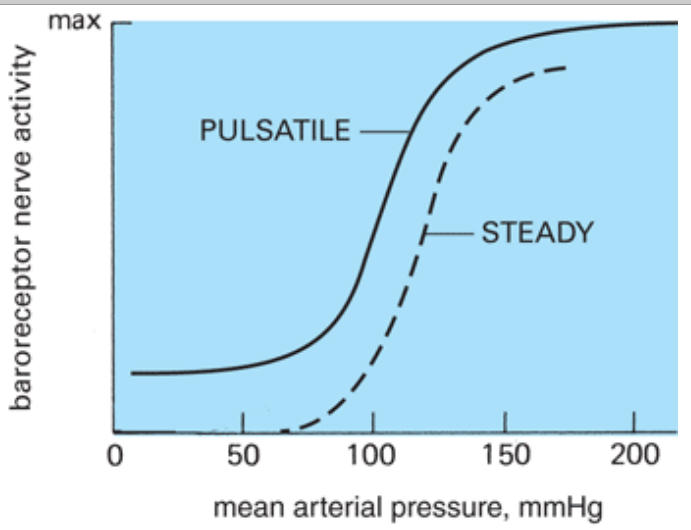
The activity of the terminal postganglionic fibers of the autonomic nervous system is determined by the

activity of *preganglionic fibers* whose cell bodies lie within the central nervous system. In the sympathetic pathways, the cell bodies of the preganglionic fibers are located within the spinal cord. These preganglionic neurons have spontaneous activity that is modulated by excitatory and inhibitory inputs, which arise from centers in the brainstem and descend in distinct *excitatory* and *inhibitory* spinal pathways. In the parasympathetic system, the cell bodies of the preganglionic fibers are located within the brainstem. Their spontaneous activity is modulated by inputs from adjacent centers in the brainstem.

AFFERENT PATHWAYS

Sensory receptors, called *arterial baroreceptors,* are found in abundance in the walls of the aorta and carotid arteries. Major concentrations of these receptors are found near the arch of the aorta (the *aortic baroreceptors*) and at the bifurcation of the common carotid artery into the internal and external carotid arteries on either side of the neck (the *carotid sinus baroreceptors*). The receptors themselves are mechanoreceptors that sense arterial pressure indirectly from the degree of stretch of the elastic arterial walls.[1] In general, *increased stretch causes an increased action potential generation rate by the arterial baroreceptors.* Baroreceptors actually sense not only absolute stretch but also the rate of change of stretch. For this reason, both the mean arterial pressure and arterial pulse pressure affect baroreceptor firing rate as indicated in Figure 9–2. The dashed curve in Figure 9–2 shows how baroreceptor firing rate is affected by different levels of a steady arterial pressure. The solid curve in Figure 9–2 indicates how baroreceptor firing rate is affected by the mean value of a pulsatile arterial pressure. Note that the presence of pulsations (that of course are normal) increases the baroreceptor firing rate at any given level of mean arterial pressure. Note also that changes in mean arterial pressure near the normal value of 100 mmHg produce the largest changes in baroreceptor discharge rate.

Figure 9–2.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Effect of mean arterial pressure on baroreceptor nerve activity.

If arterial pressure remains elevated over a period of several days for some reason, the arterial baroreceptor firing rate will gradually return toward normal. Thus, arterial baroreceptors are said to *adapt* to long-term changes in arterial pressure. For this reason, the arterial baroreceptor reflex cannot serve as mechanism for the long-term regulation of arterial pressure.

Action potentials generated by the carotid sinus baroreceptors travel through the carotid sinus nerves

(Hering's nerves), which join with the glossopharyngeal nerves (ninth cranial nerves) before entering the central nervous system. Afferent fibers from the aortic baroreceptors run to the central nervous system in the vagus nerves (tenth cranial nerves). (The vagus nerves contain both afferent and efferent fibers, including, for example, the parasympathetic efferent fibers to the heart.)

[1] Baroreceptor discharge rate can be enhanced by mechanical manipulation of the arterial walls. For example, the carotid sinus baroreceptor firing rate can be increased by massaging the neck over the carotid sinus area.

CENTRAL INTEGRATION

Much of the central integration involved in reflex regulation of the cardiovascular system occurs in the medulla oblongata in what are traditionally referred to as the *medullary cardiovascular centers.* The neural interconnections between the diffuse structures in this area are complex and not completely mapped. Moreover, these structures appear to serve multiple functions including respiratory control, for example. What is known with a fair degree of certainty is where the cardiovascular afferent and efferent pathways enter and leave the medulla. For example, as indicated in Figure 9–1, the afferent sensory information from the arterial baroreceptors enters the medullary *nucleus tractus solitarius,* where it is relayed via polysynaptic pathways to other structures in the medulla (and higher brain centers, such as the hypothalamus, as well). The cell bodies of the efferent vagal parasympathetic cardiac nerves are located primarily in the medullary *nucleus ambiguus.* The sympathetic autonomic efferent information leaves the medulla predominantly from the *rostral ventrolateral medulla* group of neurons (via an excitatory spinal pathway) or the *raphé nucleus* (via an inhibitory spinal pathway). The intermediate processes involved in the actual integration of the sensory information into appropriate sympathetic and parasympathetic responses are not well understood at present. Whereas much of this integration takes place within the medulla, higher centers such as the hypothalamus are probably involved as well. In this context, knowing the details of the integration process is not as important as appreciating the overall effects that changes in arterial baroreceptor activity have on the activities of parasympathetic and sympathetic cardiovascular nerves.



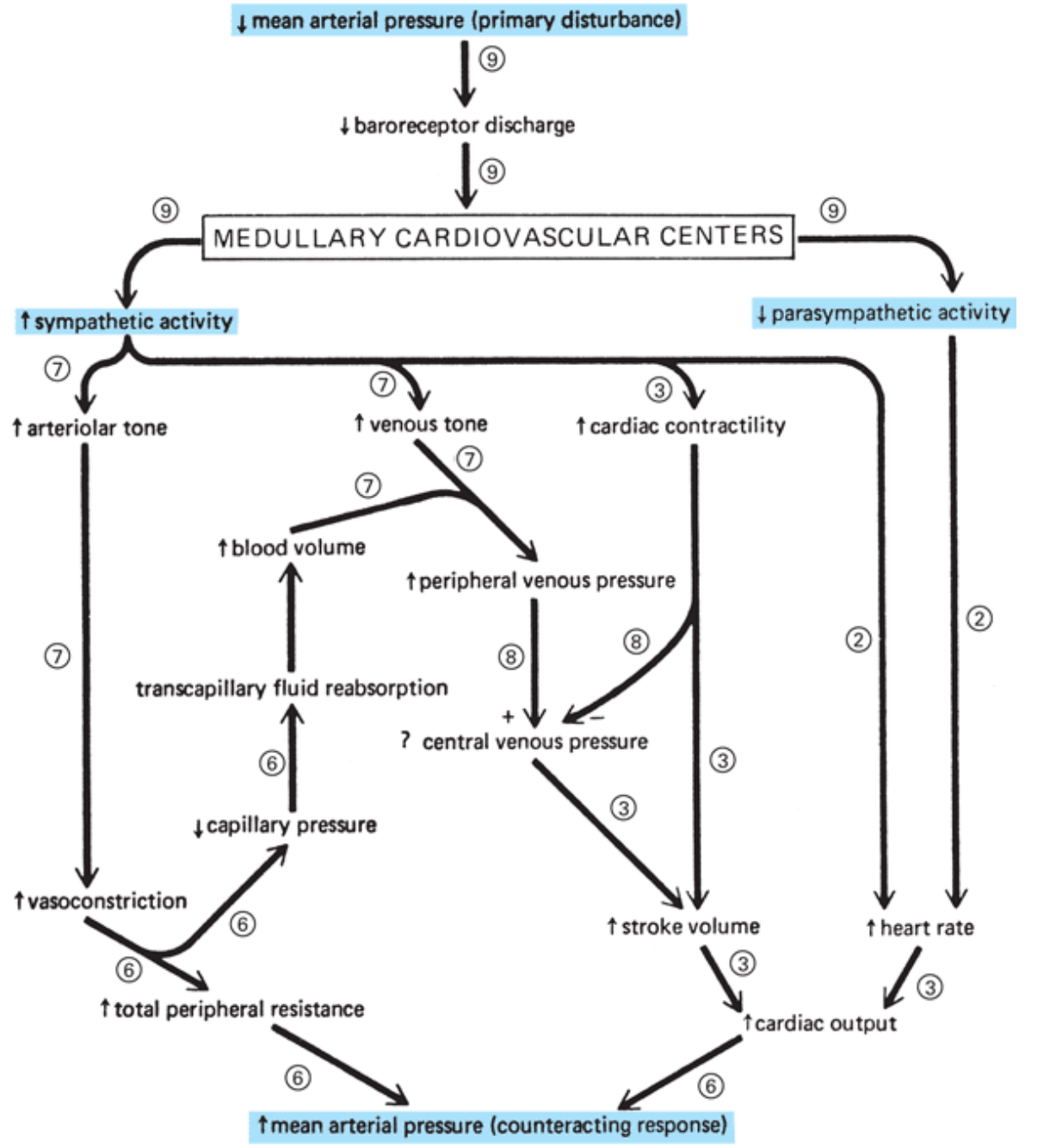
Several functionally important points about the central control of the autonomic cardiovascular nerves are illustrated in Figure 9–1. The major external influence on the cardiovascular centers comes from the arterial baroreceptors. Because the arterial baroreceptors are active at normal arterial pressures, they supply a tonic input to the central integration centers. As indicated in Figure 9–1, the integration process is such that increased input from the arterial baroreceptors tends to simultaneously: (1) inhibit the activity of the spinal sympathetic excitatory tract, (2) stimulate the activity of the spinal sympathetic inhibitory tract, and (3) stimulate the activity of parasympathetic preganglionic nerves. Thus, an increase in the arterial baroreceptor discharge rate (caused by increased arterial pressure) causes a decrease in the tonic activity of cardiovascular sympathetic nerves and a simultaneous increase in the tonic activity of cardiac parasympathetic nerves. Conversely, decreased arterial pressure causes increased sympathetic and decreased parasympathetic activity.

OPERATION OF THE ARTERIAL BARORECEPTOR REFLEX

The arterial baroreceptor reflex is a continuously operating control system that automatically makes adjustments to prevent disturbances on the heart and/or vessels from causing large changes in mean arterial pressure. The arterial baroreceptor reflex mechanism acts to regulate arterial pressure in a *negative feedback* manner that is analogous in many ways to the manner in which a thermostatically controlled home heating system operates to regulate inside temperature despite disturbances such as changes in the weather or open windows.[2]

Figure 9–3 shows many events in the arterial baroreceptor reflex pathway that occur in response to a disturbance of decreased mean arterial pressure. All of the events shown in Figure 9–3 have already been discussed, and each should be carefully examined (and reviewed if necessary) at this point because a grea many of the interactions that are essential to understanding cardiovascular physiology are summarized in this figure.

Figure 9–3.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Immediate cardiovascular adjustments caused by a decrease in arterial blood pressure. Circled numbers indicate the chapter in which each interaction is discussed.

Note in Figure 9–3 that the overall response of the arterial baroreceptor reflex to the disturbance of decreased mean arterial pressure is increased mean arterial pressure (ie, the response tends to counteract the disturbance). A disturbance of increased mean arterial pressure would elicit events exactly opposite to those shown in Figure 9–3 and produce the response of decreased mean arterial pressure; again, the response tends to counteract the disturbance. The homeostatic benefits of the reflex action should be apparent.

One should recall that nervous control of vessels is more important in some areas such as the kidney, the skin, and the splanchnic organs than in the brain and heart muscle. Thus, the reflex response to a fall in arterial pressure may, for example, include a significant increase in renal vascular resistance and a decrease in renal blood flow without changing the cerebral vascular resistance or blood flow. The peripheral vascular adjustments associated with the arterial baroreceptor reflex take place primarily in organs with strong sympathetic vascular control.

[2] In this analogy, arterial pressure is likened to temperature; the heart is the generator of pressure as the furnace is the generator of heat; dilated arterioles dissipate arterial pressure like open windows lose heat; the arterial baroreceptors monitor arterial pressure as the sensor of a thermostat monitors temperature; and the electronics of the thermostat control the furnace as the medullary cardiovascular centers regulate the operation of the heart. Because home thermostats do not usually also regulate the operation of windows, there is no analogy to the reflex medullary control of arterioles. The pressure that the arterial baroreflex strives to maintain is analogous to the temperature setting on the thermostat dial.

Other Cardiovascular Reflexes & Responses

Seemingly in spite of the arterial baroreceptor reflex mechanism, large and rapid changes in mean arterial pressure occur in certain physiological and pathological situations. These reactions are caused by influences on the medullary cardiovascular centers *other* than those from the arterial baroreceptors. As outlined in the following sections, these inputs on the medullary cardiovascular centers arise from many types of peripheral and central receptors as well as from "higher centers" in the central nervous system such as the hypothalamus and the cortex.

The analogy was made earlier that the arterial baroreceptor reflex operates to control arterial pressure somewhat as a home heating system acts to control inside temperature. Such a system automatically acts to counteract changes in temperature caused by such things as an open window[3] or a dirty furnace. It does not, however, resist changes in temperature caused by someone's resetting of the thermostat dial—in fact the basic temperature regulating mechanisms cooperate wholeheartedly in adjusting the temperature to the new desired value. The temperature setting on a home thermostat's dial has a useful conceptual analogy in cardiovascular physiology often referred to as the "*set point*" for arterial pressure. *The many influences that are about to be discussed all influence arterial pressure as if they changed the arterial baroreceptor reflex's set point for pressure regulation.* Consequently, the arterial baroreceptor reflex does not resist these pressure disturbances but actually assists in producing them.

[3] In Minnesota, an open window is an obvious temperature lowering disturbance.

REFLEXES FROM RECEPTORS IN HEART & LUNGS

A host of mechanoreceptors and chemoreceptors that can elicit reflex cardiovascular responses have been identified in the atria, ventricles, coronary vessels, and lungs. The role of these *cardiopulmonary receptors* in the neurohumoral control of the cardiovascular system is, in most cases, incompletely understood, but evidence is accumulating that they may be involved significantly in many physiological and pathological

states.

One general function that the cardiopulmonary receptors perform is sensing the pressure (or volume) in the atria and central venous pool. Increased central venous pressure and volume cause receptor activation by stretch, which elicits a reflex decrease in sympathetic activity. Decreased central venous pressure produces the opposite response. Whatever the details, it is clear that cardiopulmonary baroreflexes normally exert a tonic inhibitory influence on sympathetic activity and play an arguably important, but not yet completely defined, role in normal cardiovascular regulation.

Certain other reflexes originating from receptors in the cardiopulmonary region have been described that may be important in specific pathological situations. For example, the *Bezold-Jarisch* reflex that involves marked bradycardia and hypotension is elicited by application of strong stimuli to coronary vessel (or myocardial) chemoreceptors concentrated primarily in the posterior wall of the left ventricle. There is mucl clinical evidence that myocardial infarctions involving this region of the ventricle can elicit the Bezold-Jarisch reflex and cause certain myocardial infarction patients to present with bradycardia. (Far more commonly, patients with myocardial infarction have hypotension, as would be expected from compromised myocardial function, and *tachycardia* as would be expected from an arterial baroreceptor response to hypotension.)

CHEMORECEPTOR REFLEXES

Low P_{O_2} and/or high P_{CO_2} levels in the arterial blood cause reflex increases in respiratory rate *and* mean arterial pressure. This appears to be a result of increased activity of *arterial chemoreceptors,* located in the carotid arteries and the arch of the aorta, and *central chemoreceptors,* located somewhere within the central nervous system. Chemoreceptors probably play little role in the normal regulation of arterial pressure because arterial blood P_{O_2} and P_{CO_2} are normally held very nearly constant by respiratory control mechanisms.

An extremely strong reaction called the *cerebral ischemic response* is triggered by inadequate brain blood flow (ischemia) and can produce a more intense sympathetic vasoconstriction and cardiac stimulation than is elicited by any other influence on the cardiovascular control centers. Presumably the cerebral ischemic response is initiated by chemoreceptors located within the central nervous system. However, if cerebral blood flow is severely inadequate for several minutes, the cerebral ischemic response wanes and is replaced by marked loss of sympathetic activity. Presumably this situation results when function of the nerve cells in the cardiovascular centers becomes directly depressed by the unfavorable chemical conditions in the cerebrospinal fluid.

Whenever intracranial pressure is increased—for example, by tumor growth or trauma-induced bleeding within the rigid cranium—there is a parallel rise in arterial pressure. This is called the *Cushing reflex.* It can cause mean arterial pressures of more than 200 mmHg in severe cases of intracranial pressure elevation. The obvious benefit of the Cushing reflex is that it prevents collapse of cranial vessels and thus preserves adequate brain blood flow in the face of large increases in intracranial pressure. The mechanisms responsible for the Cushing reflex are not known but could involve the central chemoreceptors.

REFLEXES FROM RECEPTORS IN EXERCISING SKELETAL MUSCLE

Reflex tachycardia and increased arterial pressure can be elicited by stimulation of certain afferent fibers from skeletal muscle. These pathways may be activated by chemoreceptors responding to muscle ischemia which occurs with strong, sustained static (isometric) exercise. This input may contribute to the marked increase in blood pressure that accompanies such isometric efforts. It is uncertain as to what extent this reflex contributes to the cardiovascular responses to dynamic (rhythmic) muscle exercise.

THE DIVE REFLEX

Aquatic animals respond to diving with a remarkable bradycardia and intense vasoconstriction in all systemic organs except the brain and heart. The response serves to allow prolonged submersion by limitin the rate of oxygen use and by directing blood flow to essential organs. A similar but less dramatic dive reflex can be elicited in humans by simply immersing the face in water. (Cold water enhances the response.) The response involves the unusual combination of bradycardia produced by enhanced cardiac parasympathetic activity and peripheral vasoconstriction caused by enhanced sympathetic activity that is a rare exception to the general rule that sympathetic and parasympathetic nerves are activated in reciprocal fashion. The dive reflex is sometimes used clinically (as is massage of the neck over the carotid sinus) to reflexly activate cardiac parasympathetic nerves for the purpose of interrupting atrial tachyarrhythmias.

CARDIOVASCULAR RESPONSES ASSOCIATED WITH EMOTION

Cardiovascular responses are frequently associated with certain states of emotion. These responses originate in the cerebral cortex and reach the medullary cardiovascular centers through corticohypothalamic pathways. The least complicated of these responses is the *blushing* that is often detectable in individuals with lightly pigmented skin during states of embarrassment. The blushing response involves a loss of sympathetic vasoconstrictor activity *only* to particular cutaneous vessels, and this produces the blushing by allowing engorgement of the cutaneous venous sinuses.

Excitement or a sense of danger often elicits a complex behavioral pattern called the *alerting reaction* (also called the "defense" or "fight or flight" response). The alerting reaction involves a host of responses such a pupillary dilation and increased skeletal muscle tenseness that are generally appropriate preparations for some form of intense physical activity. The cardiovascular component of the alerting reaction is an increas in blood pressure caused by a general increase in cardiovascular sympathetic nervous activity and a decrease in cardiac parasympathetic activity. Centers in the *posterior hypothalamus* are presumed to be involved in the alerting reaction because many of the components of this multifaceted response can be experimentally reproduced by electrical stimulation of this area. The general cardiovascular effects are mediated via hypothalamic communications with the medullary cardiovascular centers.

Some individuals respond to situations of extreme stress by fainting, a situation referred to clinically as *vasovagal syncope.* The loss of consciousness is due to decreased cerebral blood flow that is itself produce by a sudden dramatic loss of arterial blood pressure that, in turn, occurs as a result of a sudden loss of sympathetic tone and a simultaneous large increase in parasympathetic tone and decrease in heart rate. The influences on the medullary cardiovascular centers that produce vasovagal syncope appear to come from the cortex via depressor centers in the *anterior hypothalamus.* It has been suggested that vasovagal syncope is analogous to the "playing dead" response to peril used by some animals. Fortunately, unconsciousness (combined with becoming horizontal) seems to quickly remove this serious disturbance to the normal mechanisms of arterial pressure control in humans.

The extent to which cardiovascular variables, in particular blood pressure, are normally affected by emotional state is currently a topic of extreme interest and considerable research. As yet the answer is unclear. However, the therapeutic value of being able, for example, to learn to consciously reduce one's blood pressure would be incalculable.

CENTRAL COMMAND

The term *central command* is used to imply an input from the cerebral cortex to lower brain centers during voluntary muscle exercise. The concept is that the same cortical drives that initiate somatomotor (skeletal muscle) activity also simultaneously initiate cardiovascular (and respiratory) adjustments appropriate to support that activity. In the absence of any other obvious causes, central command is at present the best explanation as to why both mean arterial pressure and respiration increase during voluntary exercise.

REFLEX RESPONSES TO PAIN

Pain can have either a positive or negative influence on arterial pressure. Generally, superficial or cutaneous pain causes a rise in blood pressure in a manner similar to that associated with the alerting response and perhaps over many of the same pathways. Deep pain from receptors in the viscera or joints, however, often causes a cardiovascular response similar to that which accompanies vasovagal syncope, ie, decreased sympathetic tone, increased parasympathetic tone, and a serious decrease in blood pressure. This response may contribute to the state of shock that often accompanies crushing injuries and/or joint displacement.

TEMPERATURE REGULATION REFLEXES

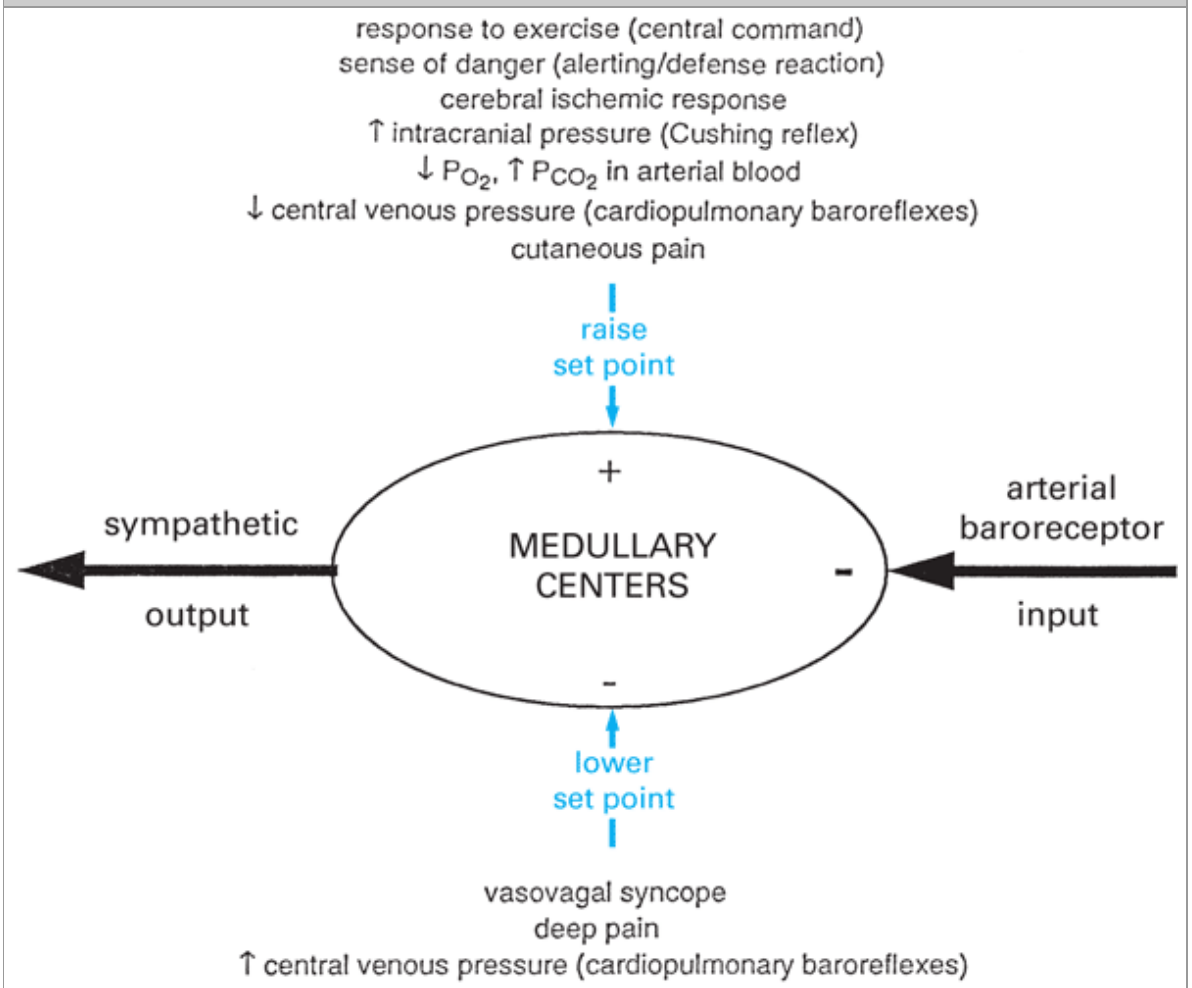
Certain special cardiovascular reflexes that involve the control of skin blood flow have evolved as part of the body temperature regulation mechanisms. Temperature regulation responses are controlled primarily by the hypothalamus, which can operate through the cardiovascular centers to discretely control the sympathetic activity to cutaneous vessels and thus skin blood flow. The sympathetic activity to cutaneous vessels is extremely responsive to changes in hypothalamic temperature. Measurable changes in cutaneou blood flow result from changes in hypothalamic temperature of tenths of a degree Celsius.

Cutaneous vessels are influenced by reflexes involved in both arterial pressure regulation and temperature regulation. When the appropriate cutaneous vascular responses for temperature regulation and pressure regulation are contradictory, as they are, for example, during strenuous exercise in a hot environment, then the temperature-regulating influences on cutaneous blood vessels usually prevail.

