CECIL
ESSENTIALS OF MEDICINE

SECOND EDITION

PREFACE

This Second Edition of CECIL ESSENTIALS OF MEDICINE renews and advances the goals of its predecessor. Specifically, we have attempted to provide, in this companion to the encyclopedic CECIL TEXTBOOK OF MEDICINE, a succinct and readable text that covers the indispensable elements of the principles and practice of the broad field of internal medicine. Thus this book especially addresses the needs of undergraduate students of the medical sciences, as well as other health care providers who wish to obtain a concise account of current knowledge and practices in internal medicine.

As with the First Edition of ESSENTIALS, this book contains 12 major sections focused either on different organ systems—for example, cardiac diseases and diseases of the nervous system—or on groups of diseases sharing a common theme—for example, infectious diseases and neoplastic disorders. Each section begins with a description of the pertinent signs and symptoms of disease followed by an account of relevant anatomic and physiologic considerations. A series of chapters follow that describe the relevant clinical and laboratory findings of disease states, as well as their therapy. Each of the sections has undergone critical scrutiny by external reviewers, and the editors have revised each section thoroughly to include the latest available information that pertains to the modern practice of internal medicine. Put another way, we intend that ESSENTIALS provide a "core" that students of medicine may digest and assimilate during the traditional undergraduate medical clerkship.

This Second Edition of ESSENTIALS, like its predecessor, includes original contributions by a small number of authors. Each chapter makes generous use of tabular and graphic illustrative material to facilitate the reader's learning. We are grateful to these authors, as well as to residents, fellows, and many colleagues at and outside of our own institutions for advising us on the content and for reviewing critically each of the chapters submitted for this edition.

We are especially grateful to Mr. John Dyson, Senior Medical Editor of the W.B. Saunders Company, for meticulous editorial assistance, and to Mrs. Lorraine Kilmer, Manager of Editorial/Design/Production of the W.B. Saunders Company, for her elegant contributions to the design and preparation of this Second Edition of ESSENTIALS. We also thank our able secretarial staffs, especially Ms. Clementine M. Whitman (Little Rock); Ms. Barbara S. Ryan (Providence); Mr. Lew Brockway (New York); and Ms. Judith A. Serrell (San Francisco).

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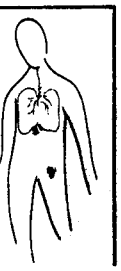

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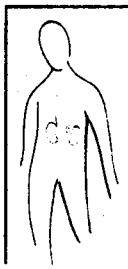

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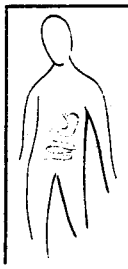

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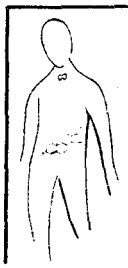

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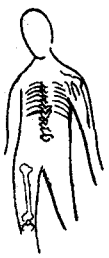

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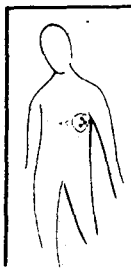

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SECTION

I

CARDIOVASCULAR DISEASES

1

STRUCTURE AND FUNCTION OF THE NORMAL HEART AND BLOOD VESSELS

GROSS ANATOMY

About two thirds of the heart is left of the midline, resulting in an apical impulse normally palpated in the fourth to fifth left intercostal space at the midclavicular line. Two relatively thin-walled upper chambers, the right and left atria, and two thicker-walled lower chambers, the right and left ventricles, compose the heart (Fig. 1–1). The left ventricle has walls significantly thicker than those of the right ventricle because of the considerably higher systemic arterial pressure into which it pumps blood. The interventricular septum separates the two ventricles. The lower and much larger part of the interventricular system is termed the muscular interventricular septum and is composed of muscle the same thickness as that of the left ventricular free wall. The uppermost portion of the septum, termed the membranous interventricular septum, also forms a portion of the right atrial wall.