SUMMARY

Most of the influences on the medullary cardiovascular centers that have been discussed in the preceding sections are summarized in Figure 9–4. This figure is intended first to reemphasize that the arterial baroreceptors normally and continually supply the major input to the medullary centers. The arterial baroreceptor input is shown as inhibitory because an increase in arterial baroreceptor firing rate results in a decrease in sympathetic output. (Decreased sympathetic output should be taken to imply also simultaneous increase in parasympathetic output, which is not shown.) As indicated in Figure 9–4, the nonarterial baroreceptor influences on the medullary cardiovascular centers fall into two categories: (1) those that *increase* arterial pressure by raising the set point for the arterial baroreceptor reflex and thus cause an increase in sympathetic activity, and (2) those that *decrease* arterial pressure by lowering the se point for the arterial baroreceptor reflex and thus cause a decrease in sympathetic activity. Note that certain responses that have been discussed are not included in Figure 9–4. The complex combination of stimuli involved in the dive reflex cause simultaneous sympathetic and parasympathetic activation and cannot be simply classified as either pressure raising or pressure lowering. Also, temperature stimuli that discretely affect cutaneous vessels but not general cardiovascular sympathetic and parasympathetic activit have not been included in Figure 9–4.

Figure 9–4.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Summary of the factors that influence the set point of the arterial baroreceptor reflex.

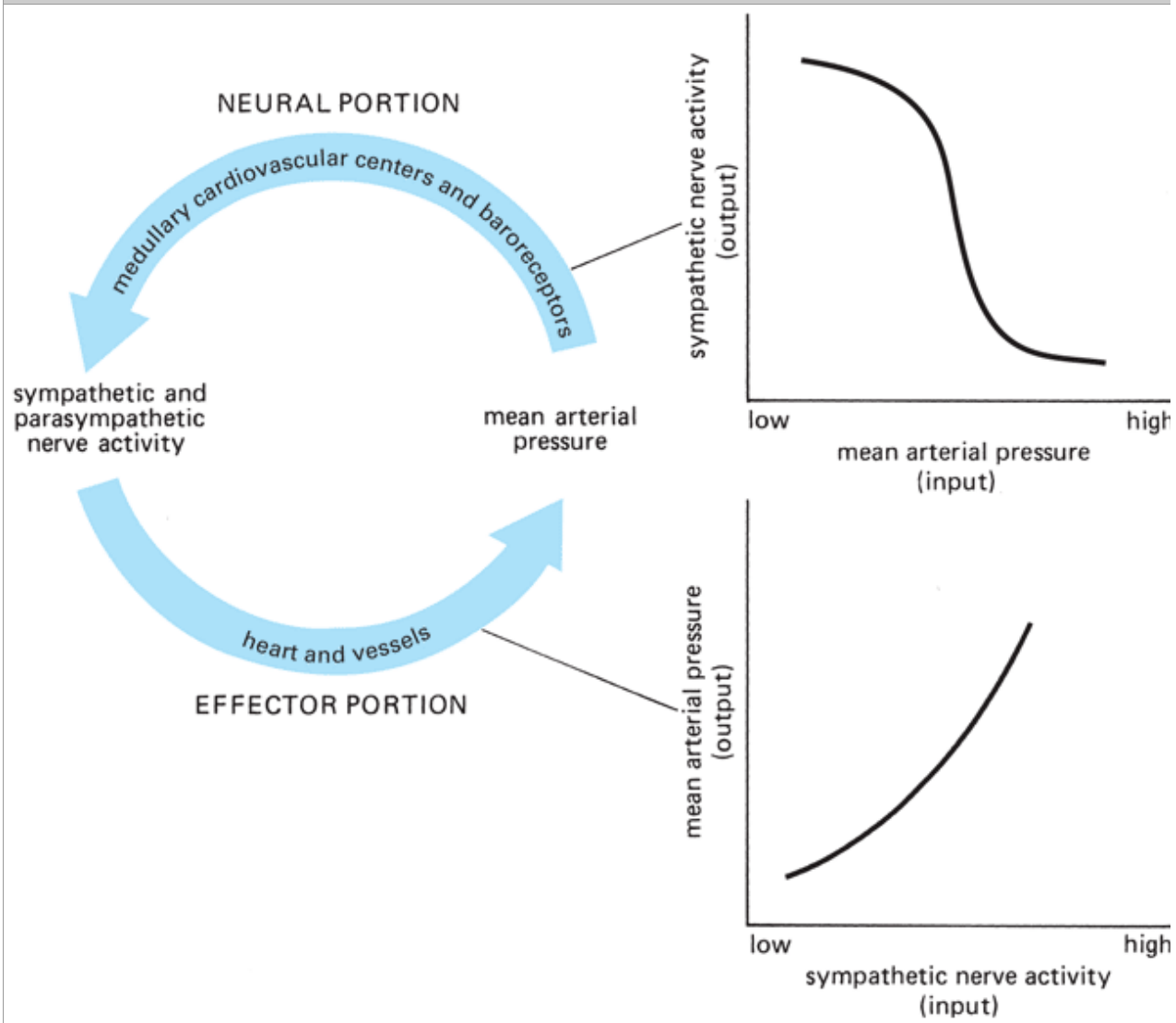
The nonarterial baroreceptor influences shown in Figure 9–4 may be viewed as disturbances on the cardiovascular system that act on the medullary cardiovascular centers as opposed to disturbances that ac on the heart and vessels. These disturbances cause sympathetic activity and arterial pressure to change in the*same direction*. Recall from the discussion of the arterial baroreceptor reflex that cardiovascular disturbances that act on the heart or vessels (such as blood loss or heart failure) produce *reciprocal* changes in arterial pressure and sympathetic activity. These facts are often useful in the clinical diagnoses of blood pressure abnormalities. For example, patients commonly present in the doctor's office with high blood pressure in combination with elevated heart rate (implying elevated sympathetic activity). These same-direction changes in arterial pressure and sympathetic activity suggest that the problem lies not in the periphery but rather with an abnormal pressure-raising input to the medullary cardiovascular centers. The physician should immediately think of those set-point raising influences listed in the top half of Figure 9–4 that would simultaneously raise sympathetic activity and arterial pressure. Often, such a patient does not have chronic hypertension but rather is just experiencing a temporary blood pressure elevation due to the anxiety of undergoing a physical examination.

Systems Analysis of the Arterial Baroreflex

For most purposes, the preceding "thermostat analogy" provides a sufficient understanding of how the arterial baroreflex operates. In certain situations—especially when there are multiple disturbances on the cardiovascular system—a more detailed understanding is helpful. Consequently, this section will analyze the operation of the arterial baroreflex with a more formal control systems approach.

The complete arterial baroreceptor reflex pathway is a control system made up of two distinct portions as shown in Figure 9–5: (1) an *effector portion,* including the heart and peripheral blood vessels, and (2) a *neural portion,* including the arterial baroreceptors, their afferent nerve fibers, the medullary cardiovascular centers, and the efferent sympathetic and parasympathetic fibers. Mean arterial pressure is the *output* of the effector portion and simultaneously the *input* to the neural portion. Similarly, the activity of the sympathetic (and parasympathetic)[4] cardiovascular nerves is the *output* of the neural portion of the arterial baroreceptor control system and, at the same time, the *input* to the effector portion.

Figure 9–5.



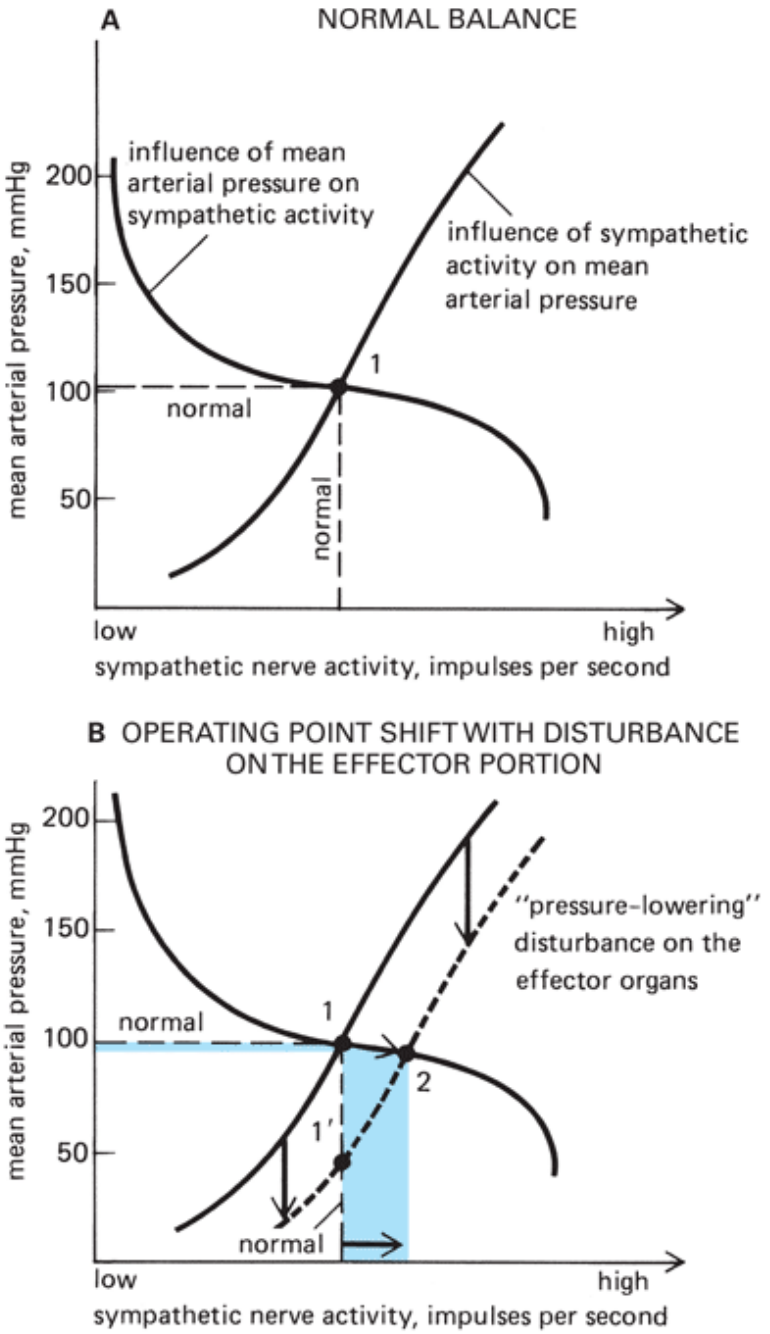
Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Neural and effector portions of the arterial baroreceptor control system.

A host of reasons why mean arterial pressure *increases* when the heart and peripheral vessels receive *increased* sympathetic nerve activity was discussed in Chapters 2, 3, 4, 5, 6, 7, and 8. All this information is summarized by the curve shown in the lower graph of Figure 9–5 that describes the operation of the effector portion of the arterial baroreceptor system alone. In this chapter, how *increased* mean arterial pressure acts through the arterial baroreceptors and medullary cardiovascular centers to *decrease* the sympathetic activity has also been discussed. This information is summarized by the curve shown in the upper graph of Figure 9–5 that describes the operation of the neural portion of the arterial baroreceptor system*alone*.

When the arterial baroreceptor system is intact and operating as a closed loop, the effector portion and neural portion retain their individual rules of operation as described by their individual function curves in Figure 9–5. Yet in the closed loop, the two portions of the system must interact until they come into balance with each other at some operating point with a mutually compatible combination of mean arterial pressure and sympathetic activity. The analysis of the complete system begins by plotting the operating curves for the neural and effector portions of the systems together on the same graph as in Figure 9–6A. To accomplish this superimposition, the graph for the neural portion (the upper graph in Figure 9–5) was flipped to interchange its vertical and horizontal axes. Consequently, the neural curve (but not the effector curve) in Figure 9–6A must be read in the unusual sense that its independent variable, arterial pressure, is on the vertical axis and its dependent variable, sympathetic nerve activity is on the horizontal axis.

Figure 9–6.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Operation of the arterial baroreceptor control system. A: Normal balance. B: Operating point shift with disturbance on the effector portion.

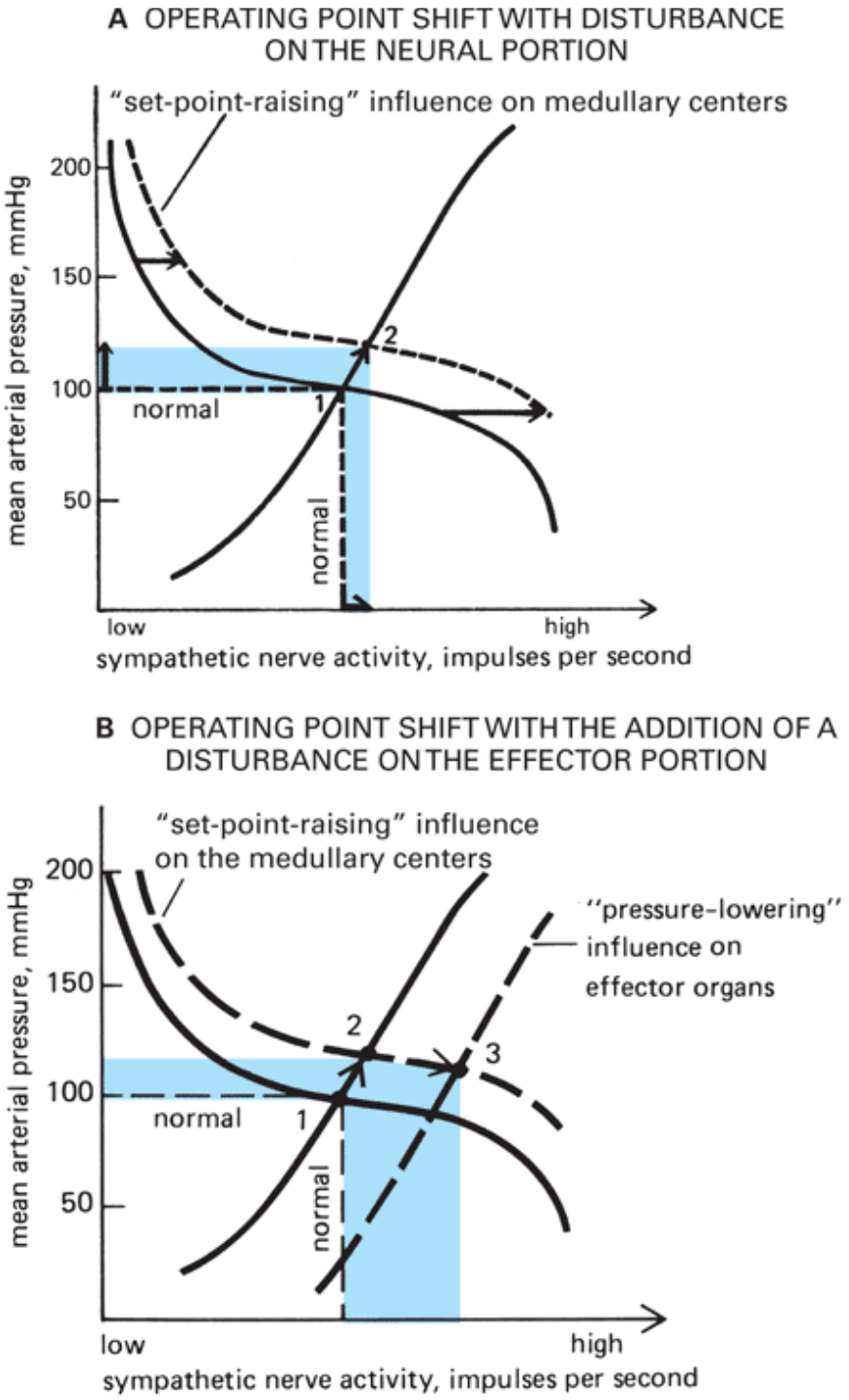
Whenever there is any outside disturbance on the cardiovascular system, the operating point of the arteria baroreceptor system shifts. This happens because *all* cardiovascular disturbances cause a shift in one or th other of the two curves in Figure 9–6A. For example, Figure 9–6B shows how the operating point for the arterial baroreceptor system is shifted by a cardiovascular disturbance that lowers the operating curve of the effector portion. The disturbance in this case could be anything that reduces the arterial pressure

produced by the heart and vessels *at each given level of sympathetic activity.* Blood loss, for example, is such a disturbance because it lowers central venous pressure and, through Starling's law, lowers cardiac output and thus mean arterial pressure at any given level of cardiac sympathetic nerve activity. Metabolic vasodilation of arterioles in exercising skeletal muscle is another example of a pressure-lowering disturbance on the effector portion of the system because it lowers the total peripheral resistance and thus the arterial pressure that the heart and vessels produce at any given level of sympathetic nerve activity.

As shown by point 2 in Figure 9–6B, any pressure-lowering disturbance on the heart or vessels causes a new balance to be reached within the baroreceptor system at a slightly lower than normal mean arterial pressure and a higher than normal sympathetic activity level. Note that the point 1' in Figure 9–6B indicates how far the mean arterial pressure would have fallen as a consequence of the disturbance had no the sympathetic activity been automatically increased above normal by the arterial baroreceptor system.[5]

As indicated previously in this chapter, many disturbances act on the neural portion of the arterial baroreceptor system rather than directly on the heart or vessels. These disturbances shift the operating point of the cardiovascular system because they alter the operating curve of the neural portion of the system. For example, the influences listed in Figure 9–4 that raise the set point for arterial pressure do so by shifting the operating curve for the neural portion of the arterial baroreceptor system to the right as shown in Figure 9–7A because they increase the level of sympathetic output from the medullary cardiovascular centers *at each and every level of arterial pressure* (ie, at each and every level of input from the arterial baroreceptors). For example, a sense of danger will cause the components of the arterial baroreceptor system to come into balance at a higher than normal arterial pressure and a higher than normal sympathetic activity as shown by point 2 in Figure 9–7A. Conversely, but not shown in Figure 9–7, any of the set-point-lowering influences listed in Figure 9–4 acting on the medullary cardiovascular centers will shift the operating curve for the neural portion of the arterial baroreceptor system to the left and a new balance will be reached at lower than normal arterial pressure and sympathetic activity.

Figure 9–7.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Effect of neural influences on the arterial baroreceptor control system. A: Operating point shift with disturbance on the neural portion. B: Operating point shift with disturbances on both neural and effector portions.

Many physiological and pathological situations involve simultaneous disturbances on both the neural and effector portions of the arterial baroreceptor system. Figure 9–7B illustrates this type of situation. The set-point-increasing disturbance on the neural portion of the system alone causes the equilibrium to shift from

point 1 to point 2. Superimposing a pressure-lowering disturbance on the heart or vessels further shifts th equilibrium from point 2 to point 3. Note that, although the response to the pressure-lowering disturbance in Figure 9–7B (point 2 to point 3) starts from a higher than normal arterial pressure, it is essentially identical to that which occurs in the absence of a set-point-increasing influence on the cardiovascular center (see Figure 9–6B). Thus, the response is an attempt to prevent the arterial pressure from falling below that at point 2. The overall implication is that any of the set-point-increasing influences on the medullary cardiovascular centers listed in Figure 9–4 cause the arterial baroreceptor system to regulate arterial pressure to a higher than normal value. Conversely, the set-point-lowering influences on the medullary cardiovascular centers listed in Figure 9–4 would cause the arterial baroreceptor system to regulate arterial pressure to a lower than normal value.

Several situations that involve a higher than normal sympathetic activity at a time when arterial pressure i itself higher than normal will be discussed in Chapters 10 and 11. It should be noted that higher than normal sympathetic activity and higher than normal arterial pressure can exist together only when there is a set-point-raising influence on the *neural* portion of the arterial baroreceptor system.

[4] For convenience, we will omit continual reference to parasympathetic nerve activity in the following discussion. Throughout, however, an indicated change in sympathetic nerve activity should also be taken t imply a reciprocal change in the activity of the cardiac parasympathetic nerves unless otherwise noted.

[5] In the absence of an arterial baroreflex, sympathetic nerve activity would remain constant despite changes in arterial pressure. In this case, the operating curve for the neural portion of the system would b a vertical line in Figure 9–6B—ie, one fixed sympathetic nerve activity regardless of arterial pressure.

LONG-TERM REGULATION OF ARTERIAL PRESSURE

Fluid Balance & Arterial Pressure

Several key factors in the long-term regulation of arterial blood pressure have already been considered. First is the fact that the baroreceptor reflex, however well it counteracts temporary disturbances in arterial pressure, cannot effectively regulate arterial pressure in the long term for the simple reason that the baroreceptor firing rate adapts to prolonged changes in arterial pressure.

The second pertinent fact is that circulating blood volume can influence arterial pressure because:

↓ Blood volume
↓
↓ Peripheral venous pressure
↓
Left shift of venous function curve
↓
↓ Central venous pressure
↓
↓ Cardiac output
↓
↓ Arterial pressure

A fact yet to be considered is that arterial pressure has a profound influence on urinary output rate and thus affects total body fluid volume. Because blood volume is one of the components of the total body fluid, blood volume alterations accompany changes in total body fluid volume. The mechanisms are such that an *increase in arterial pressure* causes an increase in urinary output rate and thus a *decrease in blood*

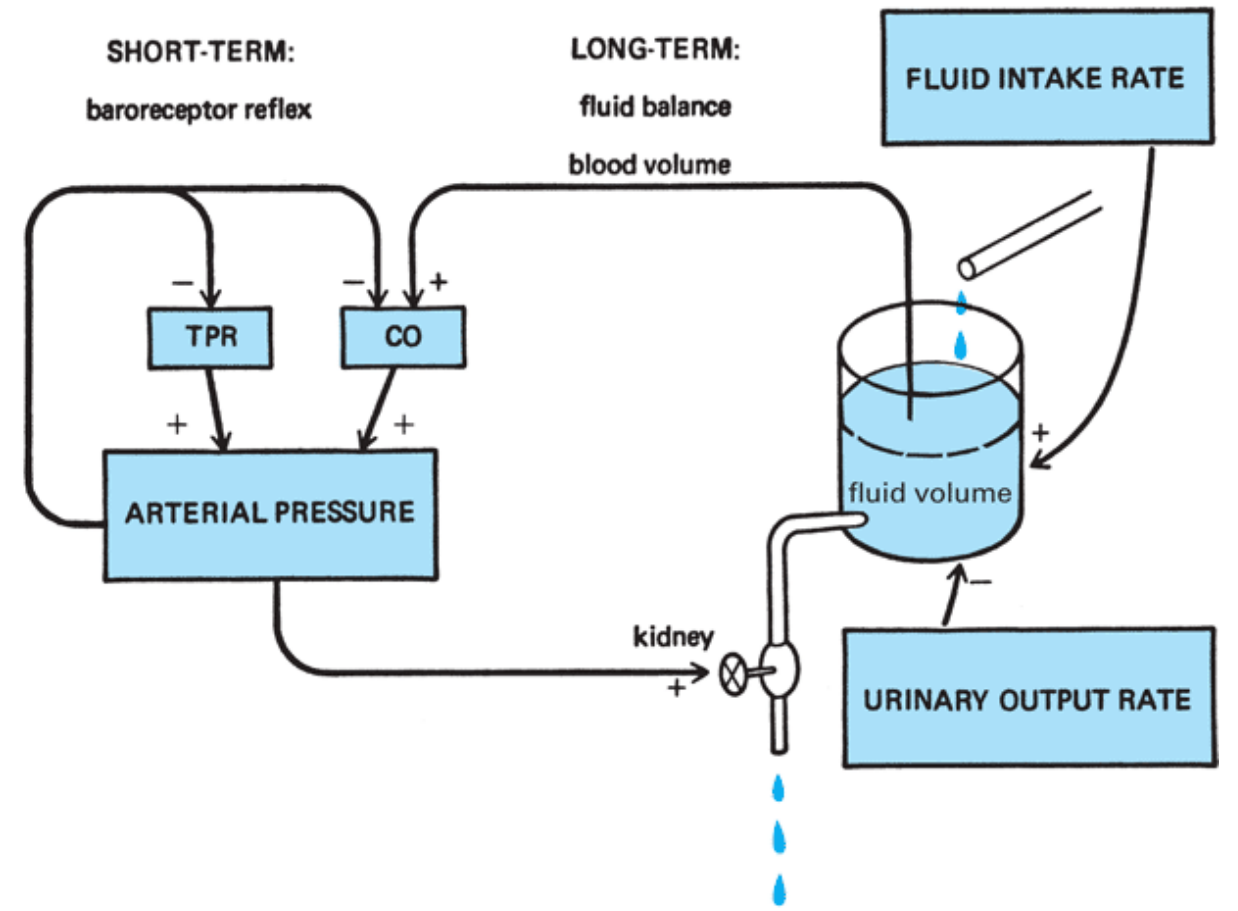
volume. But, as outlined in the preceding sequence, decreased blood volume tends to lower arterial pressure. Thus, the complete sequence of events that are initiated by an increase in arterial pressure can be listed as follows:

↑ Arterial pressure (disturbance)
↓
↑ Urinary output rate
↓
↓ Fluid volume
↓
↓ Blood volume
↓
↓ Cardiac output
↓
↓ Arterial pressure (compensation)

Note the negative feedback nature of this sequence of events: increased arterial pressure leads to fluid volume depletion, which tends to lower arterial pressure. Conversely, an initial disturbance of decreased arterial pressure would lead to fluid volume expansion, which would tend to increase arterial pressure. Because of negative feedback, these events constitute a *fluid volume mechanism* for regulating arterial pressure.

As indicated in Figure 9–8, both the arterial baroreceptor reflex and this fluid volume mechanism are negative feedback loops that regulate arterial pressure. Whereas the arterial baroreceptor reflex is very quick to counteract disturbances in arterial pressure, hours or even days may be required before a change in urinary output rate produces a significant accumulation or loss of total body fluid volume. Whatever this fluid volume mechanism lacks in speed, however, it more than makes up for in persistence. As long as there is any inequality between the fluid intake rate and the urinary output rate, fluid volume is changing and this fluid volume mechanism has not completed its adjustment of arterial pressure. The fluid volume mechanism is in equilibrium only when the urinary output rate exactly equals the fluid intake rate.[6] *In the long term, the arterial pressure can only be that which makes the urinary output rate equal to the fluid intake rate.*

Figure 9–8.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Mechanisms of short- and long-term regulation of arterial pressure. TPR, total peripheral resistance; CO, cardiac output.

The baroreceptor reflex is, of course, essential for counteracting rapid changes in arterial pressure. The fluid volume mechanism, however, determines the long-term level of arterial pressure because it slowly overwhelms all other influences. Through adaptation, the baroreceptor mechanism adjusts itself so that it operates to prevent acute changes in blood pressure from the prevailing long-term level as determined through fluid balance.

[6] In the present discussion, assume that fluid intake rate represents that in excess of the obligatory fluid losses that normally occur in the feces and by transpiration from the skin and structures in the respiratory tract. The processes that regulate voluntary fluid intake (thirst) are not well understood but seem to involve many of the same factors that influence urinary output (eg, blood volume and osmolality). Angiotensin II may be an important factor in the regulation of thirst.

Effect of Arterial Pressure on Urinary Output Rate

A key element in the fluid balance mechanism of arterial pressure regulation is the effect that arterial pressure has on the renal urine production rate. The mechanisms responsible for this will be briefly described here with emphasis on their cardiovascular implications.

As indicated in Chapter 1, the kidneys play a major role in homeostasis by regulating the electrolyte composition of the plasma and thus the entire internal environment. One of the major plasma electrolytes

regulated by the kidneys is the sodium ion. To regulate the electrolyte composition, a large fraction of the plasma fluid that flows into the kidneys is filtered across the *glomerular capillaries* so that it enters the *renal tubules.* The fluid that passes from the blood into the renal tubules is called the *glomerular filtrate,* and the rate at which this process occurs is called the *glomerular filtration rate.* Glomerular filtration is a transcapillary fluid movement whose rate is influenced by hydrostatic and oncotic pressures as indicated in Chapter 6. The primary cause of continual glomerular filtration is that glomerular capillary hydrostatic pressure is normally very high (60 mmHg). The glomerular filtration rate is decreased by factors that decrease glomerular capillary pressure, eg, decreased arterial blood pressure or vasoconstriction of preglomerular renal arterioles.

Once fluid is filtered into the renal tubules, it either (1) is *reabsorbed* and reenters the cardiovascular system or (2) is passed along renal tubules and eventually *excreted* as urine. Thus, urine production is the net result of glomerular filtration and renal tubular fluid reabsorption:

$$\text{Urinary output rate} = \text{glomerular filtration rate} - \text{renal fluid reabsorption rate}$$

Actually, most of the reabsorption of fluid that has entered renal tubules as glomerular filtrate occurs because sodium is actively pumped out of the tubules by cells in the tubular wall. When sodium leaves the tubules, osmotic forces are produced that cause water to leave with it. Thus, any factor that promotes renal tubular sodium reabsorption (sodium retention) tends to increase the renal fluid reabsorption rate and consequently decrease the urinary output rate. The blood concentration of the hormone *aldosterone,* which is produced by the adrenal glands, is the primary regulator of the rate of sodium reabsorption by renal tubular cells. Adrenal release of aldosterone is, in turn, regulated largely by the circulating level of another hormone, *angiotensin II,* whose plasma concentration is determined by the plasma concentration of*renin,* an enzyme that is produced in the kidneys. Renin actually catalyzes the formation of an inactive decapeptide,*angiotensin I,* from *angiotensinogen,* a circulating precursor protein. Angiotensin I then gets quickly converted to angiotensin II (an octapeptide) by the action of *angiotensin-converting enzyme* (*ACE*) that is located on the surface of endothelial cells. The combination of elements involved in this whole sequence of events is referred to as the *renin-angiotensin-aldosterone system.*

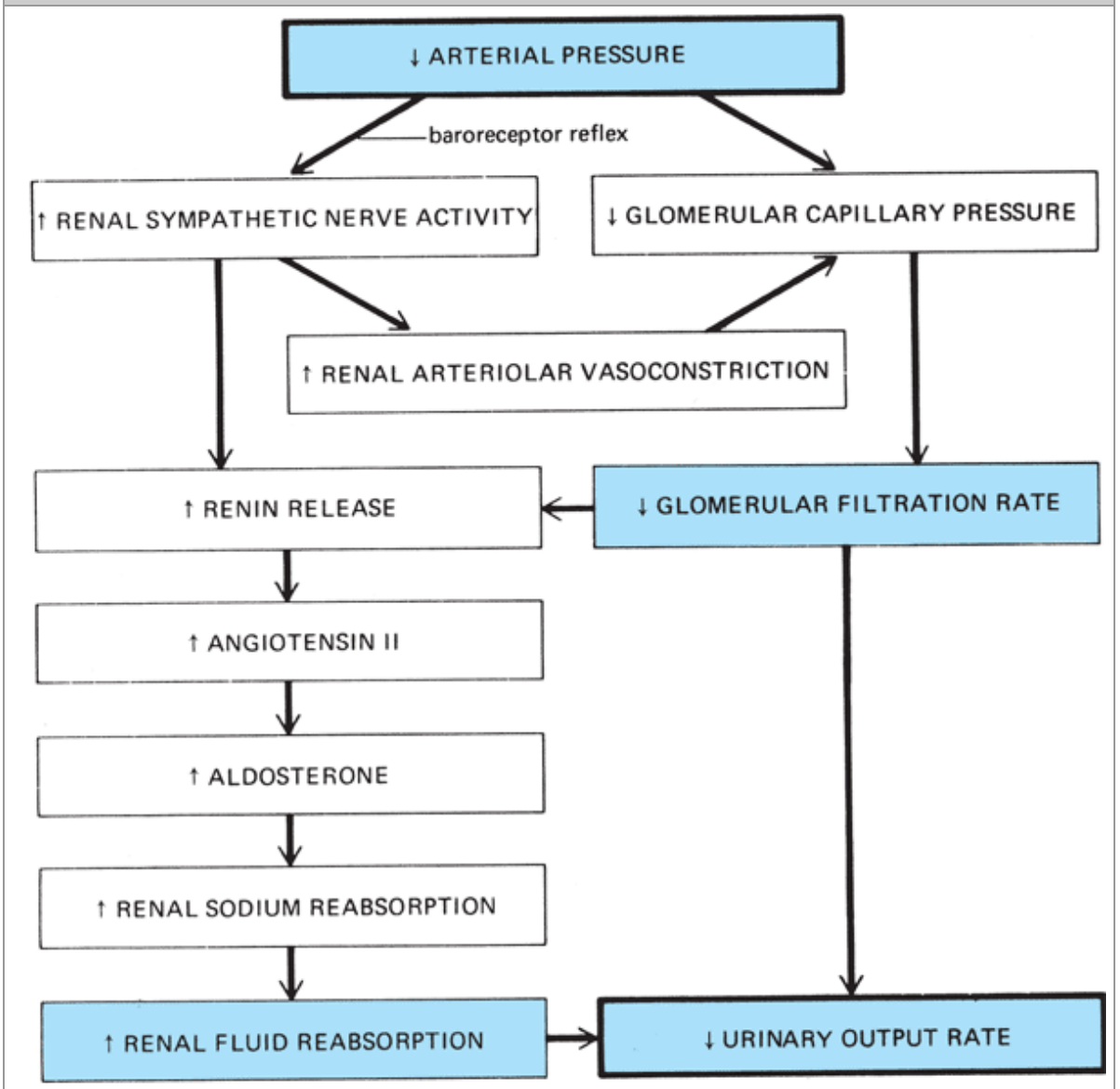
The rate of renin release by the kidneys is influenced by several factors. An increase in the activity of renal sympathetic nerves causes a direct release of renin through a β_1-adrenergic mechanism. Also, renin release is triggered by factors associated with a lowered glomerular filtration rate. The activation of sympathetic vasoconstrictor nerves to renal arterioles thus indirectly causes renin release via lowered glomerular capillary hydrostatic pressure and glomerular filtration rate. The important fact to keep in mind from a cardiovascular standpoint, is that anything that causes renin release causes a decrease in urinary output rate because increased renin causes increased sodium (and therefore fluid) reabsorption from renal tubules.[7]

Urinary output rate is also influenced by vasopressin (antidiuretic hormone, ADH) released from the posterior pituitary. Vasopressin regulates the permeability of certain portions of the kidney tubule in such a way that when the blood levels of the hormone are elevated, water is reabsorbed from the tubule and the kidney produces only small volumes of highly concentrated urine. The production of vasopressin in the hypothalamus and its release from the pituitary are stimulated by many factors including increased extracellular fluid osmolality, decreased input from cardiopulmonary baroreceptors, and decreased input from arterial baroreceptors. In the case of the latter two influences on vasopressin release, the overall result is to decrease urinary output rate whenever arterial pressure and/or central blood volume are below normal.

Some major mechanisms that lead to decreased urinary output rate are summarized in Figure 9–9. Most

important, this figure shows that urinary output rate is linked to arterial pressure by many synergistic pathways. Because of this, modest changes in arterial pressure are associated with large changes in urinar output rate.

Figure 9–9.



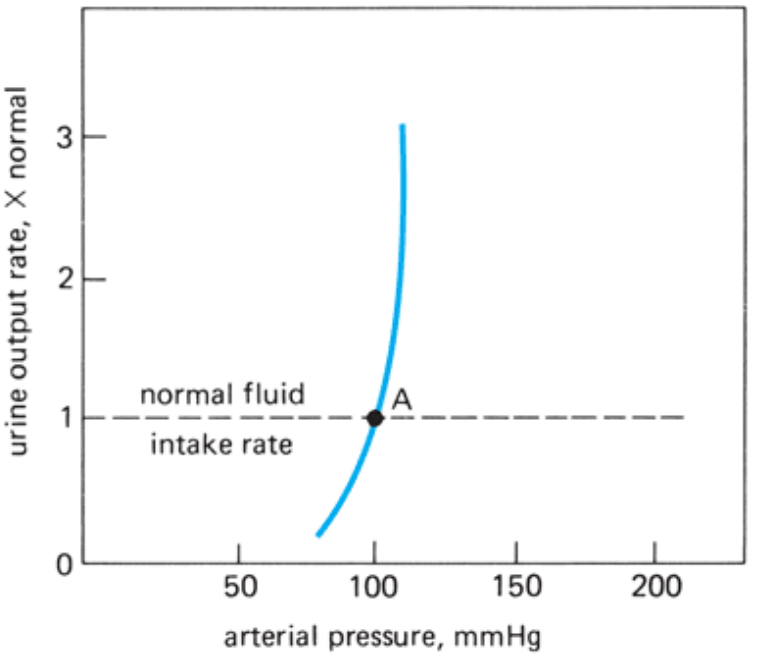
Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Mechanisms by which arterial pressure influences urinary output rate.

The observed relation between arterial pressure and urinary output for a normal person is shown in Figure 9–10. Recall that, in the steady state, the urinary output rate must always equal the fluid intake rate and that changes in fluid volume will automatically adjust arterial pressure until this is so. Thus, a normal person with a normal fluid intake rate will have, as a long-term average, the arterial pressure associated with point A in Figure 9–10. Because of the steepness of the curve shown in Figure 9–10, even rather

marked changes in fluid intake rate have rather minor influences on the arterial pressure of a normal individual.

Figure 9–10.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Effect of arterial pressure on urinary output rate in a normal person.

[7] Although the renin-angiotensin-aldosterone system is clearly the primary mechanism for the regulation o renal tubular sodium reabsorption, many believe that other factors are involved. A polypeptide natriuretic (salt-losing) factor has been identified in granules of cardiac atrial cells. Atrial distention causes the releas of this *atrial natriuretic peptide* (ANP) into the blood. The possibility that the heart itself may serve as an endocrine organ in the regulation of body fluid volume is stimulating much research interest.

KEY CONCEPTS

Arterial pressure is closely regulated to ensure adequate blood flow to the tissues.

The arterial baroreceptor reflex is responsible for regulating arterial pressure in the short term on a second-to-second and moment-to-moment basis.

The arterial baroreceptor reflex involves the following: pressure sensing by stretch-sensitive baroreceptor nerve endings in the walls of arteries; neural integrating centers in the brainstem that adjust autonomic nerve activity in response to the pressure information they receive from the arterial baroreceptors; and responses of the heart and vessels to changes in autonomic nerve activity.

Overall, the arterial baroreflex operates such that increases in arterial pressure lead to an essentially immediate decrease in sympathetic nerve activity and a simultaneous increase in parasympathetic nerve activity (and vice versa).

The brainstem integrating centers also receive nonarterial baroreceptor inputs that can raise or lower the set point for short-term arterial pressure regulation.

In the long term, arterial pressure is regulated by changes in blood volume that come about because arterial pressure has a strong influence on urinary output rate by the kidney.

STUDY QUESTIONS

9–1. Consider the various components of the arterial baroreceptor reflex and predict whether the following variables will increase or decrease in response to a rise in arterial pressure.

a. Arterial baroreceptor firing rate

b. Parasympathetic activity to the heart

c. Sympathetic activity to the heart

d. Arteriolar tone

e. Venous tone

f. Peripheral venous pressure

g. Total peripheral resistance

h. Cardiac output

9–2. Massage of the neck over the carotid sinus area in a person experiencing a bout of paroxysmal atrial tachycardia is often effective in terminating the episode. Why?

9–3. Indicate whether mean arterial pressure, after all adjustments, is increased or decreased by the following stimuli:

a. Low oxygen in arterial blood

b. Increased intracranial pressure

c. Increased cardiac filling pressure

d. Sense of danger

e. Visceral pain

9–4. Describe the immediate direct and reflex cardiovascular consequences of giving a normal person a drug that blocks α_1-adrenergic receptors.

9–5. What net short-term alterations in mean arterial pressure and sympathetic activity would the followin produce?

a. Blood loss through hemorrhage

b. Cutaneous pain

c. Systemic hypoxia

d. Local metabolic vasodilation in skeletal muscle

9–6. Your patient has lower than normal mean arterial pressure and higher than normal pulse rate. Which of the following are possible diagnoses?

a. Low blood volume

b. Anxiety

c. A cardiac valve problem

d. Elevated intracranial pressure

See answers.

SUGGESTED READINGS

Anderson MC, Kunze DL. Nucleus tractus solitarius—gateway to neural circulatory control. *Annu Rev Physiol.* 1994;56:93–116.

Antunes-Rodrigues J, deCastro M, Elias LL, et al. Neuroendocrine control of body fluid metabolism. *Physiol Rev.* 2004;84:169–208. [PMID: 14715914]

Butler PJ, Jones DR. Physiology of diving birds and mammals. *Physiol Rev.* 1997;77:837–899. [PMID: 9234967]

Calaresu FR, Yardley CP. Medullary basal sympathetic tone. *Annu Rev Physiol.* 1988;50:511–524. [PMID: 3288103]

Cowley AW Jr. Long-term control of arterial blood pressure. *Physiol Rev.* 1992;72:231–300. [PMID: 1731371]

Cushing H. Concerning a definite regulatory mechanism of the vasomotor center which controls blood pressure during cerebral compression. *Bull Johns Hopkins Hosp.* 1901;12:290.

Dampney RA, Coleman MJ, Fontes MA, et al. Central mechanisms underlying short- and long-term regulation of the cardiovascular system. *Clin Exp Pharmacol Physol.* 2002;29:261–268. [PMID: 11985533]

DiCarlo SE, Bishop VS. Central baroreflex resetting as a means of increasing and decreasing sympathetic outflow and arterial pressure. *Ann NY Acad Sci.* 2001;940:324–337. [PMID: 11458690]

Eckberg DL, Sleight P. *Human Baroreflexes in Health and Disease.* Oxford: Clarendon Press; 1992.

Hainsworth R. Reflexes from the heart. *Physiol Rev.* 1991;71:617–658. [PMID: 2057525]

Marshall JM. Peripheral chemoreceptors and cardiovascular regulation. *Physiol Rev.* 1994;74:543–594. [PMID: 8036247]

Melo LG, Pang SC, Achermann U. Atrial natriuretic peptide: regulator of chronic arterial blood pressure. *News Physiol Sci.* 2000;15:143–149. [PMID: 11390897]

Mifflin SW. What does the brain know about blood pressure? *News Physiol Sci.* 2001;16:266–271. [PMID: 11719602]

Parati G, DiRienzo M, Mancia G. How to measure baroreflex sensitivity: from the cardiovascular laboratory to daily life. *J. Hypertens.* 2000;18:7–19. [PMID: 10678538]

Pilowsky PM, Goodchild A. Baroreceptor reflex pathways and neurotransmitters: 10 years on. *J Hypertens.* 2002;20:1675–1688. [PMID: 12195099]

Sato T, Kawada T, Inagaki M, et al. New analytic framework for understanding sympathetic baroreflex control of arterial pressure. *Am J Physiol.* 1999;276:H2251–H2261.

Spyer KM. Central nervous system mechanisms contributing to cardiovascular control. *J Physiol.* 1994;474:1–19. [PMID: 8014887]

Sunagawa K, Sato T, Kawada T. Integrative sympathetic baroreflex regulation of arterial pressure. *Ann NY Acad Sci.* 2001;940:314–323. [PMID: 11458689]

Taylor EW, Jordan D, Coote JH. Central control of the cardiovascular and respiratory systems and their interaction in vertebrates. *Physiol Rev.* 1999;79:855–916. [PMID: 10390519]

Vander AJ. *Renal Physiology.* 6th ed, New York, NY: McGraw-Hill; 2004.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.
Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.

Medical a silverchair information system The McGraw-Hill Companies

McGraw-Hill's ACCESSMedicine

Note: Large images and tables on this page may necessitate printing in landscape mode.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.

OBJECTIVES

The student understands the general mechanisms involved in the cardiovascular responses to any *given no system and can predict the resulting alterations in all important cardiovascular variables:*

- *Identifies the primary disturbances that the situation places on the cardiovascular system.*
- *Lists how the primary disturbances change the influence on the medullary cardiovascular centers from*
- *States what immediate* reflex compensatory *changes will occur in sympathetic and parasympathetic r medullary cardiovascular centers.*
- *Indicates what immediate* reflex compensatory *changes will occur in basic cardiovascular variables su arteriolar tone, venous tone, peripheral venous pressure, central venous pressure, total peripheral res through any major organ.*
- *Predicts what the net effect of the primary disturbance and reflex compensatory influences on the car will be on mean arterial pressure.*
- *States whether mean arterial pressure and sympathetic nerve activity will settle above or below their*
- *Predicts whether and states how cutaneous blood flow will be altered by temperature regulation reflex*
- *Indicates whether and how transcapillary fluid movements will be involved in the overall cardiovascula*
- *Indicates whether, why, how, and with what time course renal adjustments of fluid balance will partic*
- *Predicts how each of the basic cardiovascular variables will be influenced by long-term adjustments in*

The student understands how respiratory activities influence the cardiovascular system:

- *Describes how the "respiratory pump" promotes venous return.*
- *Identifies the primary disturbances on cardiovascular variables associated with normal respiratory act*
- *Describes the reflex compensatory responses to respiratory activity.*
- *Defines the causes of "normal sinus arrhythmia."*
- *Lists the cardiovascular consequences of the Valsalva maneuver and of positive pressure artificial ven*

The student understands the specific processes associated with the homeostatic adjustments to the effects

- *States how gravity influences arterial, venous, and capillary pressures at any height above or below t*
- *Describes and explains the changes in central venous pressure and the changes in transcapillary fluid caused by standing upright.*
- *Describes the operation of the "skeletal muscle pump" and explains how it simultaneously promotes v in the muscle vascular beds.*
- *Identifies the primary disturbances and compensatory responses evoked by acute changes in body po*
- *Describes the chronic effects of long-term bed rest on cardiovascular variables.*

The student understands the specific processes associated with the homeostatic adjustments to exercise:

- *Identifies the primary disturbances and compensatory responses evoked by acute episodes of dynami*
- *Describes the conflict between pressure reflexes and temperature reflexes on cutaneous blood flow.*
- *Indicates how the "skeletal muscle pump" and the "respiratory pump" contribute to cardiovascular ad*
- *Compares the cardiovascular responses to static exercise with those to dynamic exercise.*
- *Lists the effects of chronic exercise and physical conditioning on cardiovascular variables.*

The student understands that gender may influence the cardiovascular system:

- *Describes gender-dependent differences in cardiovascular variables.*

The student understands the cardiovascular alterations that accompany birth, growth, and aging:

- *Identifies the pathway of blood flow through the fetal heart and describes the changes that occur at b*
- *Indicates the normal changes that occur in cardiovascular variables during childhood.*
- *Identifies age-dependent changes that occur in cardiovascular variables such as cardiac index, arteria*
- *Describes age-dependent changes in the arterial baroreceptor reflex.*
- *Distinguishes between age- and disease-dependent alterations that occur in cardiovascular function o*

CARDIOVASCULAR RESPONSES TO PHYSIOLOGICAL STRESSES: INTROD

This chapter as well as Chapter 11 will show how the basic principles of cardiovascular physiology which ha system. A variety of situations that tend to disturb homeostasis will be presented. The key to understandir recall that the arterial baroreceptor reflex and renal fluid balance mechanisms always act to blunt changes *blood flow to the brain and the heart muscle is maintained in any circumstance.*


The cardiovascular alterations in each of the following examples are produced by the combined effects the cardiovascular variables and (2) the reflex compensatory adjustments that are triggered by the primar similar in all situations. Rather than trying to memorize the cardiovascular alterations that accompany eac response in terms of the primary disturbances and reflex compensatory reactions involved. To aid in this p determinants may be found in Appendix C.

A list of important study questions is supplied for Chapters 10 and 11. These questions are intended to rei cardiovascular responses and provide a review of basic cardiovascular principles.

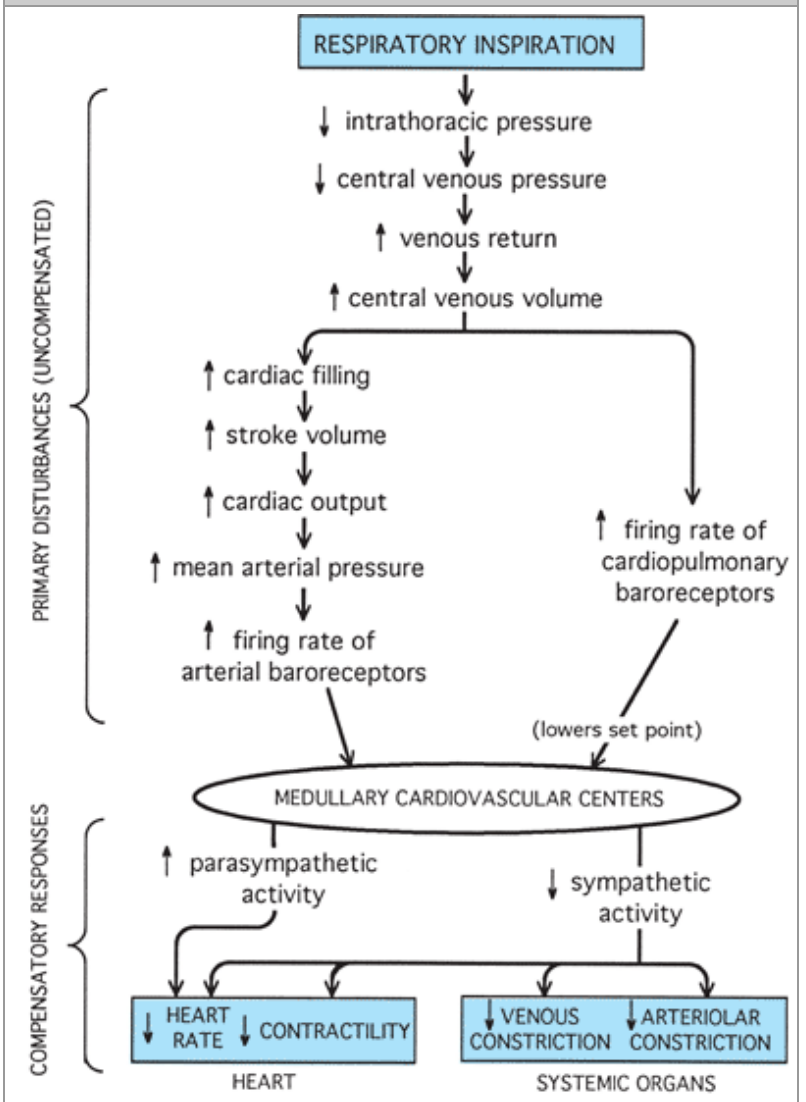
EFFECT OF RESPIRATORY ACTIVITY


The physical processes associated with inhaling air into and exhaling air out of the lungs can have ma normal inspiration, intrathoracic pressure falls by about 7 mmHg as the diaphragm contracts and the chest expiration. These periodic pressure fluctuations not only promote air movement into and out of the lungs b veins in the thorax to influence venous return to the heart from the periphery. Because of the venous valv decreased by expiration. The net effect is that venous return from the periphery is generally facilitated by by respiration. This phenomenon is often referred to as the *"respiratory pump."*

Because of these changes in venous return, normal breathing is associated with transient cyclical changes normal individuals also fluctuates in synchrony with the respiratory rate. This is referred to as "normal sinu and compensatory responses involved in the cardiovascular effects of respiration are illustrated in Figure 1

than shown. Filling of the right side of the heart is transiently increased during inspiration and, by Starling' transiently increased. Since changes in output of the right side of the heart induce changes in output of the transient increase in stroke volume and cardiac output from the left ventricle. This will lead to a transient i firing of the arterial baroreceptors. In addition, because of the inspiration-induced decrease in intrathoraci vascular and cardiac walls will be stretched and will increase their firing rate. These baroreceptor inputs wi reflex adjustments to lower arterial pressure: that is, increase cardiac parasympathetic nerve activity and conditions, the cyclic change in heart rate is the most apparent cardiovascular response to respiration.[1]

Figure 10–1.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Cardiovascular effects of respiratory inspiration.