The tricuspid valve is a three-leaflet structure. The mitral valve has only two leaflets, a large anteromedial and a small posterolateral leaflet. A fibrous ring called the annulus supports each valve and forms a portion of the fibrous structural skeleton of the heart. Chords of fibrous tissue, the chordae tendineae, extend from the ventricular surfaces of both atrioventricular (AV) valves and attach to the papillary muscles. Papillary muscles are bundles of cardiac muscle (myocardium) arising from the interior of the ventricular walls. As the ventricles contract, the papillary muscles also contract, pulling taut the chordae tendineae and preventing the AV valves from prolapsing back into the atria and leaking. There are two papillary muscles in the left ventricle (anteromedial and posterolateral) and three in the right ventricle, connected via the chordae tendineae to each valve leaflet.

A somewhat different type of valve, the semilunar valve, separates the ventricles from their respective outflow tracts. The pulmonic valve is composed of three fibrous leaflets or cusps that are forced open against the walls of the pulmonary artery during ventricular ejection of blood but fall back into the pulmonary outflow tract during diastole, their free edges coapting to prevent blood from returning into the right ventricle. The aortic valve is a thicker but similar three-valved structure. The aortic wall behind each aortic valve cusp bulges outward, forming three structures known as sinuses of Valsalva. The left and right coronary arteries emerge from the aortic wall of two of these sinuses of Valsalva. The two most anterior aortic cusps are known as the left and right coronary cusps because of the respective origins of the left and right coronary arteries, while the remaining posterior cusp is known as the noncoronary cusp.

The pericardium, a double-layered fibrous structure, encloses the heart. The visceral layer is immediately adjacent to the heart and forms part of the epicardium (outer layer) of the heart. The parietal layer is exterior to the heart and is separated from the visceral layer by a thin film of lubricating fluid (10 to 20 ml total) that allows the heart to move freely within the pericardial sac.

Venous blood returning from the body enters the right atrium through the inferior vena cava from below and the superior vena cava from above (Fig. 1–2). Most venous blood returning from the coronary circulation enters the right atrium via the coronary sinus. Blood from these three sources mixes and enters the right ventricle during diastole, when the tricuspid valve is open. The right ventricle subsequently contracts (systole), closing the tricuspid valve to prevent retrograde blood flow, and ejects blood through the

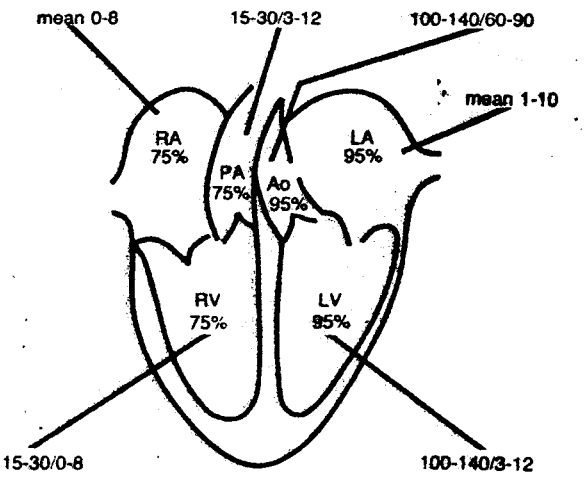

FIGURE 1–1. Orientation of the cardiac chambers and great vessels with normal intracardiac pressures (mm Hg) and oxygen saturations (%).