There are a number of instances when cardiovascular effects of respiratory efforts are extremely importan contributes significantly to the venous return. *Yawning* is a complex event that includes a significant transi increasing venous return (especially when combined with stretching). In contrast, *coughing* is associated w as a prolonged "fit," can lead to such severe reductions in cardiac output as to cause fainting.

The cardiovascular consequences of changes in intrathoracic pressure are also important during the *Valsal* glottis. This maneuver is normally performed by individuals during defecation ("straining at stool"), or whe when forced expirations are made against a high output resistance, such as when blowing up one of those cardiovascular reaction. At the initiation of the Valsalva maneuver, arterial pressure is abruptly elevated fo transmitted to the thoracic aorta. The sustained elevation in intrathoracic pressure leads to a fall in venous compensatory reflex increase in heart rate and peripheral vasoconstriction. (During this period, the red fac peripheral venous pressures.) At the cessation of the maneuver, there is an abrupt fall in pressure for a co Venous blood then moves rapidly into the central venous pool; stroke volume, cardiac output, and arterial The combination of an episode of high peripheral venous pressure followed by an episode of high arterial p people who are candidates for cerebral vascular accidents (strokes) because this combination may rupture

Artificial changes in intrathoracic pressure evoked during forced respiration with a positive pressure ventila When the lungs are inflated artificially, intrathoracic pressure goes up (rather than down, as occurs during pump*increasing* venous return during inspiration, the positive pressure ventilator *decreases* venous return intrathoracic pressure tends to compress the pulmonary microcirculation and this increases right ventricula

[1] Although the respiratory effects of right heart filling are emphasized in Figure 10–1, respiration also direc somewhat different because both the left atria and the whole of the pulmonary vascular system are affecte some time delays between changes in right heart filling and left ventricular stroke volume that are ignored the respiratory cycle and the cardiovascular effects are influenced by respiratory rate and depth as well as

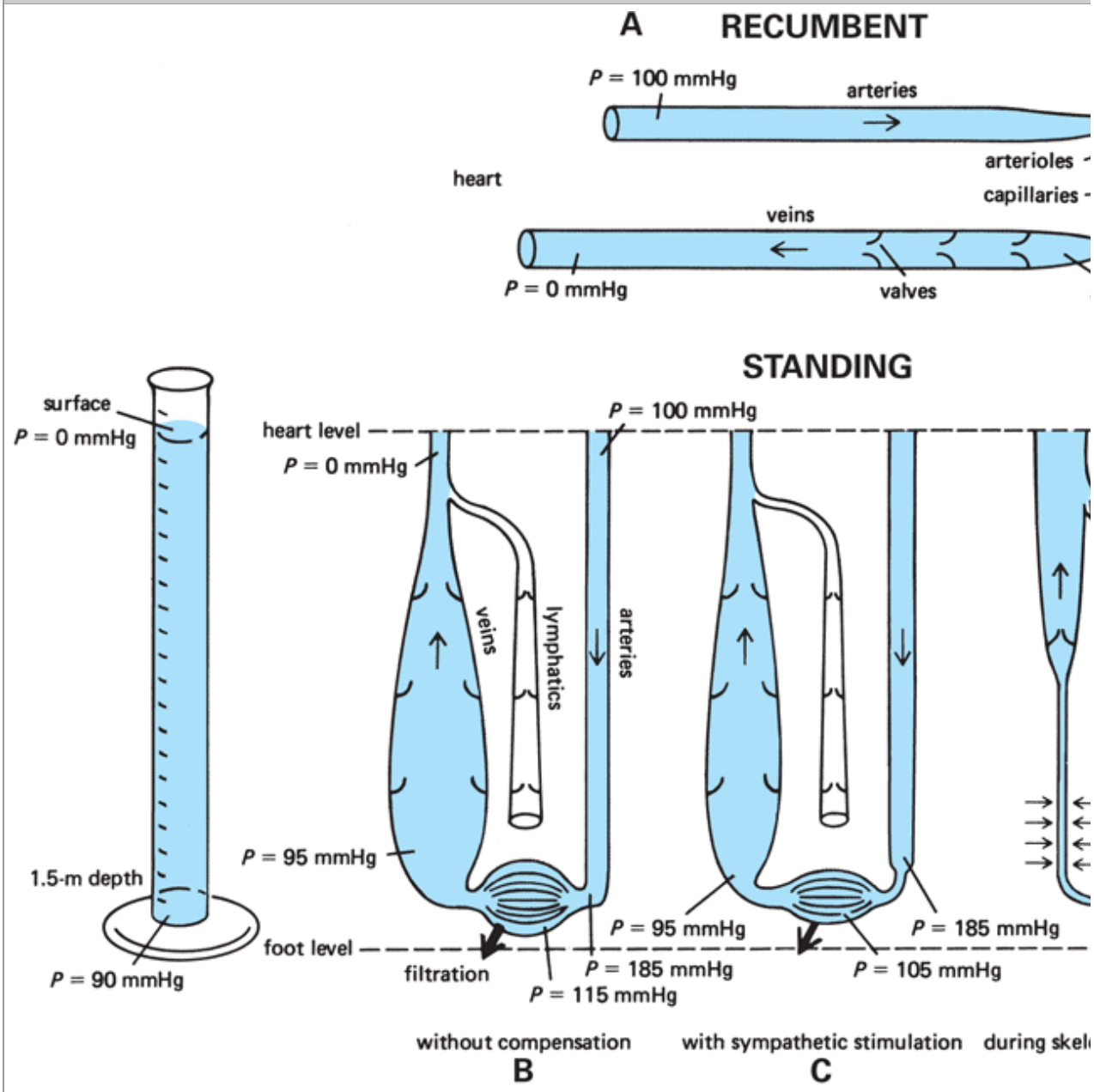
EFFECT OF GRAVITY

Responses to Changes in Body Position



Significant cardiovascular readjustments accompany changes in body position because gravity has an the preceding chapters, the influence of gravity was ignored and pressure differences between various poi vascular resistance ($\triangle P = \dot{Q}R$). As shown in Figure 10–2, this is approximately true only for a recumbent in pressure differences exist between the heart and regions that are not at heart level. This is most importan indicated in Figure 10–2B, all intravascular pressures in the feet may be increased by 90 mmHg simply fro to and from the feet. Note by comparing Figure 10–2A and B that standing upright does not in itself chang the same effect on arterial and venous pressures and thus does not change the *arteriovenous pressure dif* major direct effects of the increased pressure in the lower extremities that are shown in Figure 10–2B: (1) compliant peripheral veins and greatly increases peripheral venous volume by as much as 500 mL in a nor hydrostatic pressure causes a tremendously high transcapillary filtration rate.

Figure 10–2.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Effect of gravity on vascular pressure (A and B) with compensatory influences of sympathetic stimulation

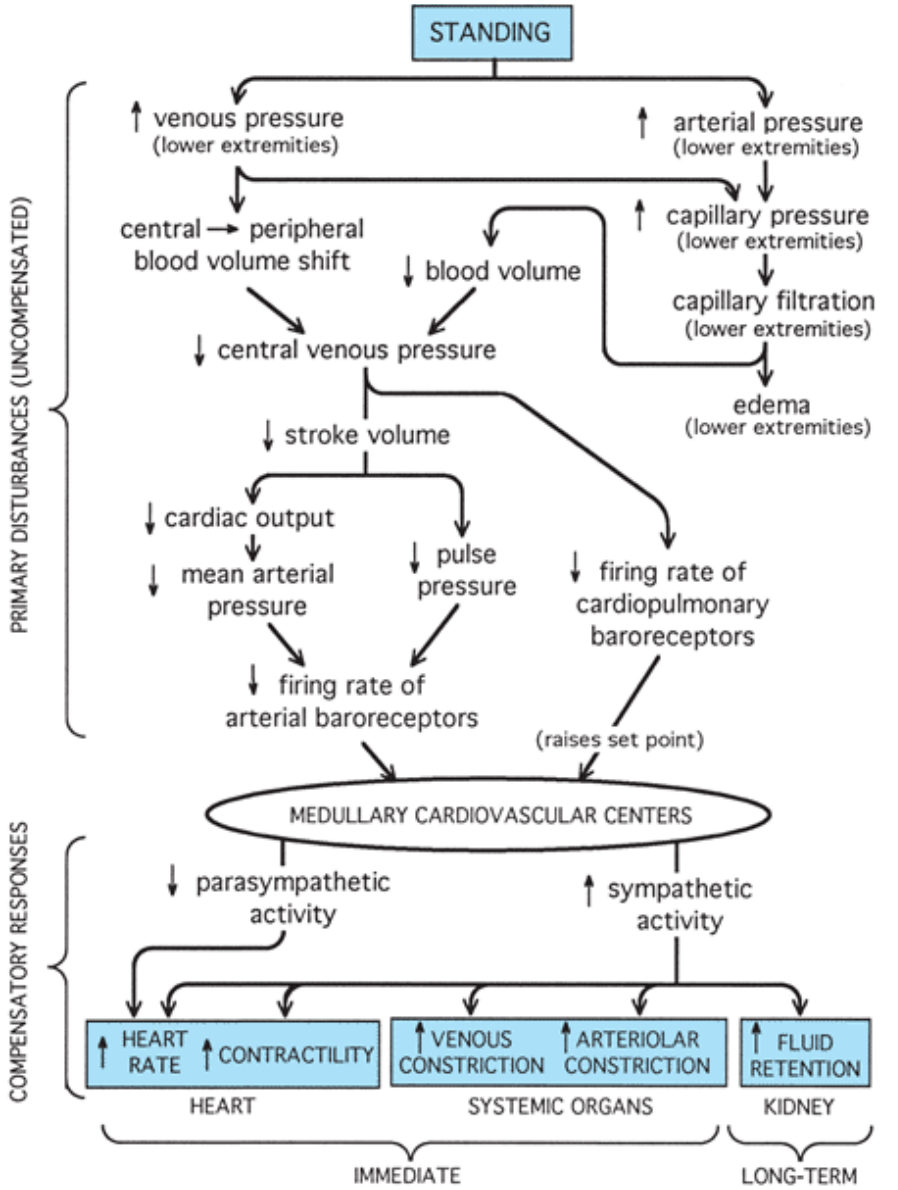
For reasons to be described, a reflex activation of sympathetic nerves accompanies the transition from a re
shows how vasoconstriction from sympathetic activation is only marginally effective in ameliorating the ad
constriction can cause a greater pressure drop across arterioles, but this has only a limited effect on capilla
high. Filtration will continue at a very high rate. In fact, the normal cardiovascular reflex mechanisms alon
aid of the "skeletal muscle pump." A person who remained upright without intermittent contraction of the s

10–20 minutes because of the decreased brain blood flow that would stem from diminished central blood v
pressure.

The effectiveness of the skeletal muscle pump in counteracting venous blood pooling and edema formation
Figure 10–2D and E. The compression of vessels during skeletal muscle contraction expels both venous blo
10–2D). Immediately after a skeletal muscle contraction, both veins and lymphatic vessels are relatively e
of previously expelled fluid (Figure 10–2E). Most important, the weight of the venous and lymphatic fluid c
valve leaflets. Consequently, venous pressure is drastically lowered immediately after skeletal muscle cont
from the capillaries. Thus capillary pressure and transcapillary fluid filtration rate are dramatically reduced
Periodic skeletal muscle contractions can keep the average value of venous pressure at levels that are only
increased pressure drop across vasoconstricted arterioles, prevents capillary pressures from rising to intole
fluid filtration is still present, but the increased lymphatic flow resulting from the skeletal muscle pump is r
the feet.


The actions of the skeletal muscle pump, however beneficial, do not completely prevent a rise in the a
extremities on standing. Thus, assuming an upright position upsets the cardiovascular system and elicits r

Figure 10–3.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Cardiovascular mechanisms involved when changing from a recumbent to a standing position.

As with all cardiovascular responses, the key to understanding the alterations associated with standing is t compensatory responses. As shown in the top part of Figure 10–3, the immediate consequence of standing lower extremities. The latter causes a major redistribution of blood volume out of the central venous pool. influence the cardiovascular centers by lessening the normal input from both the arterial and the cardiopul

The result of a decreased baroreceptor input to the cardiovascular centers will be reflex adjustments appro parasympathetic nerve activity and increased activity of the cardiovascular sympathetic nerves as shown i contractility will increase, as will arteriolar and venous constriction in most systemic organs (brain and hea

Heart rate and total peripheral resistance are higher when an individual stands than when the individual is variables are not directly influenced by standing but *are* changed by the compensatory responses. Stroke decreased below their recumbent values during quiet standing despite the reflex adjustments that tend to

not quite overcome the primary disturbance on these variables caused by standing. This is in keeping with compensations never completely correct the initial disturbance.

Mean arterial pressure is often found to increase when a person changes from the recumbent to the standi of cardiovascular system operation. How can a compensation be more than complete? Moreover, how is in normal mean arterial pressure in the first place? In the case of standing, there are many answers to these discharge rate can actually decrease in spite of a small increase in mean arterial pressure *if* there is simult Second, mean arterial pressure determined by sphygmomanometry from the arm of a standing individual sensed by the baroreceptors in the carotid sinus region of the neck because of gravitational effects. Third, cardiopulmonary receptors is being interpreted as a decrease in blood volume and may raise the arterial p

The kidney is especially susceptible to changes in sympathetic nerve activity, and consequently, as shown activity has influences on fluid balance that become important in the long term. Standing, which is associa in an increase in fluid volume. The ultimate benefit of this is that an increase in blood volume generally rec tolerate upright posture.

Responses to Long-Term Bed Rest (or Zero Gravity)

The cardiovascular system of an individual who is subjected to long-term bed rest undergoes a variety of a by people who travel outside of the earth's atmosphere at zero gravity. In both cases, the consequences o

The most significant immediate change that occurs upon assuming a recumbent position (or entering a gra extremities to the upper portions of the body. The consequences of this shift include distention of the heac decreases in calf girth and leg volume. In addition, the increase in central blood volume stimulates the car function by neural and hormonal pathways to reduce sympathetic drive and promote fluid loss. The individ hypovolemic (by normal earth standards).

When the bedridden patient initially tries to stand up (or when the space traveler reenters earth's gra described in Figure 10–3 are not as effective, primarily because of the substantial decrease in circulating b venous pool into the peripheral veins, stroke volume falls and the individual often becomes dizzy and may phenomenon is referred to as *orthostatic* or *postural hypotension.* Because there are other cardiovascular complete reversal of this orthostatic intolerance may take several days or even weeks.

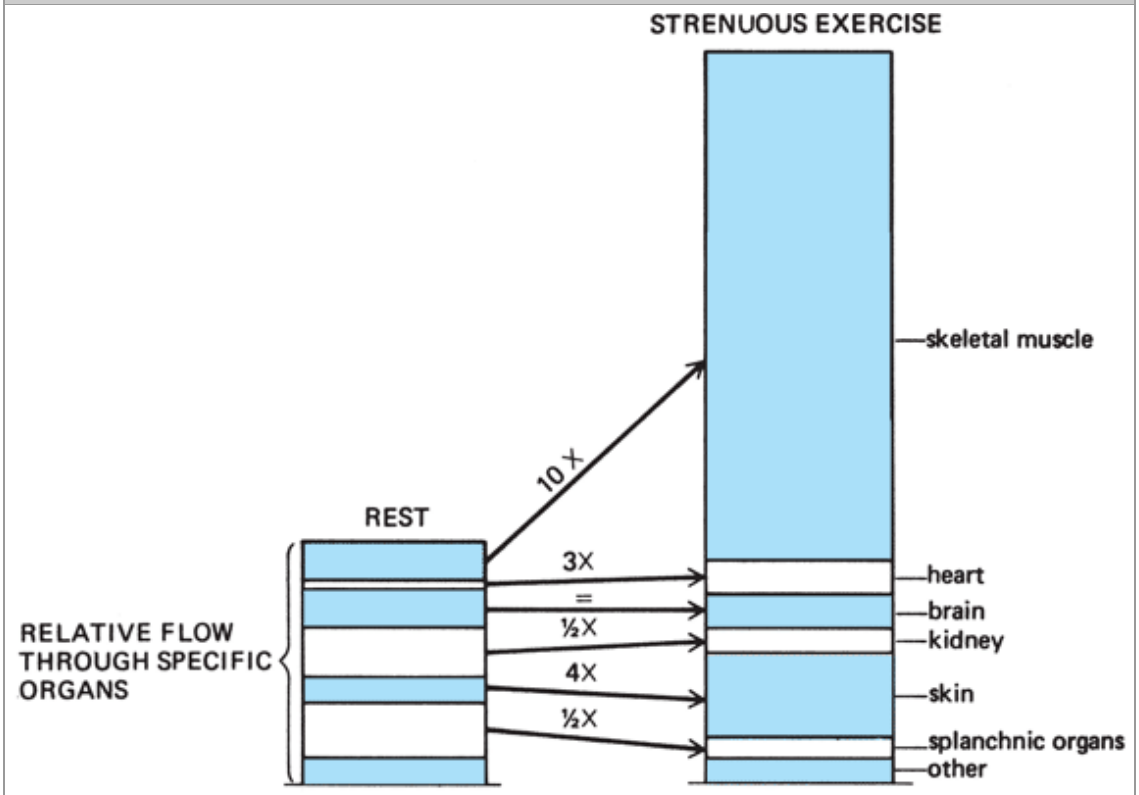
Efforts made to diminish the cardiovascular changes for the bedridden patient may include intermittent sit retention mechanisms. Efforts made in space to accomplish the same end may include exercise programs, loading. (These interventions have met with limited success.)

EFFECT OF EXERCISE

Responses to Acute Exercise

Physical exercise is one of the most ordinary yet taxing situations with which the cardiovascular system mu that occur during exercise depend on several factors including: (1) the type of exercise—ie, whether it is p (isometric); (2) the intensity and duration of the exercise; (3) the age of the individual; and (4) the level o 10–4 is typical of the cardiovascular alterations that might occur in a normal, untrained, middle-aged adul Note especially that heart rate and cardiac output increase greatly during exercise and that mean arterial p These alterations ensure that the increased metabolic demands of the exercising skeletal muscle are met b

Figure 10–4.



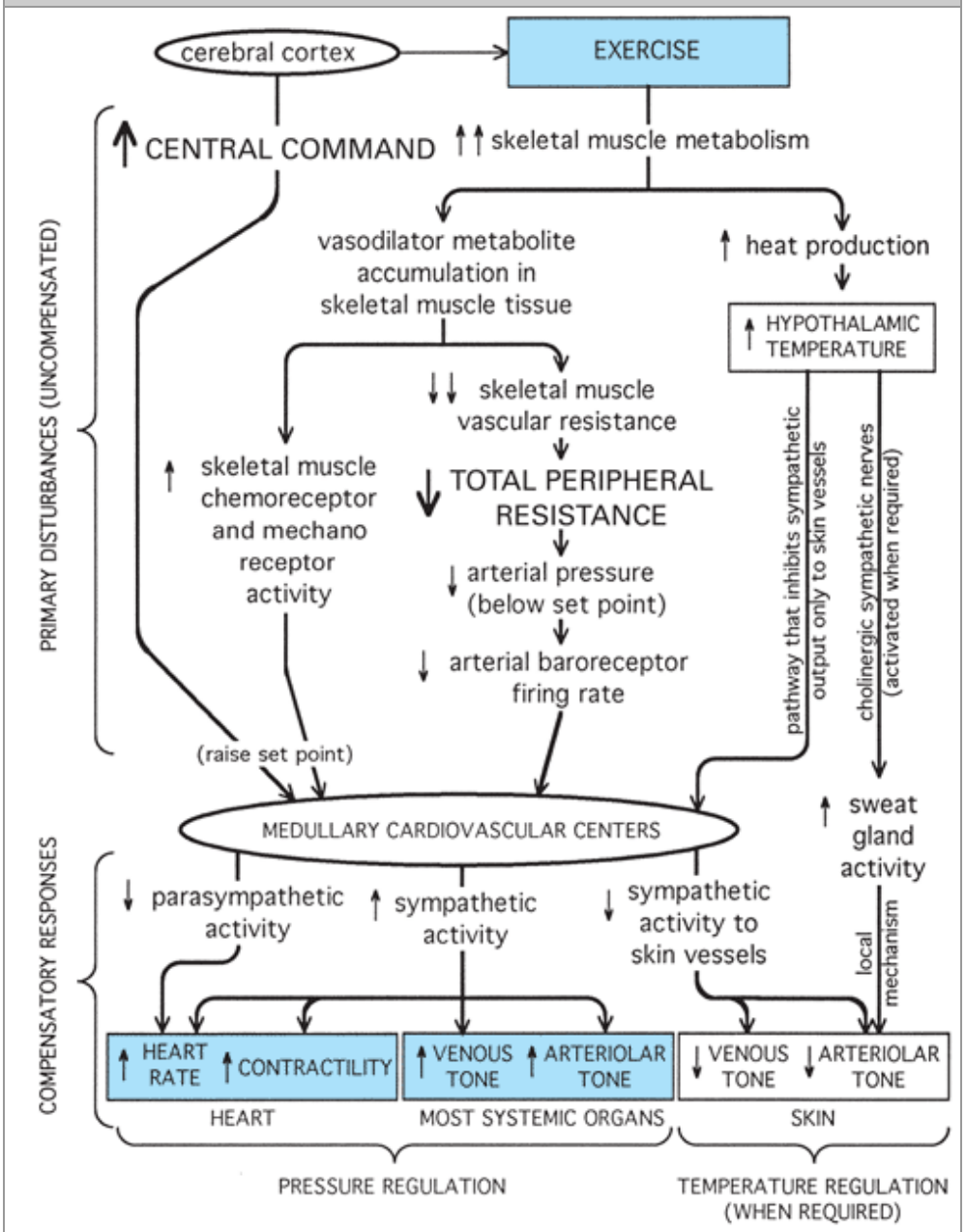
cardiac output	6 L/min	18 L/min
heart rate	70 beats per minute	160 beats per minute
ejection fraction	60%	80%
arterial pressure	120/80 mmHg	150/80 mmHg
central venous pressure	2 mmHg	2 mmHg

Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Cardiovascular adjustments to strenuous exercise.

Many of the adjustments to exercise are due to a large increase in sympathetic activity, which results primary disturbances associated with the stress and/or anticipation of exercise originates within the cerebr cardiovascular centers through corticohypothalamic pathways. This set-point-raising influence, referred to arterial baroreceptor system and causes mean arterial pressure to be regulated to a higher than normal le indicated in Figure 10–5 is the possibility that a second set-point-raising influence may reach the cardiovas in the active skeletal muscles. Such inputs would also contribute to the elevations in sympathetic activity a

Figure 10–5.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Cardiovascular mechanisms involved during exercise.

A major primary disturbance on the cardiovascular system during dynamic exercise, however, is the g metabolic vasodilator accumulation and decreased vascular resistance in active skeletal muscle. As indicat pressure-lowering disturbance that elicits a strong increase in sympathetic activity through the arterial bar

Although mean arterial pressure is above normal during exercise, the decreased total peripheral resistance be regulated by the set-point-raising influences on the cardiovascular center alone. The arterial barorecept large increase in sympathetic activity (see Figure 9–7B). Thus, the arterial baroreceptor reflex is responsib

that accompanies exercise despite the seemingly contradictory fact that arterial pressure is higher than no reflex, the decrease in total peripheral resistance that occurs during exercise would cause mean arterial pr

As discussed in Chapter 9, and indicated in Figures 10–4 and 10–5, cutaneous blood flow may increase du vasoconstrictor tone because thermal reflexes can override pressure reflexes in the special case of skin blo usually activated during strenuous exercise to dissipate the excess heat being produced by the active skel of exercise (as part of the generalized increase in arteriolar tone from increased sympathetic vasoconstrict body heat and temperature build up.

In addition to the increases in skeletal muscle and skin blood flow, coronary blood flow increases substanti metabolic vasodilation of coronary arterioles as a result of increased cardiac work and myocardial oxygen c

Two important mechanisms that participate in the cardiovascular response to dynamic exercise are not sho which was discussed in connection with upright posture. The skeletal muscle pump is a very important fact thus preventing the increased heart rate and cardiac contractility and therefore increased cardiac output fr second factor is the respiratory pump, which also promotes venous return during exercise. Exaggerated re the effectiveness of the respiratory pump and thus enhance venous return and cardiac filling.

As indicated in Figure 10–4, the average central venous pressure does not change much, if at all, during st output and the venous return curves are both shifted upward during exercise. Therefore, the cardiac outpu change in central venous pressure. Thus, the increase in stroke volume that accompanies exercise largely ejection fraction with decreased end-systolic ventricular volume.

In summary, the profound cardiovascular adjustments to dynamic exercise shown in Figure 10–5 all c normal cardiovascular control mechanisms. The tremendous increase in skeletal muscle blood flow is accor by diverting flow away from the kidneys and the splanchnic organs.

Static exercise (ie, isometric) presents a much different disturbance on the cardiovascular system than doe dynamic exercise produces large reductions in total peripheral resistance because of local metabolic vasod moderate intensity, cause a compression of the vessels in the contracting muscles and a reduction in the b does not usually fall during strenuous static exercise and may even increase significantly. The primary dist exercise seem to be set-point-raising inputs to the medullary cardiovascular centers from the cerebral cort mechanoreceptors in the contracting muscle. These inputs result in another example of what is termed the

Cardiovascular effects of static exercise include increases in heart rate, cardiac output, and arterial pressu drive. Static exercise, however, produces less of an increase in heart rate and cardiac output and more of than does dynamic exercise. Because of the higher afterload on the heart during static exercise, cardiac wo

The time course of recovery of the various cardiovascular variables after a bout of exercise depends on ma exercise as well as the overall fitness of the individual. Muscle blood flow normally returns to a resting valu an abnormal arterial obstruction prevents a normal *active hyperemia* from occurring during dynamic exerc isometric exercise, muscle blood flow often rises to near maximum levels before returning to normal with a the effort. Part of the increase in muscle blood flow that follows isometric exercise might be classified as *re* caused by compressional forces within the muscle during the exercise.

Responses to Chronic Exercise

Physical training or "conditioning" produces substantial beneficial effects on the cardiovascular system. The exercise, the intensity and duration of the training period, the age of the individual, and his or her original

In general, however, repeated physical exercise over a period of several weeks is associated with an i alterations associated with conditioning may include increases in circulating blood volume, decreases in he

in arterial blood pressure at rest. During exercise, a trained individual will be able to achieve a given workl stroke volume than will be possible by an untrained individual. These changes produce a general decrease *cardiac reserve* (potential for increasing cardiac output) that can be called on during times of stress. Ventr exercise conditioning regimes (endurance training) whereas increases in myocardial mass and ventricular v conditioning regimes (strength training). These structural alterations improve the pumping capabilities of t of the exercise program and the changes rapidly reverse.

It is clear that exercise and physical conditioning can significantly reduce the incidence and mortality of ca specific mechanisms for these beneficial effects, there is a positive correlation between physical inactivity a disease. It is increasingly evident that recovery from a myocardial infarction or cardiac surgery is enhanced benefits of cardiac rehabilitation programs include improvement in various indices of cardiac function as w fat, serum lipids, psychological sense of well-being and quality of life.

[2] However, as will be described in the next chapter, ventricular chamber enlargement and myocardial hype performance but may be adaptive responses to various pathological states which, if extreme, may not be h

AGE-DEPENDENT CARDIOVASCULAR CHANGES

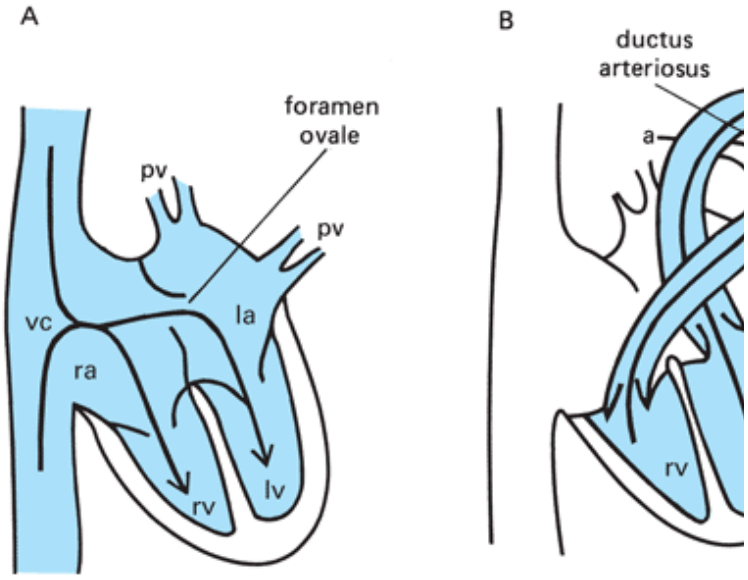
Up to this point, the cardiovascular system of a normal adult has been described. However, there are some birth, growth and aging. The material in the following section is a brief overview of these changes.

Fetal Circulation & Changes at Birth

During fetal development, the exchange of nutrients, gases, and waste products between fetal and ma by diffusion between separate fetal and maternal capillaries without any direct connection between the fet standpoint, the placenta represents a temporary additional large systemic organ for both the fetus and the vascular resistance and receives a substantial portion of the fetal cardiac output.

Blood circulation in the developing fetus completely bypasses the collapsed fetal lungs. No blood flows into the collapsed fetal lungs is essentially infinite. By the special structural arrangements shown in Figure 10–(to pump blood through the systemic organs and the placenta. As shown in Figure 10–6A, fetal blood return left and right hearts together because of an opening in the intraatrial septum called the *foramen ovale*. As fetal right heart does not enter the occluded pulmonary circulation but rather is diverted into the aorta thr and the aorta called the *ductus arteriosis*.

Figure 10–6.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Fetal circulation during cardiac filling A and cardiac ejection B. pv, pulmonary veins; la, left atrium; lv, lef cavae; a, aorta; pa, pulmonary artery.

An abrupt decrease in pulmonary vascular resistance occurs at birth with the onset of lung ventilation. This pulmonary artery and tends to lower pulmonary arterial pressure. Meanwhile, total systemic vascular resis through the placenta. This causes a rise in aortic pressure, which retards or even reverses the flow through incompletely understood but clearly linked to a rise in blood oxygen tension, the ductus arteriosis gradually ranging from hours to a few days. The circulatory changes that occur at birth tend to simultaneously increa that on the right. This indirectly causes left atrial pressure to increase above that in the right atrium so tha is reversed. Reverse flow through the foramen ovale is, however, prevented by a flaplike valve that covers ovale eventually is closed permanently by the growth of fibrous tissue.

Pediatric Cardiovascular Characteristics

Cardiovascular variables change significantly between birth and adulthood. The normal neonate has, by ad beats/min) and a low arterial blood pressure (average of 60/35 mmHg). These values rapidly change over respectively). By the time the child enters adolescence, these values are near adult levels.

Pulmonary vascular resistance decreases precipitously at birth as described above and then continues to d pressures resemble adult levels. These resistance changes appear to be due to a progressive remodeling o diameter vessels to thin-walled large diameter microvessels.

It is noteworthy that distinct differences between right and left ventricular mass and wall thickness develop hypertrophic response of the left ventricle to the increased afterload it must assume at birth. Accordingly, ventricular dominance (electrical axis orientation) that converts to the normal left ventricular dominance d

Heart murmurs are also quite common in childhood and have been reported to be present in as many as 5 category of "innocent" murmurs resulting from normal cardiac tissue vibrations, high flow through valves, easy to hear. Less than 1% of them result from various congenital heart defects.

Growth and development of the vascular system parallels growth and development of the body with most shortly after birth.

Cardiovascular Changes with Normal Aging

In general, as persons get older, they get slower, stiffer, and drier. Connective tissue becomes less elastic activity of dividing cells becomes slower, and fixed postmitotic cells (such as nerve and muscle fibers) are physiological processes, they do have an influence upon the rate at which various homeostatic mechanism


Age-dependent changes that occur in the heart include: (1) a decrease in the resting and maximum c an increase in the contraction and relaxation time of the heart muscle, (4) an increase in the myocardial st functioning myocytes, and (6) an accumulation of pigment in the myocardial cells.

Changes that occur in the vascular bed with age include a decrease in capillary density in some tissues, a peripheral vascular resistance. These changes combine to produce the age-dependent increases in arterial discussed in Chapter 6. The increases in arterial pressure impose a greater afterload upon the heart, and t decreases in cardiac index.

Arterial baroreceptor-induced responses to changes in blood pressure are blunted with age. This is due in baroreceptors because of the age-dependent increase in arterial rigidity. In addition, the total amount of n of the myocardium decreases with age, and the myocardial responsiveness to catecholamines declines. Th compromised. These changes may partially account for the apparent age-dependent sluggishness in the re

It is important (although often difficult) to separate age-dependent alterations from disease-induced chang the major cause of death in an aging population. Atherosclerosis and hypertension are the primary culprits necessary to be categorized as aging processes but generally occur with increasing incidence in the older p risk factors (smoking, obesity, high fat or high sodium diets, inactivity) by modification of lifestyle can alte diseases. It is also possible that some of the previously mentioned interventions may prevent early expres life span of a given individual. No practical intervention, however, is currently available that will increase th

EFFECT OF GENDER


There are a few well-documented gender-dependent differences in the cardiovascular system. Compa lower left ventricular mass to body mass ratio, which may reflect a lower cardiac afterload in women. This aortic compliance, and improved ability to induce vasodilatory mechanisms (such as endothelial-dependen thought to be related to protective effects of estrogen and may account for the lowered risk of premenopa menopause, these gender differences disappear. In fact, older women with ischemic heart disease often ha

There are also gender-dependent differences in cardiac electrical properties. Women have lower intrinsic h greater risk for developing long-QT syndrome and torsades de pointes. They are also twice as likely as me

However, it should be noted that most basic cardiovascular physiological processes are not greatly influenc physiological responses within genders are usually as large as, or larger than, differences between genders

KEY CONCEPTS

1. Cardiovascular responses to physiological stresses should be evaluated in terms of the initial effects o reflex compensatory responses.

2. Changes in intrathoracic pressure due to respiratory activity have significant effects on the cardiovasc cardiac filling.

3. Gravity, and hence body position, has a significant effect on the cardiovascular system, and various re venous pooling that accompanies the upright position.

4. Long-term bed rest causes decreases in circulating blood volume that contributes to orthostatic hypot

5. The primary cardiovascular disturbances of exercise (central command and muscle vasodilation) evok major changes in muscle blood flow and cardiac output.

6. Chronic exercise (training) evokes compensatory adjustments in cardiovascular characteristics and mu efficiency.

7. Circulatory pathways in the fetus are significantly different from those of the newborn and change abr

8. Aging results in decreases in the maximal capabilities of cardiovascular responses that are distinct fro

9. Gender influences several cardiovascular characteristics and disease susceptibility particularly before t

STUDY QUESTIONS

10–1. How are the thin-walled capillaries in the feet able to withstand pressures greater than 100 mmHg in

10–2. Soldiers faint when standing at attention on a very hot day more often than on a cooler day. Why?

10–3. For several days after an extended period of bed rest, patients often become dizzy when they stand arterial pressure (*orthostatic hypotension*). Why might this be so?

10–4. Vertical immersion to the neck in tepid water produces a diuresis in many individuals. What mechani

10–5. How is the decrease in skeletal muscle vascular resistance evident from the data presented in Figure

10–6. Is a decrease in total peripheral resistance implied in Figure 10–4?

10–7. What in Figure 10–4 implies increased sympathetic activity?

10–8. From the information given in Figure 10–4,

a. Calculate the resting and exercising stroke volumes (SVs).

b. Calculate the resting and exercising end-diastolic volumes (EDVs).

c. Calculate the resting and exercising end-systolic volumes (ESVs).

d. Construct a sketch that indicates, as accurately as possible, how this exercise affects the left ventricul

10–9. The "iron lung," used to help polio victims breathe in the mid 20th century, applied an external inter How is this better than positive pressure ventilation of the patient's lungs?

10–10. Blood pressure can rise to extremely high levels during strenuous isometric exercise maneuvers lik

See answers.

SUGGESTED READINGS

Aukland K. Why don't our feet swell in the upright position? *News Physiol Sci.* 1994;9:214–219.

Blomqvist CG, Saltin B. Cardiovascular adaptations to physical training. *Annu Rev Physiol.* 1983;45:169–1

Clifford PS, Hellsten Y. Vasodilatory mechanisms in contracting skeletal muscle. *J Appl Physiol.* 2004;97:39

Ferrari AU, Radaelli A, Centola M. Invited review: aging and the cardiovascular system. *J Appl Physiol.* 200

Jones JH, Linstedt SL. Limits to maximum performance. *Annu Rev Physiol.* 1993;55:547–569. [PMID: 8466

Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: C vascular disease—107:139–146, Part II: The aging heart in health: links to heart disease—107:346–354, F aging—107:490–497.

Longhurst JC. Cardiopulmonary receptors: their function in health and disease. *Prog Cardiovasc Dis.* 1984;

Monos E, Lorant M, Dornyie G, et al. Long-term adapation mechanisms in extremity veins supporting ortho [PMID: 14500802]

Perko MJ, Nielsen HB, Skak C, et al. Mesenteric, coeliac and splanchnic blood flow in humans during exerci

Reckelhoff JF. Gender differences in the regulation of blood pressure. *Hypertension* 2001;37:1199–1208. [

Reckelhoff JF, Fortepiani LA. Novel mechanisms responsible for postmenopausal hypertension. *Hypertensio*

Rowell LB. Neural control of muscle blood flow: importance during dynamic exercise. *Clin Exp Pharmacol Pl*

Rowell LB, Shepherd JT, eds. *Handbook of Physiology.* section 12: Exercise: Regulation and Integration of 1996.

Sejersted OM, Sjogaard G. Dynamics and consequences of potassium shifts in skeletal muscle and heart du 11015618]

Stamler JS, Meissner G. Physiology of nitric oxide in skeletal muscle. *Physiol Rev.* 2001;81:209–237. [PMI

Sussman MA, Anversa P. Myocardial aging and senescence: where have the stem cells gone? *Annu Rev Phy*

Villareal RP, Woodruff AL, Massumi A. Gender and cardiac arrhythmias. *Tex Heart Inst J.* 2001;28:265–27

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.
Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.



a silverchair information system

Note: Large images and tables on this page may necessitate printing in landscape mode.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.

OBJECTIVES

The student understands the primary disturbances, compensatory responses, decompensatory processes, a possible therapeutic interventions that pertain to various abnormal cardiovascular situations.

- *Defines circulatory shock.*
- *Identifies the primary disturbances that can account for cardiogenic, hypovolemic, anaphylactic, septi and neurogenic shock states.*
- *Lists the compensatory processes that may arise during shock.*
- *Identifies the decompensatory processes that may arise during shock and describes how these lead to irreversible shock states.*
- *Indicates how coronary artery disease may lead to abnormal cardiac function.*
- *Defines the term* angina pectoris *and describes the mechanisms that promote its development.*
- *Indicates the mechanisms by which various therapeutic interventions may alleviate angina and myocardial ischemia in association with coronary artery disease.*
- *Defines the term* heart failure *and differentiates between systolic and diastolic dysfunction.*
- *Identifies the short-term and long-term compensatory processes that accompany heart failure.*
- *Describes the advantages and disadvantages of the fluid accumulation that accompanies heart failure*
- *Defines*arterialhypertension.
- *Identifies the various factors that may contribute to the development of primary hypertension.*
- *Describes the role of the kidney in establishing and/or maintaining hypertension.*

CARDIOVASCULAR FUNCTION IN PATHOLOGICAL SITUATIONS: INTRODUCTION

In this last chapter, some of the pathological situations that can interfere with the homeostatic functions o cardiovascular system will be introduced. It is not intended as an in-depth coverage of cardiovascular dise but rather as an introductory presentation of how the physiological processes described previously are evo and/or altered during various abnormal cardiovascular states. In each case there is generally a primary disturbance that evokes appropriate compensatory reflex responses. Often, however, pathological situatio also lead to inappropriate "decompensatory processes" which tend to accelerate the deterioration of cardiovascular function. Therapeutic interventions may be required and are often designed to limit or reve these decompensatory processes.

CIRCULATORY SHOCK



A state of circulatory shock exists whenever there is a generalized, severe reduction in blood supply t body tissues and the metabolic needs of the tissues are not met. Even with all cardiovascular compensato

mechanisms activated, arterial pressure is usually (though not always) low in shock.

Primary Disturbances

In general, the shock state is precipitated by either severely depressed myocardial functional ability o grossly inadequate cardiac filling due to low mean circulatory filling pressure. The former situation is calle *cardiogenic shock* and occurs whenever cardiac pumping ability is compromised (eg, severe arrhythmias, abrupt valve misfunction, coronary occlusions, and myocardial infarction). The latter situation can be caus any of the conditions itemized below that decrease central venous volume and/or ventricular filling:

1. *Hypovolemic shock* accompanies significant hemorrhage (usually greater than 20% of blood volume) severe burns, chronic diarrhea, or prolonged vomiting. These situations can induce shock by depleting l fluids and thus circulating blood volume.

   The occurrence of a *pulmonary embolus* (a clot mobilized from systemic veins lodging in a pulmonary vessel) may evoke a shock state that resembles hypovolemic shock in that left ventricular filling may b compromised. While small emboli have minor functional consequences, large emboli not only reduce cardiac output but interfere with adequate gas exchange in the lungs.

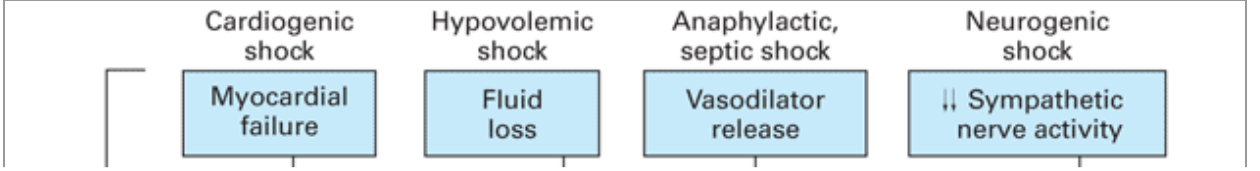
2. *Anaphylactic shock* occurs as a result of a severe allergic reaction to an antigen to which the patient developed a sensitivity (eg, insect bites, antibiotics, certain foods). This immunological event, also calle an "immediate hypersensitivity reaction," is mediated by several substances (such as histamine, prostaglandins, leukotrienes, bradykinin) that, by multiple mechanisms not well understood, results in substantial peripheral vasodilation and increases microvascular permeability.

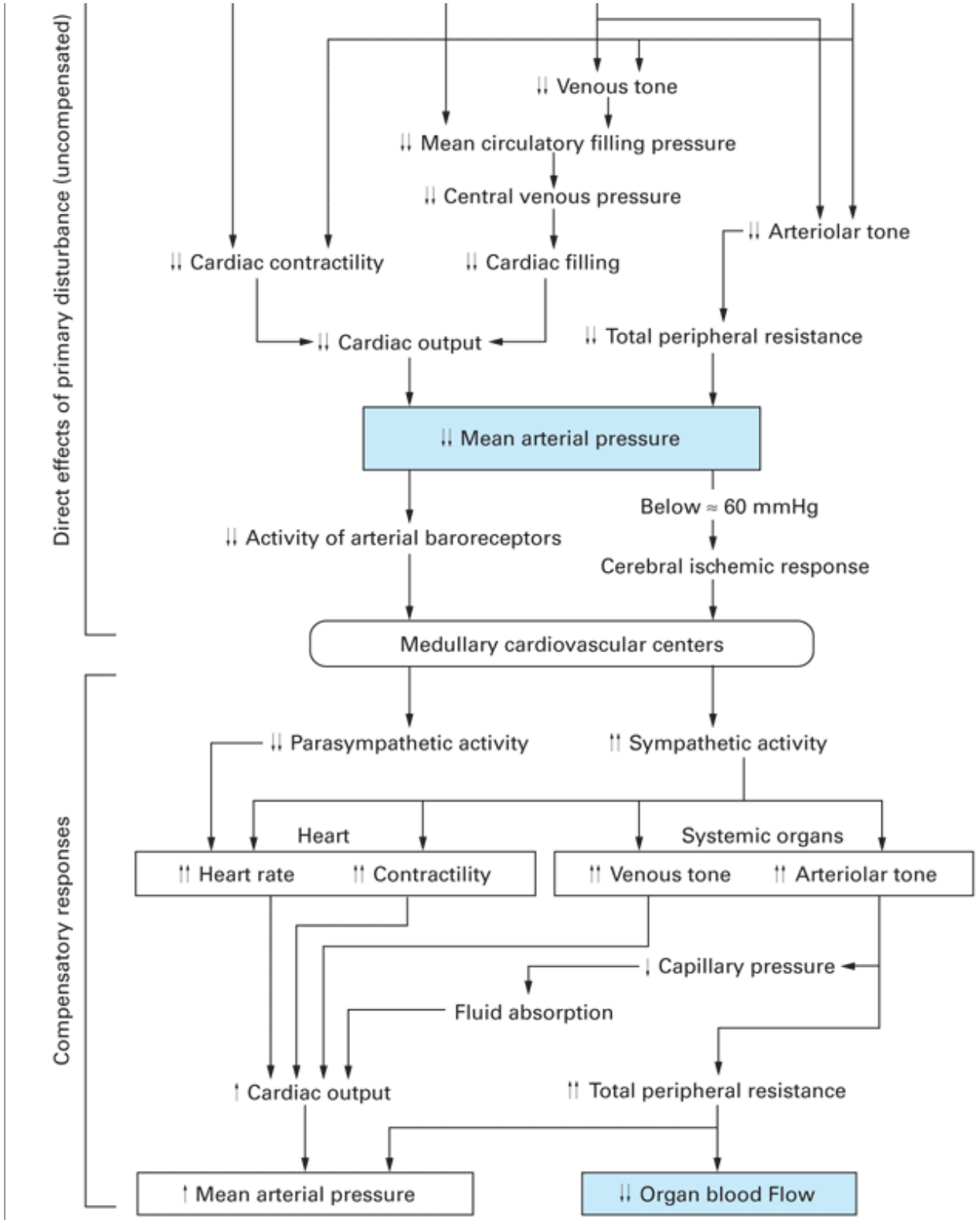
3. *Septic shock* is caused by vasodilator effects of substances released into the circulating blood by infective agents. One of the most common is *endotoxin,* a lipopolysaccharide released from bacteria. Th substance induces the formation of a nitric oxide synthase (called *inducible* nitric oxide synthase to distinguish it from the normally present *constitutive* nitric oxide synthase) in endothelial cells, vascular smooth muscle, and macrophages which then produce large amounts of the vasodilator nitric oxide.

4. *Neurogenic shock* is produced by loss of vascular tone due to inhibition of the normal tonic activity o sympathetic vasoconstrictor nerves and often occurs with deep general anesthesia or in reflex response deep pain associated with traumatic injuries. The transient vasovagal syncope that may be evoked by strong emotions is a mild form of neurogenic shock.

As shown in the top half of Figure 11–1, the common primary disturbances in all forms of shock are decrea cardiac output and decreased mean arterial pressure. Generally, the reduction in arterial pressure is substantial, and so therefore is the influence on the cardiovascular centers from reduced arterial barorecep discharge rate. In addition, in the case of hypovolemic, anaphylactic, and septic shock, diminished activity the cardiopulmonary baroreceptors due to a decrease in central venous pressure and/or volume acts on th medullary cardiovascular centers to stimulate sympathetic output.[1] If arterial pressure falls below about 6 mmHg, brain blood flow begins to fall and this elicits the cerebral ischemic response. As indicated in Chapt the cerebral ischemic response causes the most intense of all activation of the sympathetic nerves.

Figure 11–1.





Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Cardiovascular alterations in shock.

[1] In the case of cardiogenic shock, central venous pressure will increase; and in the case of neurogenic sho
central venous pressure cannot be predicted because both cardiac output and venous return are likely to b

depressed. Thus, in these instances, it is not clear how the cardiopulmonary baroreceptors affect autonom output.

Compensatory Mechanisms

In general, the various forms of shock elicit the compensatory responses in the autonomic nervous sy that we would expect from a fall in blood pressure.[2] These are indicated in the bottom half of Figure 11–1. These compensatory responses to shock, however, may be much more intense than those that accompany more ordinary cardiovascular disturbances. Many of the commonly recognized symptoms of shock (eg, pal cold clammy skin, rapid heart rate, muscle weakness, venous constriction) are a result of greatly increased sympathetic nerve activity. When the immediate compensatory processes are inadequate, the individual m also show signs of abnormally low arterial pressure, such as dizziness, confusion, or loss of consciousness.

There are some additional compensatory processes that are initiated during the shock state:

1. Breathing is rapid and shallow, which promotes venous return to the heart by action of the respiratory pump.

2. The release of renin from the kidney as a result of sympathetic stimulation promotes the formation of th hormone angiotensin II, which is a potent vasoconstrictor and participates in the increase in total peripher resistance even in mild shock states.

3. Circulating levels of epinephrine from the adrenal medulla increase in response to sympathetic stimulati and contribute to the vasoconstriction.

4. The increase in arteriolar constriction reduces capillary hydrostatic pressure. Because plasma oncotic pressure has not changed (at least initially), there is a net shift of fluid from the interstitial space into the vascular space.

5. Glycogenolysis in the liver induced by epinephrine and norepinephrine results in a release of glucose an rise in blood (and interstitial) glucose levels and, more importantly, a rise in extracellular osmolarity by as much as 20 mOsm. This will induce a shift of fluid from the intracellular space into the extracellular (includ intravascular) space.

The latter two processes result in a sort of "autotransfusion" that can move as much as 1 L of fluid into the vascular space in the first hour after the onset of the shock episode. This fluid shift accounts for the reduct in hematocrit that is commonly observed in hemorrhagic shock.

In addition to the immediate compensatory responses shown in Figure 11–1, fluid retention mechanisms a evoked by hypovolemic states that affect the situation in the long term. Recall that a decrease in activity o cardiopulmonary baroreceptors causes production and release of the antidiuretic hormone (vasopressin) fr the posterior pituitary. In addition to being a potent vasoconstrictor and contributing to the increase in tot peripheral resistance in severe shock states, this hormone promotes water retention by the kidneys. Furthermore, activation of the renin-angiotensin-aldosterone pathway promotes renal sodium retention (vi aldosterone) and the thirst sensation and drinking behavior (via angiotensin II). These processes contribut the replenishment of extracellular fluid volume within a few days of the shock episode.

[2] Two primary exceptions to this statement include (1) neurogenic shock, where reflex responses may be absent or lead to further depression of blood pressure, and (2) certain instances of cardiogenic shock associated with inferoposterior myocardial infarctions, which elicit a reflex bradycardia and decrease sympathetic drive (the Bezold-Jarisch reflex).