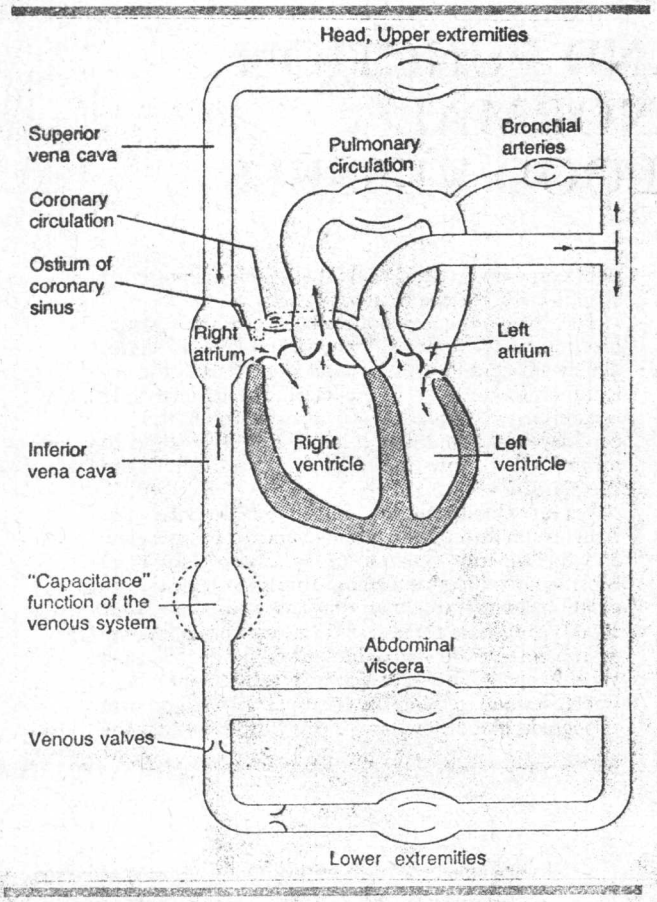

FIGURE 1–2. Schematic representation of the systemic and pulmonary circulatory systems. The venous system contains the greatest amount of blood at any one time and is highly distensible, accommodating a wide range of blood volumes (high capacitance).

pulmonic valve into the pulmonary artery. The right ventricle is anterior to the left ventricle, and the pulmonary artery is anterior to the aorta. The pulmonary artery bifurcates into left and right branches that travel to the left and right lungs. The pulmonary artery has thinner walls than the aorta, and pulmonary arterial pressure is normally much less than aortic pressure. The pulmonary artery progressively divides into smaller and smaller arteries, arterioles, and eventually capillaries, where carbon dioxide is exchanged for oxygen via the pulmonary alveoli. The capillaries lead to pulmonary veins that coalesce to form the four larger pulmonary veins entering the left atrium posteriorly. Oxygenated blood from the pulmonary veins passes from the left atrium through the mitral valve to the left ventricle, which ejects blood during systole across the aortic valve into the aorta. The aorta divides into branches that deliver blood to the entire body (Fig. 1–3). The division continues to form smaller arteries, arterioles, and eventually capillaries that deliver oxygen and metabolic substrates to the tissues in exchange for CO_2 and other waste products. Blood collected from the peripheral capillaries is returned to the right atrium via the venous system.

The right and left coronary arteries course over the epicardial surface of the heart to distribute blood to the myocardium (Fig. 1–4). The left main coronary artery bifurcates within a few centimeters of its origin into two major vessels. The left anterior descending coronary artery proceeds anteriorly in the anterior interventricular groove (between both ventricles) toward the apex of the heart, supplying the anterior free wall of the left ventricle and the anterior two thirds of the septum. The circumflex coronary artery travels posteriorly in the atrioventricular groove (between left atrium and ventricle) and usually supplies a portion of the posterolateral surface of the heart. The right coronary artery courses in the right atrioventricular groove (between right atrium and ventricle) and distributes several branches to the right ventricle before reaching the left ventricle, where the atrioventricular grooves meet the posterior interventricular groove (the "crux" of the heart). In 90 per cent of patients the right coronary artery reaches the crux of the heart and supplies the branches to the AV node and the inferobasal third of the septum (posterior descending artery). This pattern is termed "right dominant distribution" (even though the left coronary artery supplies the majority of the coronary circulation). In approximately 10 per cent of patients, a relatively large circumflex coronary artery reaches the crux of the heart and gives rise to the posterior descending coronary artery and the branch to the AV node. This situation is termed "left dominant," and the diminutive right coronary artery supplies only the right ventricle. Blood is supplied to the sinus node via a branch of the right coronary artery (55 per cent of cases) or the circumflex coronary artery (45 per cent). Most of the venous network of the heart coalesces to form the coronary sinus. Some of the right ventricular and atrial venous drainage occurs via much smaller anterior cardiac veins and tiny thebesian veins, most of which drain directly into the right atrium.