Decompensatory Processes

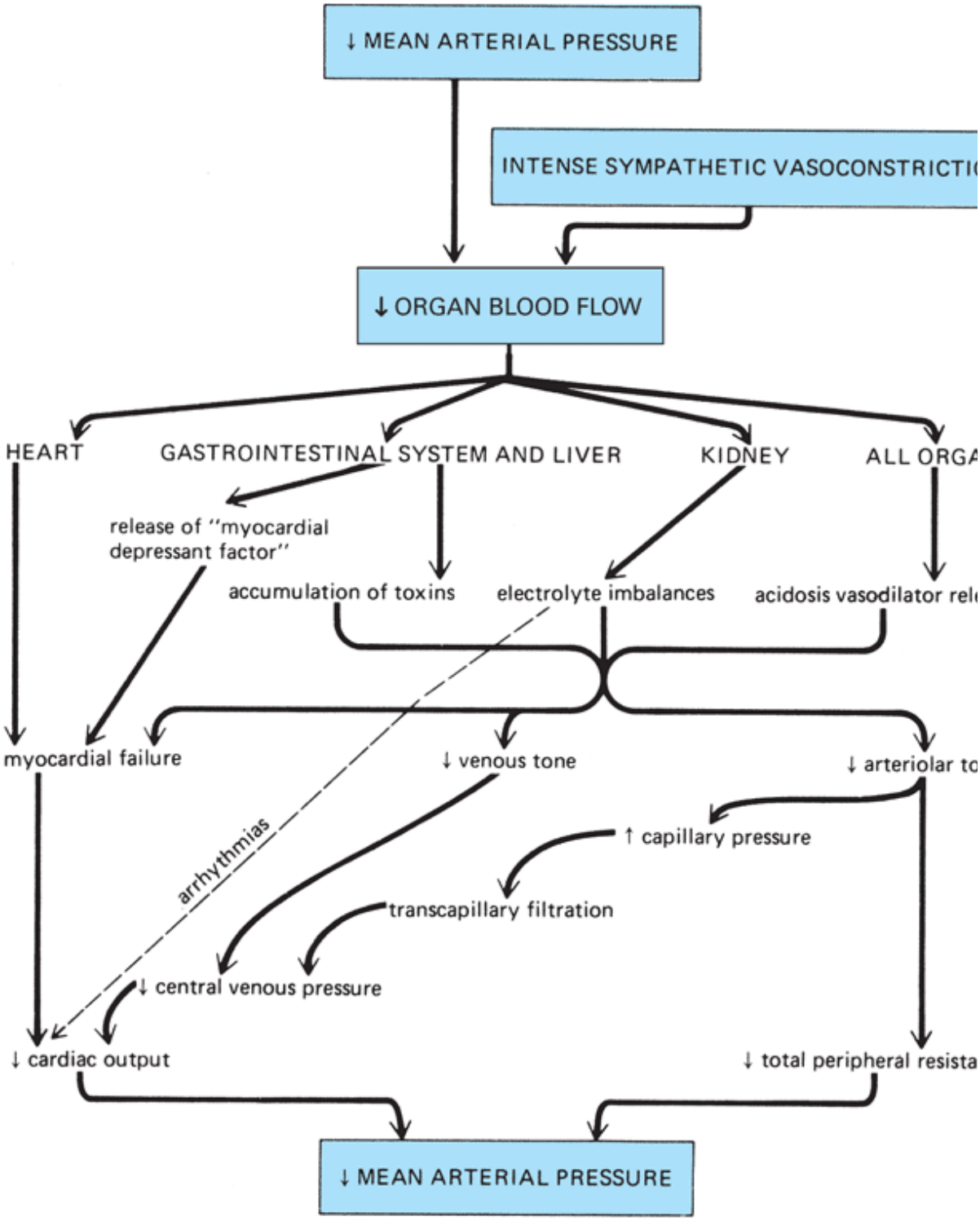
Often the strong compensatory responses elicited during shock are capable of preventing drastic

reductions in arterial pressure. However, because the compensatory mechanisms involve intense arteriolar vasoconstriction, perfusion of tissues other than the heart and brain may be inadequate despite nearly nor arterial pressure. For example, blood flow through organs such as the liver and kidneys may be reduced ne to zero by intense sympathetic activation. The possibility of permanent renal or hepatic ischemic damage i very real concern even in seemingly mild shock situations. Often, patients who have apparently recovered a state of shock die several days later because of renal failure and uremia.

The immediate danger with shock is that it may enter the *progressive stage,* wherein the general cardiovascular situation progressively degenerates, or, worse yet, enter the *irreversible stage,* where no intervention can halt the ultimate collapse of cardiovascular function that results in death.

The mechanisms behind progressive and irreversible shock are not completely understood. However, it is c from the mechanisms shown in Figure 11–2 that bodily homeostasis can progressively deteriorate with prolonged reductions in organ blood flow. These homeostatic disturbances in turn adversely affect various components of the cardiovascular system so that arterial pressure and organ blood flow are further reduce Note that the events shown in Figure 11–2 are *decompensatory mechanisms.* Reduced arterial pressure le to alterations that further reduce arterial pressure rather than correct it. These decompensatory mechanis that are occurring at the tissue level to lower blood pressure are eventually further compounded by a redu in sympathetic drive and a change from vasoconstriction to vasodilation with a further lowering of blood pressure. The factors that lead to this unexpected reduction in sympathetic drive from the medullary cardiovascular centers are not clearly understood. If the shock state is severe enough and/or has persisted long enough to enter the progressive stage, the self-reinforcing decompensatory mechanisms progressivel drive arterial pressure down. Unless corrective measures are taken quickly, death will ultimately result.

Figure 11–2.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Decompensatory mechanisms in shock.

CARDIAC DISTURBANCES

Coronary Artery Disease

Whenever coronary blood flow falls below that required to meet the metabolic needs of the heart, the myocardium is said to be *ischemic* and the pumping capability of the heart is impaired. The most common cause of myocardial ischemia is atherosclerotic disease of the large coronary arteries. In atherosclerotic disease, localized lipid deposits called *plaques* develop within the arterial walls. With severe disease these plaques may become calcified and so large that they physically narrow the lumen of arteries (producing a stenosis) and thus greatly and permanently increase the normally low vascular resistance of these large arteries. This extra resistance adds to the resistance of other coronary vascular segments and tends to red coronary flow. If the coronary artery stenosis is not too severe, local metabolic vasodilator mechanisms m reduce arteriolar resistance sufficiently to compensate for the abnormally large arterial resistance. Thus, a individual with coronary artery disease may have perfectly normal coronary blood flow when resting. A coronary artery stenosis of any significance will, however, limit the extent to which coronary flow can incre above its resting value by reducing maximum achievable coronary flow. This occurs because, even with ve low arteriolar resistance, the overall vascular resistance of the coronary vascular bed is high if arterial resistance is high.

Coronary artery disease can jeopardize cardiac function in several ways. Ischemic muscle cells are electric irritable and unstable and the danger of fibrillation is enhanced. During ischemia, the normal cardiac electr excitation pathways may be altered and often ectopic pacemaker foci develop. Electrocardiographic manifestations of myocardial ischemia can be observed in individuals with coronary artery disease during exercise stress tests. In addition, there is some evidence that platelet aggregation and clotting function m be abnormal in atherosclerotic coronary arteries and the danger of thrombus or emboli formation is enhan It appears that certain platelet suppressants or anticoagulants such as aspirin may be beneficial in the treatment of this consequence of coronary artery disease. (Details of the blood clotting process are include Appendix D.)

Myocardial ischemia not only impairs the pumping ability of the heart, but also produces intense, debilitati chest pain called *angina pectoris.* Anginal pain is often absent in individuals with coronary artery disease w they are resting but is induced during physical exertion or emotional excitement. Both of these situations e an increase in sympathetic tone that increases myocardial oxygen consumption. Myocardial ischemia and c pain will result if coronary blood flow cannot keep pace with the increase in myocardial metabolism.

Primary treatment of coronary artery disease (and atherosclerosis, in general) should include attempts to lower blood lipids by dietary and pharmacological techniques that prevent (and possibly reverse) further development of the plaques. The interested student should consult medical biochemistry and pharmacolog texts for a complete discussion of this very important topic.

Treatment of angina that is a result of coronary artery disease may involve several different pharmacologi approaches. First, vasodilator drugs such as nitroglycerin may be used to acutely increase coronary blood f In addition to increasing myocardial oxygen delivery by dilating coronary vessels, nitrates may also reduce myocardial oxygen demand by dilating systemic veins and reducing the cardiac preload and by decreasing arterial resistance and reducing the cardiac afterload. Second, β-adrenergic blocking agents such as propranolol may be used to block the effects of cardiac sympathetic nerves on heart rate and contractility. These agents limit myocardial oxygen consumption and prevent it from increasing above the level that the compromised coronary blood flow can sustain. Third, calcium channel blockers such as verapamil may be u to dilate coronary vessels. These drugs, which block entry of calcium into the vascular smooth muscle cell, interfere with normal excitation-contraction coupling. They have been found to be most useful for treating angina caused by vasoconstrictive spasms of large coronary arteries (Prinzmetal's angina).

Invasive or surgical interventions are now commonly used to eliminate coronary artery stenosis. In some

cases, x-ray techniques can be used to visualize a radiopaque, balloon-tipped catheter as it is threaded int the coronary artery to the occluded region. Rapid inflation of the balloon squeezes the plaque against the vessel wall and improves the patency of the vessel. This technique, called coronary angioplasty, may also effective in opening occlusions produced by intravascular clots associated with acute myocardial infarction. small tube-like device called a *stent* is often implanted inside the vessel at the angioplasty site. This rigid implant promotes continued patency of the vessel over a longer period than angioplasty alone. If angioplas and stent placement is inappropriate or unsuccessful, coronary bypass surgery may be performed. The ste coronary artery segments are bypassed by implanting parallel low-resistance pathways formed either from natural (eg, saphenous vein or mammary artery) or artificial vessels.

[3] Another method for treatment of acute myocardial infarction has been the intravascular injection of substances that dissolve blood clots such as streptokinase or tissue plasminogen activating factor. This me is most successful when given within a few hours of the infarction.

Chronic Heart Failure—Systolic Dysfunction

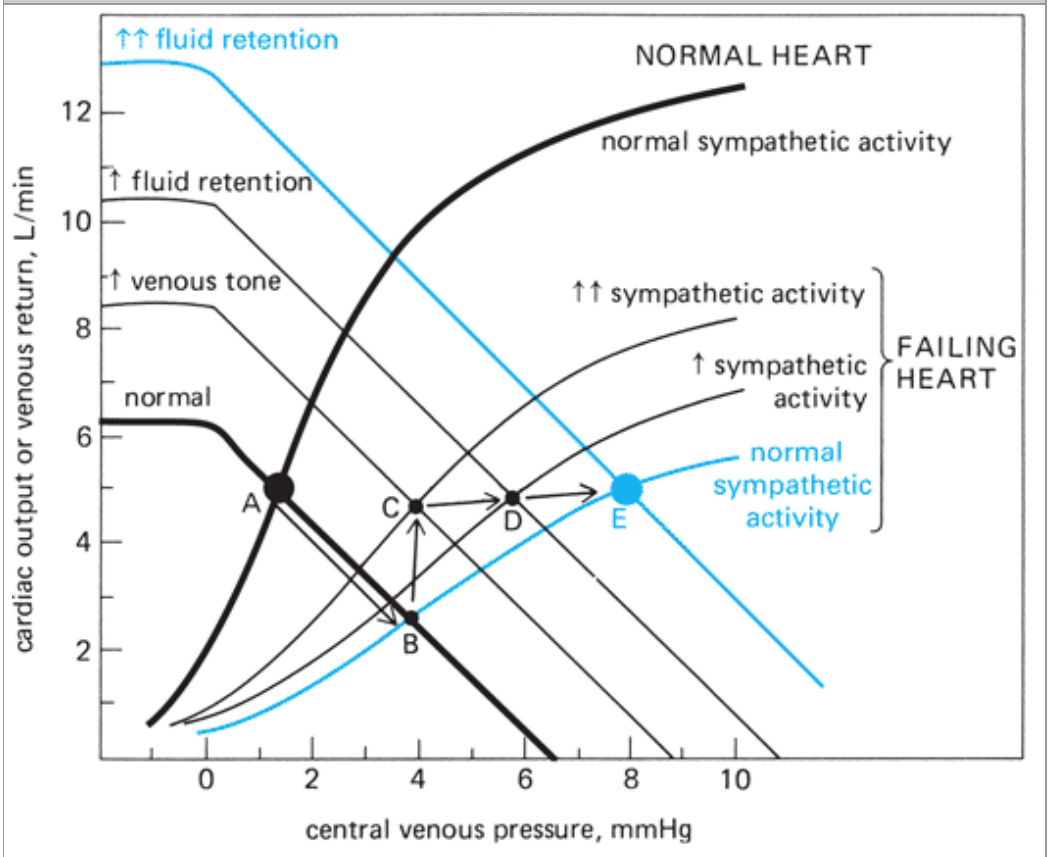
Heart (or cardiac, or myocardial) *failure* is said to exist whenever ventricular function is depressed through myocardial damage, insufficient coronary flow, or any other condition that directly impairs the mechanical performance of heart muscle. By definition, systolic heart failure implies a *lower than normal cardiac function curve,* that is, a reduced cardiac output at any given filling pressure. Acute heart failure ha already been discussed in the context of cardiogenic shock and as part of the decompensatory mechanisms operating in progressive and irreversible shock. Often, however, sustained cardiac "challenges" may induce chronic state of heart failure. Such challenges might include (1) progressive coronary artery disease, (2) sustained elevation in cardiac afterload as that which accompanies arterial hypertension or aortic valve stenosis, or (3) reduced functional muscle mass following myocardial infarction. In some instances, extern causes of cardiac failure cannot be identified and some primary myocyte abnormality is to blame. This situ is referred to as *primary cardiomyopathy.* Regardless of the precipitating cause, most forms of failure are associated eventually with a reduced myocyte function. Many specific structural, functional, and biochemic myocyte alterations accompany severe heart failure. Some of the more well-documented abnormalities inc (1) reduced calcium sequestration by the sarcoplasmic reticulum and up-regulation of the sarcolemmal Na exchanger (leading to low intracellular calcium levels for excitation-contraction coupling), (2) low affinity o troponin for calcium (leading to reduced cross-bridge formation and contractile ability), (3) altered substra metabolism from fatty acid to glucose oxidation, and (4) impaired respiratory chain activity (leading to impaired energy production).

The primary disturbance in systolic heart failure (acute or chronic) is depressed cardiac output and thus lowered arterial pressure. Consequently, all the compensatory responses important in shock (Figure 11–1) also important in heart failure. In chronic heart failure, however, the cardiovascular disturbances may not sufficient to produce a state of shock. Moreover, long-term compensatory mechanisms are especially impo in chronic heart failure.

The circumstances of chronic heart failure are well illustrated by cardiac output and venous function curves such as those shown in Figure 11–3. The normal cardiac output and normal venous function curves interse point A in Figure 11–3. A cardiac output of 5 L/min at a central venous pressure of less than 2 mmHg is indicated by the normal operating point (A). With heart failure, the heart operates on a much lower than normal cardiac output curve. Thus, heart failure alone (uncompensated) shifts the cardiovascular operation from the normal point (A) to a new position, as illustrated by point B in Figure 11–3—ie, cardiac output fal below normal while central venous pressure rises above normal. The decreased cardiac output leads to decreased arterial pressure and reflex activation of the cardiovascular sympathetic nerves. Increased

sympathetic nerve activity tends to (1) raise the cardiac function curve toward normal and (2) increase peripheral venous pressure through venous constriction and thus raise the venous function curve above normal. Cardiovascular operation will shift from point B to point C in Figure 11–3. Thus, the depressed car output is substantially improved by the immediate consequences of increased sympathetic nerve activity. I however, that the cardiac output at point C is still below normal. The arterial pressure associated with cardiovascular operation at point C is likely to be near normal, however, because higher than normal total peripheral resistance will accompany higher than normal sympathetic nerve activity.

Figure 11–3.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Cardiovascular alterations with compensated chronic systolic heart failure.

In the long term, cardiovascular operation cannot remain at point C in Figure 11–3. Operation at poin involves higher than normal sympathetic activity, and this will inevitably cause a gradual increase in blood volume by the mechanisms that were described in Chapter 9. Over several days, there is a progressive ris the venous function curve as a result of increased blood volume and, consequently, increased mean circula filling pressure. Recall that this process involves a sympathetically induced release of renin from the kidne which activates the renin-angiotensin-aldosterone system that promotes fluid retention. This will progressi shift the cardiovascular operating point from C to D to E as shown in Figure 11–3.

Note that increased fluid retention (C → D → E in Figure 11–3) causes a progressive increase in cardiac out

toward normal and simultaneously allows a *reduction in sympathetic nerve activity toward the normal valu* Reduced sympathetic activity is beneficial for several reasons. First, decreased arteriolar constriction perm renal and splanchnic blood flow to return toward more normal values. Second, myocardial oxygen consum may fall as sympathetic nerve activity falls, even though cardiac output tends to increase. Recall that incre heart rate and increased cardiac contractility greatly increase myocardial oxygen consumption. Reduced myocardial oxygen consumption is especially beneficial in situations where inadequate coronary blood flow the cause of the heart failure. In any case, once a normal cardiac output has been achieved, the individual said to be in a "compensated" state.[4]

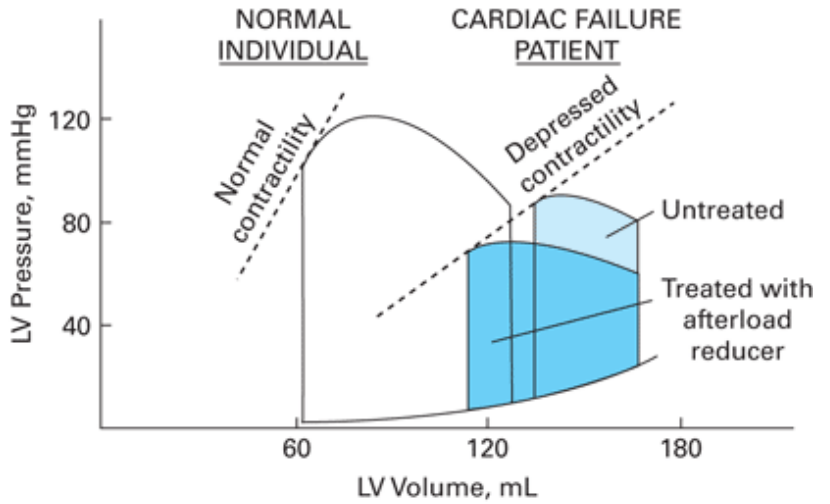
Unfortunately, the consequences of fluid retention in cardiac failure are not all beneficial. Note in Figure 11 that fluid retention (C → D → E) will cause both peripheral and central venous pressures to be much higher than their normal values. Chronically high central venous pressure causes chronically increased end-diasto volume (cardiac dilation). Up to a point, cardiac performance is improved by increased cardiac filling volum through Starling's law. Excessive cardiac dilation, however, can impair cardiac function because increased wall tension is required to generate pressure within an enlarged ventricular chamber ($T = P \times r$, Chapter 2).

The high venous pressure associated with fluid retention also adversely affects organ function because transcapillary fluid filtration, edema formation, and congestion are produced by a high venous pressure (he the commonly used term *congestive heart failure*). Pulmonary edema with dyspnea (shortness of breath)[5] respiratory crisis often accompany left heart failure. Common signs of right heart failure include distended veins, ankle edema, and fluid accumulation in the abdomen (ascites) with liver congestion and dysfunction

In the example shown in Figure 11–3, the depression in the cardiac output curve because of heart failure is only moderately severe. Thus, it is possible, through moderate fluid retention, to achieve a normal cardiac output with essentially normal sympathetic activity (point E). The situation at point E is relatively stable because the stimuli for further fluid retention have been removed. If, however, the heart failure is more severe, the cardiac output curve may be so depressed that normal cardiac output cannot be achieved by a amount of fluid retention. In these cases fluid retention is extremely marked, as is the elevation in venous pressure, and the complications of congestion are very serious problems.

Another way of looking at the effects of cardiac failure is given in Figure 11–4. The left ventricular pressure volume loops describing the events of a cardiac cycle from a failing heart are displaced far to the right of t from normal hearts. The untreated patient described in this figure is in serious trouble with a reduced strol volume and ejection fraction and high filling pressure. Furthermore, the slope of the line describing the en systolic pressure volume relationship is shifted downward and is less steep, indicating the reduced contrac of the cardiac muscle. However, because of this flatter relationship, small reductions in cardiac afterload (i arterial blood pressure) will produce substantial increases in stroke volume and significantly help this patie

Figure 11–4.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Effects of systolic cardiac failure on left ventricular volume-pressure loops.

As might be expected from the previous discussion, the most common symptoms of patients with congesti heart failure are associated with the inability to increase cardiac output (low exercise tolerance and fatigue and with the compensatory fluid accumulation (congestion, shortness of breath, peripheral swelling). In se cases, the ability of the cardiac cells to respond to increases in sympathetic stimulation is diminished by a reduction in the effective number (down-regulation) of the myocyte β_1-adrenergic receptors. This further reduces the ability of the myocytes to increase their contractility as well as the ability of the heart to incre its beating rate in response to sympathetic stimulation. Thus, low maximal heart rates contribute to the reduced exercise tolerance.

Treatment of the patient with congestive heart failure is a difficult challenge. Treatment of the precipitatin condition is of course the ideal approach, but often this cannot be done effectively. The cardiac glycosides digitalis)[7] have been used to improve cardiac contractility (ie, to shift the cardiac function curve upward, increasing contractile force of the myocyte at any given starting length).[8] These drugs are unfortunately q toxic and often have undesirable side effects.

Treatment of the congestive symptoms involves balancing the need for enhanced cardiac filling with the problems of too much fluid. Drugs that promote fluid loss (diuretics such as furosemide or thiazides) are extremely helpful as are the angiotensin-converting enzyme (ACE) inhibitors and the angiotensin II recept blockers.[9] A potent diuretic can quickly save a patient from drowning in the pulmonary exudate and reduce diastolic volume of the dilated heart to acceptable levels, but it can also lower blood pressure to dangerou levels.

[4] The extracellular fluid volume remains expanded after reaching the compensated state even though sympathetic activity may have returned to near normal levels. Net fluid loss requires a period of less than normal sympathetic activity which does not occur. For reasons not well understood, the cardiopulmonary baroreceptor reflexes apparently become less responsive to the increased central venous pressure and vol associated with heart failure.

[5] Patients often complain of difficulty breathing especially during the night (paroxysmal nocturnal dyspnea

Being recumbent promotes a fluid shift from the extremities into the central venous pool and lungs making patient's pulmonary problems worse. Such patients often sleep more comfortably when propped up.

[6] Plasma volume expansion combines with abnormal liver function to reduce the concentration of plasma proteins by as much as 30%. This reduction in plasma oncotic pressure contributes to the development of interstitial edema of congestive heart failure.

[7] A "tea" made from the leaves of the foxglove plant (digitalis purpurea) was used for centuries as a comm folk remedy for the treatment of "dropsy" (congestive heart failure with significant peripheral edema). Wit formal recognition of its medicinal benefits in the late eighteenth century by the English physician Sir Willia Withering, digitalis became a valuable official pharmacological tool.

[8] The mechanism of cardiac glycoside action is thought to involve the inhibition of the sodium/potassium adenosine triphosphatase (Na^+/K^+ ATPase) leading to increases in intracellular [Na^+], which is then excha for extracellular calcium via the Na^+/Ca^{2+} exchanger. This results in "loading" of the sarcoplasmic reticulur during diastole and increased calcium release for subsequent excitation-contraction coupling.

[9] The ACE inhibitors are very helpful to the congestive heart failure patient for several reasons. By inhibitir the conversion of angiotensin I into its more active form, angiotensin II, peripheral vasoconstriction is redu (which improves cardiac pumping by afterload reduction) and aldosterone levels are reduced (which promo diuresis). In addition, ACE inhibitors also seem to prevent some of the apparently inappropriate myocyte a collagen growth that occurs with cardiac overload and failure.

Chronic Heart Failure—Diastolic Dysfunction



Although systolic dysfunction is the primary cause of heart failure, some degree of diastolic dysfunctio also commonly present. Diastolic dysfunction implies a stiffened heart during diastole such that increases i cardiac filling pressure do not produce normal increases in end-diastolic volume. Some individuals (primari elderly patients with hypertension and cardiac hypertrophy) who have symptoms of cardiac failure (exertio dyspnea, fluid retention, pulmonary edema, and high end-diastolic pressures) seem to have normal systoli function, but with normal or even reduced ventricular end-diastolic volumes despite increased cardiac fillin pressure. Thus, the term *diastolic heart failure* has been used to describe this situation.

Potential causes of altered diastolic properties in heart failure include (1) delayed myocyte relaxation early diastole due to slow cytosolic calcium removal processes, (2) inadequate ATP levels required to disconnect myofilament cross-bridges rapidly, (3) residual, low-grade cross-bridge cycling during diastole due to calci leaking from the sarcoplasmic reticulum, (4) increased myofibrillar passive stiffness due to alterations in th myofibrillar protein titin, and (5) decreased cardiac tissue passive compliance due to extracellular remodel collagen cross-linking, and other extracellular matrix protein alterations.

At this point, therapeutic interventions that directly influence diastolic properties are not well understood. Attempts to reduce interstitial fibrosis (with ACE inhibitors and/or angiotensin receptor antagonists) and to reduce diastolic calcium leak from the sarcoplasmic reticulum (with β-adrenergic blockers) have had limite success.

HYPERTENSION



Hypertension is defined as a chronic elevation of arterial blood pressure above 140/90 mmHg for adul is an extremely common cardiovascular problem, affecting more than 20% of the adult population of the western world. It has been established beyond doubt that hypertension increases the risk of coronary arte disease, myocardial infarction, heart failure, stroke, and many other serious cardiovascular problems.

Moreover, it has been clearly demonstrated that the risk of serious cardiovascular incidents is reduced by proper treatment of hypertension.[10]

In approximately 90% of cases, the primary abnormality that produces high blood pressure is unknown. Tl term *essential hypertension* (or *primary hypertension*) is applied to this situation. In the remaining 10% of hypertensive patients, the cause can be traced to a variety of sources, including epinephrine-producing tur (pheochromocytomas), aldosterone-producing tumors (in primary hyperaldosteronism), certain forms of re disease (eg, renal artery stenosis, glomerular nephritis, toxemia of pregnancy), certain neurological disord (eg, brain tumors which increase intracranial pressure), certain thyroid and parathyroid disorders, aortic coarctation, lead poisoning, drug side effects, abuse of certain drugs, or even unusual dietary habits. The h blood pressure that accompanies such known causes is referred to as *secondary hypertension.* Most often, however, the true cause of the hypertension remains a mystery, and it is only the symptom of high blood pressure that is treated.

[10] Because recent findings have verified an increased risk of cardiovascular complications with even mildly elevated blood pressure, a new category designated *prehypertension* has been added to include blood pressures ranging from 120–139 mmHg systolic and 80–89 mmHg diastolic.

Facts About Essential Hypertension

In the midst of a bewildering amount of information about essential hypertension, a few universally accept facts stand out:

1. Genetic factors contribute importantly to the development of hypertension. Familial tendencies for high blood pressure are well documented. In addition, hypertension is generally more common in males than in females and in blacks than in whites.

2. Environmental factors can influence the development of hypertension. High salt diets and/or certain forr psychological stress may either aggravate or precipitate hypertension in genetically susceptible individuals

3. Structural changes in the left heart and arterial vessels occur in response to hypertension. Early alterati include hypertrophy of muscle cells and thickening of the walls of the ventricle and resistance vessels. Late changes associated with deterioration of function include increases in connective tissue and loss of elasticit

4. The established phase of hypertension is associated with an increase in total peripheral resistance. Card output and/or blood volume may be elevated during the early developmental phase, but these variables ar usually normal after the hypertension is established.

5. The increased total peripheral resistance associated with established hypertension may be due to (a) *rarefaction* (decrease in density) of microvessels, (b) the pronounced structural adaptations that occur in t peripheral vascular bed, (c) a continuously increased activity of the vascular smooth muscle cells,[11] (d) an increased sensitivity and reactivity of the vascular smooth muscle cells to external vasoconstrictor stimuli, and/or (e) diminished production and/or effect of endogenous vasodilator substances (eg, nitric oxide).

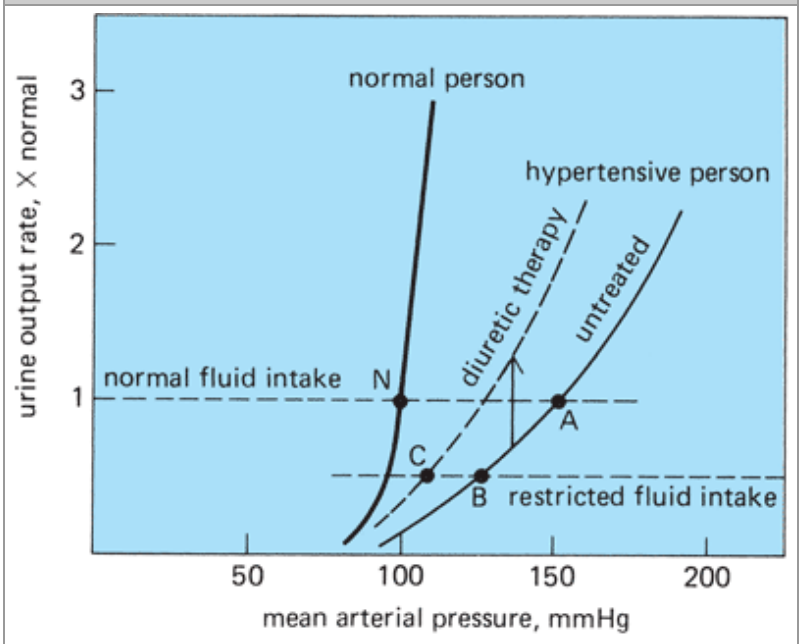
6. The chronic elevation in blood pressure does not appear to be due to a sustained elevation in sympathe vasoconstrictor neural discharge nor is it due to a sustained elevation of any blood-borne vasoconstrictive factor. (Both neural and hormonal influences, however, may help initiate primary hypertension.)

7. Blood pressure-regulating reflexes (both the short-term arterial and cardiopulmonary baroreceptor refle and the long-term, renal-dependent, pressure-regulating reflexes) become adapted or "reset" to regulate h pressure at a higher than normal level.

8. Disturbances in renal function contribute importantly to the development and maintenance of primary hypertension. Recall that the urinary output rate is influenced by arterial pressure, and, in the long term, arterial pressure can stabilize only at the level that makes urinary output rate equal to fluid intake rate. As shown by point N in Figure 11–5, this pressure is approximately 100 mmHg in a normal individual.

All forms of hypertension involve an alteration somewhere in the chain of events by which changes in arter pressure produce changes in urinary output rate (see Figure 9–9) such that the renal function curve is shif rightward as indicated in Figure 11–5. The important feature to note is that *higher than normal arterial pressure is required to produce a normal urinary output rate in hypertension.* While this condition is always present with hypertension, it is not clear whether it could be the common cause of hypertension or simply another one of the many adaptations to it.

Figure 11–5.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

Renal function curves in hypertension and hypertension therapy.

Consider that the untreated hypertensive individual in Figure 11–5 would have a very low urinary output ra at the normal mean arterial pressure of 100 mmHg. Recall from Figure 9–8 that whenever the fluid intake exceeds the urinary output rate, fluid volume must rise and consequently so will cardiac output and mean arterial pressure. With a normal fluid intake rate, this untreated hypertensive patient will ultimately stabili point A (mean arterial pressure = 150 mmHg). Recall from Chapter 9 that the baroreceptors adapt within so that they have a normal discharge rate at the *prevailing* average arterial pressure. Thus, once the hypertensive individual has been at point A for a week or more, even the baroreceptor mechanism will beg resisting acute changes from the 150-mmHg pressure level.

A most important fact to realize is that, although high blood pressure must always ultimately be sustained either high cardiac output or high total peripheral resistance, neither need be the primary cause. A shift in relationship between arterial pressure and urinary output rate, as illustrated in Figure 11–5, however, will always produce hypertension. The possibility that the kidneys actually "set" the blood pressure is supporte evidence accumulating from kidney transplant studies. In these studies, the blood pressure is shown to "fo the kidney (ie, putting a hypertensive kidney in a normotensive individual produces a hypertensive individu whereas putting a normotensive kidney in a hypertensive individual produces a normotensive individual).

[11] Continuous activation of vascular smooth muscle might be evoked by autoregulatory responses to incre blood pressure, as discussed in Chapter 6. A *total body autoregulation* could produce an increase in total

peripheral resistance so that total systemic flow (ie, cardiac output) would remain nearly normal in the presence of increased mean arterial pressure.

Therapeutic Strategies for Essential Hypertension Treatment

In certain hypertensive individuals, restricting salt intake produces a substantial reduction in blood pressur because of the reduced requirement for water retention to osmotically balance the salt load. In the examp Figure 11–5, this effect is illustrated by a shift from point A to point B. The efficacy of lowering salt intake lower arterial pressure depends heavily on the slope of the renal function curve in the hypertensive individ The arterial pressure of a normal individual, for example, is affected only slightly by changes in salt intake because the normal renal function curve is so steep.

A second common treatment of hypertension is diuretic therapy. Many diuretic drugs are available, but mo have the effect of inhibiting renal tubular salt (and therefore fluid) reabsorption. The net effect of diuretic therapy, as shown in Figure 11–5, is that the urinary output rate for a given arterial pressure is increased; diuretic therapy raises the renal function curve. The combined result of restricted fluid intake and diuretic therapy for the hypertensive individual of Figure 11–5 is illustrated by point C.

A third therapeutic intervention is treatment with β-adrenergic blockers that inhibit sympathetic influences the heart and renal renin release. This approach is most successful in hypertensive patients who have high circulating renin levels.

A fourth antihypertensive strategy is to block the effects of the renin-angiotensin system either with ACE inhibitors blocking the formation of the vasoconstrictor angiotensin II or with angiotensin II receptor block Other pharmacological interventions may include use of α-adrenergic receptor blockers, which prevent the vasoconstrictive effects of catecholamines, and calcium channel blockers, which act directly to decrease vascular smooth muscle tone.

Alterations in life style, including reduction of stress, decreases in caloric intake, limitation of the amount o saturated fats in the diet, and establishment of a regular exercise program, may help reduce blood pressu certain individuals.

KEY CONCEPTS

1. Circulatory shock is defined as a generalized, severe reduction in tissue blood flow so that metabolic n are not met.

2. The primary disturbances that can lead to shock can be categorized as those that directly interfere wit pump function (cardiogenic shock) or those that interfere with ventricular filling (hypovolemia, pulmonary embolus, or sustained vascular dilation).

3. Shock is invariably accompanied by a compensatory increase in sympathetic activity aimed at maintai arterial pressure via augmented cardiac output and vascular resistance.

4. Decompensatory processes precipitated by the shock state are generally caused by inadequate blood and loss of homeostasis and result in tissue damage with a progressive and irreversible fall in arterial pres

5. Coronary artery disease, usually associated with development of atherosclerotic plaques, results in a progressive compromise in coronary blood flow which becomes inadequate to meet the tissue's metabolic needs.


Systolic heart failure is defined as a reduction of cardiac muscle contractility and results in a depresse cardiac output at all preloads.


Compensatory fluid retention mechanisms are evoked in heart failure to improve cardiac filling, but w fluid retention is excessive, congestive complications arise (eg, pulmonary edema and abdominal ascites).


Diastolic dysfunction resulting from reduced cardiac compliance often accompanies (and may precipita heart failure.


Chronic elevation of arterial blood pressure due to unknown causes (essential or primary hypertensior a common and serious condition influenced by genetic and environmental factors.

STUDY QUESTIONS

11–1. Clinical signs of hypovolemic shock often include pale and cold skin, dry mucous membranes, weak l rapid pulse, muscle weakness, and mental disorientation or unconsciousness. What are the physiological conditions that account for these signs?

11–2. Which of the following would be helpful to hemorrhagic shock victims?

a. Keep them on their feet

b. Warm them up

c. Give them fluids to drink

d. Maintain their blood pressure with catecholamine-type drugs

11–3. What happens to hematocrit

a. During hypovolemic shock resulting from prolonged diarrhea?

b. During acute cardiogenic shock?

c. During septic shock?

d. With chronic bleeding?

11–4. Left ventricular chamber enlargement with congestive heart failure increases the wall tension require generate a given systolic pressure. True or false?

11–5 Why are diuretic drugs often helpful in treating patients in congestive heart failure?

11–6. What is the potential danger of vigorous diuretic therapy for the patient in heart failure?

11–7. Why does renal artery stenosis produce hypertension?

See answers.

SUGGESTED READINGS

Aurigemma GP, Gaasch WH. Diastolic heart failure. *N Engl J Med.* 2004;351:1097–1105. [PMID: 15356307

Chobanian AV, Bakris GL, Black HR, et al. "Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure." US Department of Health and Human Servic NIH, NHLBI, Publication 04-6230, August 2004. *Hypertension* 2003;42: 1206–1252. [PMID: 14656957]

Cohn JN. Heart failure: future treatment approaches. *Am J Hypertens.* 2000;13:74S–78S.

deWardener HE. The hypothalamus and hypertension. *Physiol Rev.* 2001;81:1599–1658.

Homy CJ, Vatner SF, Vatner DE. b-Adrenergic receptor regulation in the heart in pathophysiological states: abnormal adrenergic responsiveness in cardiac disease. *Annu Rev Physiol.* 1991;53:137–159.

Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation* 2005;111:3481–3488. [PMID: 15983262]

Meneton P, Jeunemaitre X, deWardener HE, Macgregor GA. Links between dietary salt intake, renal salt handling, blood pressure and cardiovascular diseases. *Physiol Rev.* 2005;85:679–715. [PMID: 15788708]

Murasawa S, Asahara T. Endothelial progenitor cells for vasculogenesis. *Physiology* 2005;20:36–42. [PMID 15653838]

Ruskoaho H. Cardiac hormones as diagnostic tools in heart failure. *Endocr Rev.* 2003;24:341–356. [PMID: 12788803]

Sanborn TA, Feldman T. Management strategies for cardiogenic shock. *Curr Opin Cardiol.* 2004;19: 608–6 [PMID: 15502507]

Sessler CN, Perry JC, Varney KL. Management of severe sepsis and septic shock. *Curr Opin Crit Care* 2004;10:354–363. [PMID: 15385751]

Sheldon R, Morillo C, Krahn A. Management of vasovagal syncope: 2004. *Expert Rev Cardiovasc Ther.* 2004;2:915–923. [PMID: 15500436]

Stocker R, Keaney JF Jr. Role of oxidative modifications in atherosclerosis. *Physiol Rev.* 2004;84:1381–147 [PMID: 15383655]

Weber KT. Aldosterone in congestive heart failure. *N Engl J Med.* 2001;345:1689–1697. [PMID: 11759649]

Yellon DM, Downey JM. Preconditioning the myocardium: from cellular physiology to clinical cardiology. *Physiology*2003;83:1113–1151. [PMID: 14506302]

Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: parts I and II. *Circulation*2002;105:1387–1393, 1503–1508.

Zucker IH, Schultz HD, Li YF, et al. The origin of sympathetic outflow in heart failure: the roles of angioten and nitric oxide. *Prog Biophys Mol Biol.* 2004;84:217–232. [PMID: 14769437]

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.
Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.



a silverchair information system

The McGraw-Hill Companies

Note: Large images and tables on this page may necessitate printing in landscape mode.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.

CHAPTER 1

See questions.

1–1. The lungs always receive more blood flow than any other organ because 100% of the cardiac output always passes through the lungs.

1–2. False. Flow through any vascular bed depends on its resistance to flow and the arterial pressure. As long as this pressure is maintained constant (a critical point), alterations in flow through any individual bed will have no influence on flow through other beds in parallel with it.

1–3. A leaky aortic valve will cause a diastolic murmur. Normally, the aortic valve is closed during diastole when there is a large reverse pressure difference between the aorta and left ventricle.

1–4. False. Slowing conduction through the AV node will have no effect on heart rate but will increase the time interval between atrial and ventricular excitation. Heart rate is normally slowed by decreases in the rate of action potential initiation by pacemaker cells in the SA node.

1–5. The blood flow rate through the lungs ($\dot{Q}_L$) must equal the cardiac output (CO) because of the way the cardiovascular system is arranged. ($\dot{Q}_L$) is equal to the pressure drop across the lungs (ΔP_L) divided by the resistance to flow through the lungs (R_L).

$$CO = \dot{Q}_L = \frac{\Delta P_L}{R_L} = \frac{20\ \text{mmHg}}{4\ \text{mmHg} \times \text{min/L}} = 5\ \text{L/min}$$

1–6.

(a) Since

$$\dot{Q} = \frac{\Delta P}{R}$$

then

$$R = \frac{\Delta P}{\dot{Q}}$$

Therefore,

$$R = \frac{100 \text{ mmHg}}{5 \text{ mL/min}}$$
$$= 20 \text{ mmHg} \times \text{min/mL}$$

(b) According to Poiseuille's equation

$$\dot{Q} = \Delta P \frac{\pi r^4}{8L} \frac{1}{\eta}$$

With other factors constant

$$\dot{Q} \alpha r^4$$

Thus doubling the radius with exercise increases flow 16-fold over that at rest. Therefore,

$$\dot{Q} = 16 \times 5 \text{ mL/min}$$
$$= 80 \text{ mL/min during exercise}$$

(c) Since

$$R = \frac{\Delta P}{\dot{Q}}$$

we have

$$R = \frac{100 \text{ mmHg}}{80 \text{ mL/min}}$$
$$= 1.25 \text{ mmHg} \times \text{min/mL}$$

1–7. Significant blood loss has a profound negative effect on cardiac pumping because there is not enough blood left to fill the heart properly. This results in decreased cardiac output because of Starling's law of the heart. The consequence of decreased cardiac pumping ability is a lessened pressure difference between arteries and veins. Because of the basic flow equation, less ΔP causes less flow through the systemic organs. Interstitial homeostasis is compromised when there is abnormally low blood flow through capillaries. Improper interstitial conditions impair nerve function and cognitive ability in the brain and cause weakness in skeletal muscles.

1–8. Norepinephrine is the normal sympathetic neurotransmitter substance, so the same cardiovascular effects that normally accompany activation of sympathetic nerves should be predicted. These include increased heart rate, increased forcefulness of cardiac contraction, arteriolar

constriction, and venous constriction.

1–9. Arteriolar and venous constriction would be expected because the sympathetic nerve effects on these vessels are normally mediated via alpha receptors

There would be no direct effects on the heart expected because the sympathetic effects on the heart are mediated by beta receptors.

1–10. Among other effects, β-adrenergic receptor blockade tends to reduce heart rate and the forcefulness of ventricular contraction. Both these results tend to decrease cardiac output. β-Receptor blockade does not directly influence arteriolar smooth muscle and thus does not directly change the resistance to flow through the systemic vasculature. According to the basic flow equation, less flow through a constant resistance implies a smaller pressure difference exists ($\Delta P = \dot{Q} \times R$). Because the venous pressure is normally 0 mmHg, and ΔP is arterial minus venous pressure, this translates to a lowered arterial pressure.

1–11. Plasma sodium concentration will be 140 mEq/L because serum is just plasma minus a few clotting proteins. Interstitial sodium ion concentration will also be 140 mEq/L because sodium ions are in diffusional equilibrium across capillary walls. Intracellular sodium ion concentration cannot be predicted because sodium is actively pumped out of all cells.

1–12. Severe dehydration that often accompanies loss of body fluids results in a decrease in the fluid volume of all body components, including the plasma volume. In this situation, since blood cells are not lost, hematocrit will increase.

CHAPTER 2

See questions.

2–1. a. The potassium equilibrium potential will become less negative because a lower electrical potential is required to balance the decreased tendency for net K^+ diffusion out of the cell. [$E_{eqK+} = (-61.5\ mV) \log([K^+]_i/[K^+]_o)$.]

b. Because the resting membrane is most permeable to K^+, the resting membrane potential is always close to the K^+ equilibrium potential. Lowering the absolute value of the K^+ equilibrium potential will undoubtedly also lower the absolute resting membrane potential (ie, depolarize the cells).

c. Two things happen when the resting membrane potential is decreased: (1) the potential is closer to the threshold potential which should increase excitability and (2) the fast sodium channels become inactivated, making the cell less excitable. Thus small increases in $[K^+]_o$ may increase excitability whereas large increases in $[K^+]_o$ decrease excitability.

2–2. Elevations in extracellular potassium depolarize cardiac muscle cell membranes as can be ascertained from the Nernst equation (see question 2–1). This depolarization will inactivate sodium and calcium channels, making the cells inexcitable and thus relaxing the heart. This significantly reduces oxygen demands and helps protect the heart tissue against hypoxic injury.

2–3. a. Sodium channel blockers delay the opening of the fast sodium channels in cardiac myocytes. This will slow the rate of depolarization during the action potential (phase 0) which will in turn slow conduction velocity. This results in a prolongation of the PR interval and a widening of the QRS complex.

b. Calcium channel blockers slow the firing rate of SA nodal cells by blocking the calcium component of the diastolic depolarization. They will reduce the rate of rise of the AV nodal cell action potential (which is largely due to calcium entry into the cells) and slow the rate of conduction through the AV node. In addition, calcium channel blockers will decrease the amount of calcium made available to the contractile machinery during excitation-contraction coupling and thus will decrease the tension-producing capabilities of the cardiac muscle cell.

c. Potassium channel blockers inhibit the delayed increase in potassium permeability that contributes importantly to the initiation and rate of repolarization of the cardiac myocyte. This prolongs the duration of the plateau phase of the action potential, prolongs the QT interval of the ECG, and prolongs the effective refractory period of the cell.

2–4. False. It is true that increases in sympathetic activity will increase heart rate (a positive chronotropic effect). However, the electrical refractory period of cardiac cells extends throughout the duration of the cell's contraction. This prevents individual twitches from ever occurring so closely together that they could summate into a tetanic state.

2–5. The correct answers are a and c.Increases in preload increase the amount of shortening by increasing the starting length of the muscle whereas increases in contractility increase the amount of shortening from a given starting length. Increases in afterload limit the amount of shortening because of an increase tension requirement. (See Figures 2–9 and 2–10.)

CHAPTER 3

See questions.

3–1. The ventricular systolic pressure is also 24 mmHg since the normal pulmonic valve provides negligible resistance to flow during ejection. The right ventricular diastolic pressure, however, is determined by systemic venous pressure and will be close to 0 mmHg.

3–2. False. Although there may be minor beat-to-beat inequalities, the average stroke volumes of the right and left ventricles must be equal or blood would accumulate in the pulmonic or systemic circulation.

3–3. All of them are correct answers: a by increasing preload, b by decreasing afterload, and c and d by augmenting contractility.

3–4.

$$\dot{Q} = \frac{\dot{V}_{O_2}}{[O_2]_{SA} - [O_2]_{PA}}$$

$$= \frac{600 \text{ mL/min}}{(200 - 140) \text{ mL/L}}$$

$$= 10 \text{ L/min}$$

3–5. One cannot tell from the information given because the two alterations would have opposite effects on cardiac output. A complete set of ventricular function curves, as well as quantitative information about the changes in filling pressure and sympathetic tone, would be necessary to answer the question. (See Figure 3–8.)

3–6. True. (See Figure 3–6.)

CHAPTER 4

See questions.

4–1. The correct answer is c.

4–2. The correct answer is b. According to the standard ECG polarity conventions, the P, R, and T waves will normally all be downward deflections on lead aVR.

4–3. According to the electrocardiographic conventions, the electrical axis is at 45° and falls within the normal range (in the patient's lower left quadrant). The smallest amplitude deflection will occur on the lead to which the electrical axis is most perpendicular. Lead III and lead aVL are both within 15° of being perpendicular to 45° and therefore will have equally small deflections.

CHAPTER 5

See questions.

5–1. a and b, because filling time is reduced; c, if ventricular rate is rapid; d, for obvious reasons; but not e, because ventricular pacemakers produce a lower heart rate, which is usually associated with a larger stroke volume.

5–2. (a) Aortic stenosis produces a significant pressure difference between the left ventricle and the aorta during systolic ejection.

(b) Mitral stenosis produces a significant pressure difference between the left atrium and the left ventricle during diastole.

5–3. Tricuspid insufficiency. With proper positioning of the patient, pulsations in the neck veins can be observed. Regurgitant flow of blood through a leaky tricuspid valve during systole produces this large abnormal wave.

5–4. Irregular giant a-waves (called cannon waves) are observed in the jugular veins whenever the atrium contracts against a closed tricuspid valve (ie, during ventricular systole). Since in third-degree heart block the atria and ventricles are beating independently, this situation may occur at irregular intervals.

CHAPTER 6

See questions.

6–1. The Fick principle states that

$$\dot{G}_m = \dot{Q}\left([\mathrm{G}]_a - [\mathrm{G}]_v\right)$$

Thus

$$\dot{G}_m = 60\ \mathrm{mL/min} \times \frac{(50 - 30)\ \mathrm{mg}}{100\ \mathrm{mL}} = 12\ \mathrm{mg/min}$$

6–2.

Since

$$\dot{F} = K\left[\left(P_c - P_i\right) - \left(\pi_c - \pi_i\right)\right]$$

then

$$\dot{F} = K\left[28 - (-4) - 24 + 0\right]\ \mathrm{mmHg} = K \times 8\ \mathrm{mmHg}$$

The result is positive, indicating net movement of fluid out of the capillaries.

6–3. All do: a and d by allowing interstitial protein buildup, b by raising P_C, and c for obvious reasons.

6–4. (a) By the parallel resistance equation, the equivalent resistance (R_p) for the parallel pair is $R_p = R_e/2$.

Then by the series resistance equation

$$R_n = R_e + R_p = 3R_e/2$$

(b) Since more resistance precedes the junction (R_e) than follows it ($R_e/2$), P_j will be closer to P_o than to P_i.

(c) The flow through the network (which equals the flow through the inlet vessel) is

$$\dot{Q}_n = \frac{P_i - P_o}{3R_e/2}$$

The pressure drop across the inlet vessel is equal to its resistance times the flow through it

$$P_i - P_j = R_e \frac{P_i - P_o}{3R_e/2} = 2/3\left(P_i - P_o\right)$$

6–5.

Since

$$\dot{Q} = \frac{\Delta P}{R}$$

then

$$R = \frac{\Delta P}{\dot{Q}}$$

and

$$\text{TPR} = \frac{\overline{P}_A - P_{CV}}{\text{CO}}$$

Therefore,

$$\text{TPR} = \frac{\left(100 - 0\right)\ \text{mmHg}}{6\ \text{L/min}}$$
$$= 16.7\ \text{mmHg} \times \text{min/L}$$

6–6. False. TPR is less than the resistance to flow through any of the organs. Each organ, in effect, provides an additional pathway through which blood may flow; thus the individual organ resistances must be greater than the total resistance and

$$\frac{1}{\text{TPR}} = \frac{1}{R_1} + \frac{1}{R_2} + \ldots + \frac{1}{R_n}$$

6–7. False. Since

$$\frac{1}{\text{TPR}} = \frac{1}{R_{\text{kidneys}}} + \cdots$$

a decrease in renal resistance must increase 1/TPR and therefore decrease TPR. When the resistance of any single peripheral organ changes, TPR changes in the same direction.

6–8. True. Since arteriolar constriction tends to reduce the hydrostatic pressure in the capillaries, reabsorptive forces will exceed filtration forces and net reabsorption of interstitial fluid into the vascular bed will occur.

6–9. True. $\bar{P}_A$ = CO x TPR

6–10. False. Increases in cardiac output are often accompanied by decreases in total peripheral resistance. Depending on the relative magnitude of these changes, mean arterial pressure could rise, fall, or remain constant.

6–11. True. P_p SV/C_A. Acute changes in arterial compliance usually do not occur.

6–12. False. An increase in TPR (with CO constant) will produce approximately equal increases in P_S andP_D and increase $\bar{P}_A$ with little influence on pulse pressure.

6–13.

$$\begin{aligned}\bar{P}_A &\approx P_D + \tfrac{1}{3}(P_S - P_D)\\ &\approx 70 + \tfrac{1}{3}(110 - 70)\ \text{mmHg}\\ &\approx 83\ \text{mmHg}\end{aligned}$$

6–14. (a) Recall that SV P_p x C_A.P_p increased by a factor of 1.15 (from 39 to 45 mmHg) during exercise. Since C_A is a relatively fixed parameter in the short term, the increase in P_p must have been produced by an increase in stroke volume of about 15%.

(b) Recall that CO = HR x SV. HR increased by a factor of 2 (from 70 to 140 beats per minute) during exercise, and since SV increased by a factor of about 1.15, cardiac output must have increased by about 130%. [2.0(1.15) = 2.3 times the original level.]

(c) Recall that TPR = $\bar{P}_A$/CO.P_A increased by a factor of 1.13 (from 93 to 105 mmHg) during exercise while CO increased about 2.3 times. Thus, total peripheral resistance must have decreased by about 55% (1.13/2.3 = 0.45 of the original level).

CHAPTER 7

See questions.

7–1. The correct answers are a, b, and c.

7–2. False. Autoregulation of blood flow implies that vascular resistance is adjusted to maintain constant flow in spite of changes in arterial pressure.

7–3. All, because they all increase myocardial oxygen consumption. Myocardial blood flow is controlled primarily by local metabolic mechanisms.

7–4. False. Sympathectomy will cause some dilation of skeletal muscle arterioles but not a maximal dilation because skeletal muscle arterioles have a strong inherent basic tone.

7–5. Hyperventilation decreases the blood P_{CO_2} level. This, in turn, causes cerebral arterioles to constrict (recall that cerebral vascular tone is highly sensitive to changes in P_{CO_2}). The increased cerebral vascular resistance causes a decrease in cerebral blood flow, which produces dizziness and disorientation.

7–6. It is likely that the increased metabolic demands evoked by the exercising skeletal muscle cannot be met by an appropriate increase in blood flow to the muscle. This patient may have some sort of arterial disease (atherosclerosis) that provides a high resistance to flow that cannot be overcome by local metabolic vasodilator mechanisms.

7–7. High left ventricular pressures must be developed to eject blood through the stenotic valve (Figure 5–4). This increases myocardial oxygen consumption, which tends to increase coronary flow. At the same time, however, high intraventricular pressure development enhances the systolic compression of coronary vessels and tends to decrease flow. The local metabolic mechanisms may be adequate to compensate for the increased compressional forces and meet the increased myocardial metabolic needs in a resting individual. However, they may not have enough "reserve" to meet additional needs such as those that accompany exercise. Coronary perfusion pressure may also be decreased if the systemic arterial pressure is lower than normal.

CHAPTER 8

See questions.

8–1. None of the choices is correct. (The very small change in vascular volume that accompanies a decrease in arteriolar tone is not sufficient to have a significant effect on mean circulatory filling pressure.)

8–2. Central venous pressure always settles at the value that makes cardiac output and venous return equal. Therefore anything that shifts the cardiac function curve or the venous return curve affects venous pressure (see list of influences on P_{CV} in Appendix C).

8–3. False. The Frank-Starling law says that, *if other influences on the heart are constant,* cardiac output decreases when central venous pressure decreases (eg, A→B in Figure 8–7). In the intact cardiovascular system, where many things may happen simultaneously, cardiac output and central venous pressure may change in opposite directions (eg, B→C in Figure 8–7).

8–4. None. Venous return must always equal cardiac output in the steady-state situation.

8–5. Because cardiac preload *is* central venous pressure, the physician will try to lower central venous pressure. This requires a left shift of the venous return curve. The two ways that can be done are decreasing circulating volume or decreasing venous tone. The former is often accomplished with diuretic drugs, and the latter can be achieved with certain vasodilator drugs.

CHAPTER 9

See questions.

9–1. a and b will increase; the rest will decrease.

9–2. Carotid sinus massage causes baroreceptors to fire, which in turn decreases sympathetic activity and increases parasympathetic activity from the medullary cardiovascular centers. Both act to slow the pacemaker activity and allow a more normal rhythm to be established.

9–3. a, b, and d increase mean arterial pressure; c and e decrease mean arterial pressure.

9–4. (1) The influence of sympathetic nerve activity on arteriolar tone will be blocked. Arteriolar tone will fall and thus so will TPR. An α_1-blockade represents a pressure-lowering disturbance on the effector portion of the cardiovascular system.

(2) The effector portion function curve will shift downward as shown in Figure 9–6B. (In this instance the effector function curve may also become less steep, because increases in TPR no longer aid in the production of increased $\bar{P}_A$ when sympathetic activity increases.)

(3) A new steady state will be established within the arterial baroreceptor reflex pathway at lower than normal arterial pressure and higher than normal sympathetic nerve activity, as shown in Figure 9–6B.

(4) Heart rate and cardiac output will increase because of the increased sympathetic activity. The cardiac function curve will shift upward, but the venous return curve will not because α-receptor blockade blocks the effect of increased sympathetic activity on the veins. Consequently, central venous pressure will be lower than normal (see Figure 8–6).

9–5. a and d are disturbances to the effector portion of the arterial baroreceptor control system which reduce the arterial pressure produced for any given level of sympathetic activity. Thus, as indicated in Figure 9–6B, the net results of these disturbances and subsequent adjustments to them will be a new steady state at a lower than normal mean arterial pressure and a higher than normal sympathetic activity.

b and c elicit set-point-increasing inputs to the neural portion of the arterial baroreceptor control system that result in a greater than normal sympathetic output for any given level of input from the arterial baroreceptors. Thus, as indicated in Figure 9–7A, in the presence of these disturbances the system will operate at higher than normal mean arterial pressure and sympathetic activity.

9–6. a and c. These disturbances would tend to directly lower blood pressure, which would then lead to a reflex increase in heart rate. Disturbances b and d have no direct effect on the heart or vessels. Rather they act on the medullary cardiovascular centers to raise the set point and cause an increase in sympathetic activity. Consequently, one would expect b and d to cause increases in *both* heart rate and mean arterial pressure.

CHAPTER 10

See questions.

10–1. Because capillaries have such a small radius, the tension in the capillary wall is rather modest despite very high internal pressures according to the law of Laplace ($T = P \times r$).

10–2. Fainting occurs because of decreased cerebral blood flow when mean arterial pressure falls below about 60 mmHg. On a hot day, temperature reflexes override pressure reflexes to produce the increased skin blood flow required for thermal regulation. Thus TPR is lower when standing on a hot day than on a cool one. Consequently, mean arterial pressure falls below 60 mmHg with less lowering of cardiac output on a warm day than on a cool one.

10–3. The cardiovascular response to lying down is just the opposite of that shown in Figure 10–3.

Therefore, patients tend to lose rather than retain fluid during extended bed rest and end up with lower than normal blood volumes. Thus they are less able to cope with an upright posture during the period required for blood volume to reach the value it had when periods of standing were part of the patient's normal routine.

10–4. The pressure produced by the water on the lower part of the body enhances reabsorption of fluid into the capillaries, compresses peripheral veins, reduces the peripheral venous volume, and increases the volume of blood in the central venous pool. This stimulates the cardiopulmonary mechanoreceptors and evokes a diuresis by way of the various neural and hormonal pathways discussed in Chapter 9.

10–5.$R = \bar{P}_A/\dot{Q}$. Skeletal muscle resistance must have decreased considerably during exercise because skeletal muscle flow increased 10-fold (1000%) whereas mean arterial pressure increased much less (11%).

10–6. TPR = $\bar{P}_A$/CO. Total peripheral resistance must have decreased during exercise because cardiac output increased 3-fold (300%), which is relatively much larger than the 11% increase in mean arterial pressure.

10–7. (1) The heart rate during exercise is well above the intrinsic rate (100 beats per minute). This indicates activation of the cardiac sympathetic nerves because withdrawal of cardiac parasympathetic activity cannot increase heart rate above the intrinsic rate (Chapter 2).

(2) Increased arterial pulse pressure and ejection fraction at constant central venous pressure indicates increased stroke volume and cardiac contractility and thus increased activity of cardiac sympathetic nerves (Chapter 3).

(3) Decreased renal and splanchnic blood flows in spite of increased mean arterial pressure indicate sympathetic vasoconstriction (Chapter 4).

10–8. (a) SV = CO/HR

SV = 6000/70 = 86 mL/beat at rest.

SV = 18,000/160 = 113 mL/beat during exercise.

[You may recall that, in the absence of other information, changes in SV can be estimated from changes in arterial pulse pressure, (P_p). The information in Figure 10–4 indicates that P_p increased 1.75 times (from 40 mmHg to 70 mmHg) as a result of exercise whereas SV actually increased only 1.32 times (from 86 mL to 113 mL), as calculated earlier. This discrepancy emphasizes that while SV is a major determinant of P_p, changes in other factors, such as the compliance of arteries (C_A), can influenceP_p as well (see Appendix C). Part of the increase in P_p that accompanies exercise is due to a decrease in effective arterial compliance. The latter is due to (1) an increase in mean arterial pressure with exercise, and (2) the nonlinear nature of the arterial volume-pressure relationship (see Figure 6–8).]

(b) Ejection fraction = SV/EDV, or EDV = SV/ejection fraction

EDV = 86/0.60 = 143 mL/at rest

EDV = 113/0.80 = 141 mL during exercise

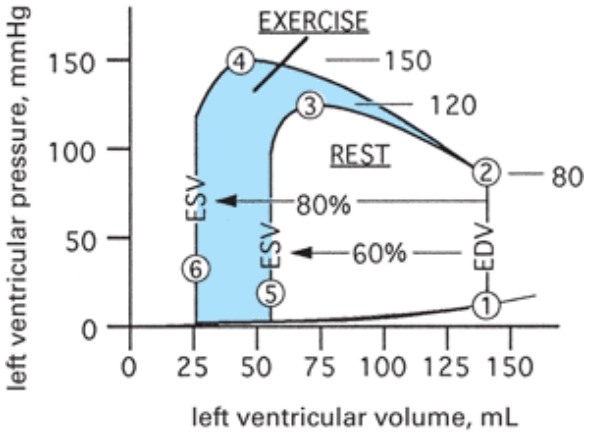
[Recall that central venous pressure, P_{CV}, is the cardiac filling pressure or preload and is therefore the primary determinant of EDV. The EDV changed little with exercise because exercise caused little or no change in P_{CV}.]

(c) SV = EDV – ESV, or ESV = EDV – SV

ESV = 143 – 86 = 57 mL at rest

ESV = 141 – 113 = 28 mL during exercise

[Recall that the primary determinants of ESV are cardiac afterload (mean arterial pressure) and myocardial contractility (see Appendix C). Cardiac afterload increases during exercise and thus goes in the wrong direction to account for a decrease in ESV. Therefore, an increased myocardial contractility, secondary to increased cardiac sympathetic nerve activity, must be primarily responsible for the decrease in ESV that accompanies exercise.]



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

(d)

Key features:

1. End-diastolic volume during both rest and exercise is about 140 mL.

2. Ventricular ejection (decreasing ventricular volume) begins when intraventricular pressure reaches the diastolic aortic pressure and the aortic valve opens. Figure 10–4 indicates an arterial diastolic pressure of 80 mmHg both at rest and during exercise. Thus, ventricular ejection will begin at an intraventricular pressure of 80 mmHg in both situations.

3 and 4. Peak intraventricular pressure normally equals peak (systolic) arterial pressure. Hence, the systolic arterial pressure values in Figure 10–4 indicate peak intraventricular pressures of 120 mmHg and 150 mmHg during rest and exercise, respectively.

5 and 6. As calculated in c earlier, end-systolic volume is 57 mL at rest and decreases to 28 mL during exercise.

10–9. The external negative pressure served to expand the thorax and "pull" air into the lungs through the patient's airways in much the same way that the thoracic muscle and diaphragm expand the thorax in normal breathing. This method of ventilating the lungs did not have the adverse cardiovascular consequences that positive pressure ventilation has.

10–10. Blood flow through muscle is reduced or stopped by compressive forces on skeletal muscle vessels during an isometric muscle contraction. Thus, during an isometric maneuver, total peripheral resistance (TPR) may be higher than normal rather than much lower than normal as it is during phasic exercises such as running. In the absence of decreased TPR but the presence of strong set-point-raising influences (central command) from the cortex on the medullary cardiovascular centers, mean arterial pressure may be regulated to very high values (see point 2 in Figure 9–7A).

CHAPTER 11

See questions.

11–1. Intense sympathetic activation drastically reduces skin blood flow, promotes transcapillary reabsorption of fluids, increases heart rate and contractility (but may not restore stroke volume because of low central venous pressure), and reduces skeletal muscle blood flow. Cerebral blood flow

falls if the compensatory mechanisms do not prevent mean arterial pressure from falling below 60 mmHg.

11–2. (a) Not helpful since gravity tends to promote peripheral venous blood pooling and cause a further fall in arterial pressure.

(b) Not helpful if carried to an extreme. Cutaneous vasodilation produced by warming adds to the cardiovascular stresses.

(c) Helpful if the victim is conscious and can drink since fluid will be rapidly absorbed from the gut to increase circulating blood volume.

(d) Might be helpful as an initial emergency measure to prevent brain damage due to severely reduced blood pressure, but prolonged treatment will promote the decompensatory mechanisms associated with decreased organ blood flow.

11–3. (a) In hypovolemic shock from diarrhea, the hematocrit will probably increase because, even though the compensatory processes will evoke a substantial "auto transfusion" by shifting fluid from the intracellular and interstitial space into the vascular space, this amount of fluid is limited to a liter or less. Therefore, a substantial loss of fluid (without red blood cells) will *raise* the hematocrit significantly.

(b) In cardiogenic shock, the hematocrit may decrease because compensatory actions evoked to maintain blood pressure may promote a fluid shift into the vascular space. However, since central venous pressure (and perhaps peripheral venous pressures) may also be elevated, capillary hydrostatic pressures (and thus fluid shifts) are difficult to predict.

(c) In septic shock, peripheral vasodilation and peripheral venous pooling may actually promote filtration of fluid out of the vasculature in some beds (which would lead to an increased hematocrit) but the low arterial and central venous pressures may counteract this shift so changes in hematocrits are difficult to predict in this situation.

(d) Chronic bleeding disorders are usually associated with low hematocrit and anemia because red blood cell production may not keep pace with red cell losses whereas the volume regulating mechanisms may be able to maintain a normal blood volume.

11–4. True. The law of Laplace states that when the radius (r) of a cylinder (or in this case the irregularly shaped ventricular chamber) increases, the wall tension (T) for a given internal pressure (P) must also increase: $T = P \times r$

11–5. Excessive fluid retention can induce decompensatory mechanisms that further compromise an already weakened heart (eg, inadequate oxygenation of the blood as it passes through edematous lungs, marked cardiac dilation and increased myocardial metabolic needs, liver dysfunction due to congestion). Diuretic therapy reduces fluid volume and the high venous pressures that are the cause of these problems.

11–6. If blood volume and central venous pressure are reduced too far with diuretic therapy, cardiac output may fall to unacceptably low levels through the Frank-Starling law of the heart.

11–7. Because of the high resistance of the stenosis and the pressure drop across it, glomerular capillary pressure and therefore glomerular filtration rate are lower than normal when arterial pressure is normal. Thus, a renal artery stenosis reduces the urinary output rate caused by a given level of arterial pressure. The renal function curve is shifted to the right, and hypertension follows.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.
Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.



a silverchair information system

The McGraw-Hill Companies

McGraw-Hill's ACCESSMedicine

Print Close Window

Note: Large images and tables on this page may necessitate printing in landscape mode.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.

NORMAL VALUES OF ERYTHROCYTES, LEUKOCYTES, AND PLATELETS IN ADULT HUMAN BLOOD

Normal Values of Erythrocytes, Leukocytes, and Platelets in Adult Human Blood[1]

Erythrocytes	4.0–5.5 million/μL of blood
Platelets	130,000–400,000/μL of blood
Leukocytes	4,000–10,000/μL of blood

Type of leukocyte	Percent total leukocytes	Primary role
Polymorphonuclear granulocytes		
Neutrophils	50–70	Phagocytosis
Eosinophils	1–4	Allergic hypersensitivity reactions
Basophils	0–0.75	Allergic hypersentivity reaction
Monocytes	2–8	Phagocytosis and antibody production
Lymphocytes	15–40	Antibody production and cell-mediated immunity

[1] Normal reference ranges vary somewhat with age, gender, and race. They also may vary from lab to lab. To confuse the issue further, various unit measurements are used to report blood data, and so caution must be used in interpreting data.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.
Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.

Medical a silverchair information system The McGraw-Hill Companies

McGraw-Hill's ACCESSMedicine

Print Close Window

Note: Large images and tables on this page may necessitate printing in landscape mode.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.

NORMAL CONSTITUENTS OF ADULT HUMAN PLASMA

Normal Constituents of Adult Human Plasma

Class	Constituent	Amount/normal concentration range
Electrolytes (inorganic)		
Cations	Sodium (Na^+)	136–145 mEq/L
	Potassium (K^+)	3.5–5.0 mEq/L
	Calcium (Ca^{2+})	4.3–5.2 mEq/L
	Magnesium (Mg^{2+})	1.2–1.8 mEq/L
	Iron (Fe^{3+})	60–160 μg/dL
	Copper (Cu^{2+})	70–155 μg/dL
	Hydrogen (H^+)	35–45 nmol/L (pH = 7.35–7.45)
Anions	Chloride (Cl^-)	98–106 mEq/L
	Bicarbonate (HCO_3^-)	23–28 mEq/L
	Lactate	0.67–1.8 mEq/L
	Sulfate (SO_4^{2-})	0.9–1.1 mEq/L
	Phosphate (HPO_4^{2-} mostly)	3.0–4.5 mg/dL
Proteins	Total (7% of plasma weight)	6–8g/dL
	Albumin	3.4–5.0 g/dL
	Globulins	2.2–4.0 g/dL
	Fibrinogen	0.3 g/dL
Nutrients	Glucose	80–120 mg/dL
	Total amino acids	40 mg/dL

	Cholesterol	150–200 mg/dL
	Phospholipids	150–220 mg/dL
	Triglycerides	35–160 mg/dL
Waste products	Uric acid (from nucleic acids)	2.6–7.2 mg/dL
	Blood urea nitrogen (from protein)	8–25 mg/dL
	Creatinine (from creatine)	0.2–0.9 mg/dL
	Bilirubin (from heme)	0.1–1.2 mg/dL

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.
Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.

Mc Graw Hill Medical a silverchair information system The McGraw-Hill Companies

McGraw-Hill's ACCESSMedicine

Print Close Window

Note: Large images and tables on this page may necessitate printing in landscape mode.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.

KEY CARDIOVASCULAR VARIABLES & THEIR NORMAL DETERMINANTS

$\bar{P}_A = CO \times TPR$

$CO = SV \times HR$

$SV = EDV - ESV$

$ejection\ fraction = SV / EDV$

$SV \xleftarrow{\text{ventricular pump}}$
- (+) ↑ cardiac preload (via effect on EDV)
- (+) ↑ cardiac contractility (via effect on ESV)
- (−) ↑ cardiac afterload (via effect on ESV)

$cardiac\ preload \propto P_{CV}$ ("∝" means "is proportional to")

$P_{CV} \xleftarrow{\text{central blood volume}}$
- (+) ↑ total blood volume
- (+) ↑ peripheral venous tone
- (+) skeletal muscle pump
- (+) respiratory pump
- (−) standing
- (−) ↑ cardiac output

venous tone ←
- (+) ↑ sympathetic activity (via NE, α-receptors)

contractility $\xleftarrow{\text{ventricular cells}}$
- (+) ↑ sympathetic activity (via NE, β-receptors)

$cardiac\ afterload \propto \bar{P}_A$

$HR \xleftarrow{\text{SA node cell firing rate}}$
- (+) ↑ sympathetic activity (via NE, β-receptors)
- (−) ↑ parasympathetic activity (via ACh)

$TPR \xleftarrow{\text{arteriolar tone}}$
- (+) ↑ sympathetic activity (via NE, α-receptors)
- (−) ↑ local metabolites (↑ local metabolic rate)

$P_P \propto SV/C_A$

$C_A \xleftarrow{\text{large artery elasticity}}$
- (−) ↑ age

$\bar{P}_A$, mean arterial pressure; *CO,* cardiac output; *TPR,* total peripheral resistance; *SV,* stroke volume; *HR,* heart rate; *ESV,* end-systolic volume; *EDV,* end-diastolic volume; P_{CV}, central venous pressure; NE, norepinephrine; ACh, acetylcholine; P_P, arterial pulse pressure; C_A, arterial compliance; SA, sinoatrial

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.
Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.



a silverchair information system

The McGraw-Hill Companies

Note: Large images and tables on this page may necessitate printing in landscape mode.

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.

HEMOSTASIS

Whenever damage occurs to a blood vessel, a variety of processes are evoked that are aimed at preventing or stopping blood from exiting the vascular space. The three primary processes are summarized in the following list:

I Platelet Aggregation and Plug Formation: occur as a result of the following steps:

A Vessel injury with endothelial damage and collagen exposure.

B Platelet adherence to collagen (mediated by the plasma protein, von Willebrand factor).

C Platelet shape change (from discs to spiny spheres) and degranulation with release of the following:

1 Adenosine diphosphate, which causes platelet aggregation and "plugs" the hole.

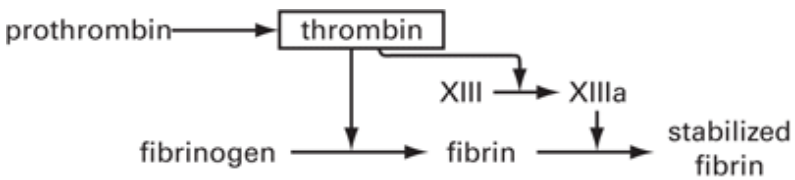
2 Thromboxane, which causes vasoconstriction and potentiates platelet adhesion and aggregation.

(*Aspirin and other cyclooxygenase inhibitors are anticoagulants because they prevent the formation of thromboxane.*)

II Local Vasoconstriction: mediated largely by thromboxane but also may be induced by local release of other chemical signals that constrict local vessels and reduce blood flow.

III Blood Clotting: the formation of a solid gel made up of the protein, fibrin, platelets, and trapped blood cells.

The critical step in blood clotting is the formation of thrombin from prothrombin, which then catalyzes the conversion of fibrinogen to fibrin. The final clot is stabilized by covalent cross-linkages between fibrin strands catalyzed by factor XIIIa (the formation of which is catalyzed by thrombin).



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

The cascade of reactions that leads from vessel injury to the formation of thrombin is shown in the figure below and is described as follows:

A Vessel injury or tissue damage with blood exposure to subendothelial cells that release thromboplastin ("tissue factor").

B The plasma protein factor VII binds to the tissue factor, which converts it to an activated form, factor VIIa.

C VIIa catalyzes conversion of both factors IX and X to activated forms, IXa and Xa, respectively.

D IXa also helps convert factor X to Xa (Stuart factor).

E Xa converts prothrombin to thrombin.

F Thrombin

1 Activates platelets (makes them sticky, induces degranulation, promotes attachment of various factors that participate in clotting).

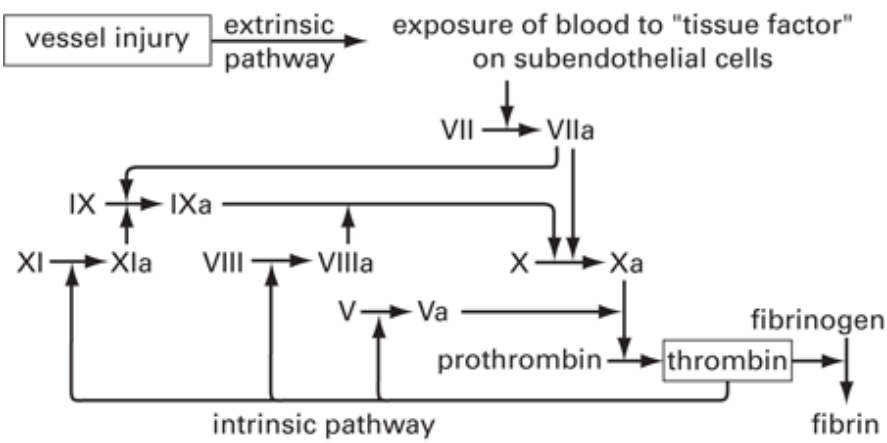
2 Converts fibrinogen to fibrin.

3 Recruits the "intrinsic pathway," which amplifies further formation of factor Xa and facilitates the conversion of prothrombin to thrombin by promoting the following reactions:

a Conversion of factor XI to its activated form, XIa, which then converts factor IX to IXa, which then attaches to activated platelets and converts factor X to Xa.

b Conversion of factor VIII (missing in hemophiliacs) to its activated form, VIIIa, which attaches to activated platelets and accelerates conversion of factor X to Xa.

c Conversion of factor V to its activated form, Va, which attaches to activated platelets and accelerates conversion of prothrombin to thrombin.



Copyright ©2006 by The McGraw-Hill Companies, Inc.
All rights reserved.

(Several agents clinically used as *anticoagulants* interfere with various steps in this clotting process. *Dicoumarol* and *coumadin* block the activity of vitamin K, which is necessary for synthesis of many of the clotting factors by the liver. *Heparin* activates a plasma protein called antithrombin III which, in turn, inactivates thrombin and several of the other clotting factors. Because calcium is an important

clotting cofactor, calcium chelators such as *EDTA, oxalate,* and *citrate* are used to prevent stored blood from clotting. Various *thrombolytic agents* modeled after the endogenous *tissue plasminogen activator (tPA)* are also available that promote dissolution of the fibrin clot after it is formed. These agents promote the formation of plasmin from plasminogen which enzymatically attacks the clot turning it into soluble peptides.)

Copyright ©2006 The McGraw-Hill Companies. All rights reserved.
Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.

Medical a silverchair information system The McGraw-Hill Companies