ELECTRICAL CONDUCTION SYSTEM (Fig. 1–5)

Cardiac electrical impulses originate in the sinus node, a spindle-shaped structure 10 to 20 mm long located near the junction of the superior vena cava and the right atrium. Even though various specialized tissues have been postulated to conduct the electrical impulse from the sinus node to the AV node, electrical transmission is probably cell-to-cell via working atrial muscle. The AV node provides the only normal conduction pathway between the atria and the ventricles. It is situated just beneath the right atrial endocardium above the insertion of the septal leaflet of the tricuspid valve and anterior to the ostium of the coronary sinus. After conduction delay in the AV node, the electrical

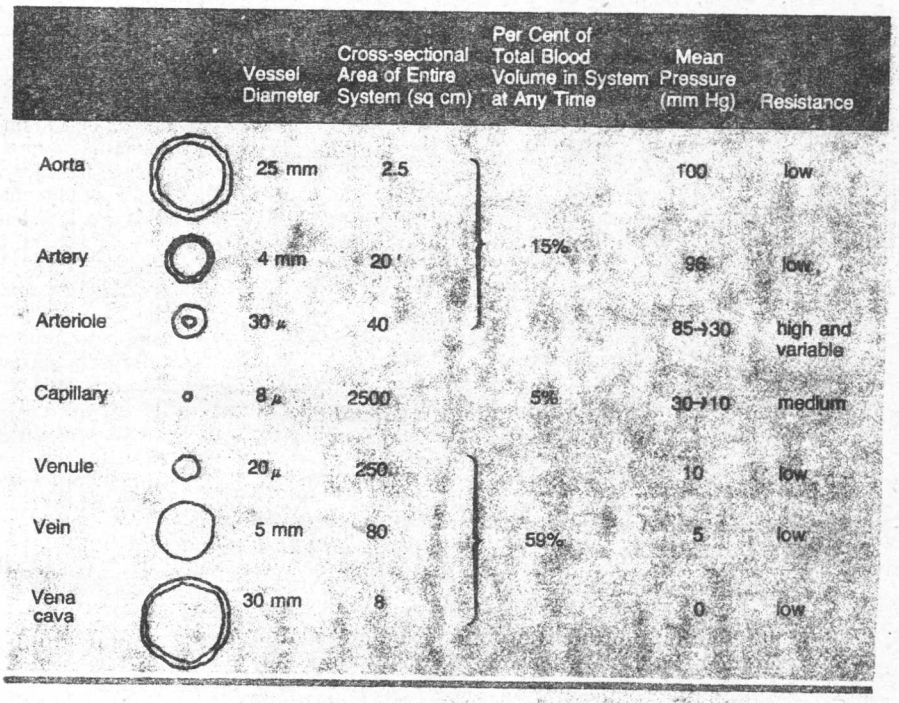

FIGURE 1–3. Major components of the systemic vascular tree. Although the capillaries are smallest in diameter, their total cross-sectional area is largest because of their tremendous numbers. The velocity of flow through any portion of the system is inversely proportional to the total cross-sectional area; therefore the flow of blood is slowest in the capillaries, allowing for exchange of fluid and nutrients. The greatest pressure decrease occurs across the arterioles because of their high resistance to flow; this resistance is variable and regulates blood flow to each vascular bed.

impulse travels to the His bundle, which descends posteriorly along the membranous interventricular septum to the top of the muscular septum. The His bundle gives rise to the right and left bundle branches. The right bundle branch is a single group of fibers that travels down the right ventricular side of the muscular interventricular septum. The left bundle branch is a larger, less discrete array of conducting fibers located on the left side of the interventricular septum. The left bundle branch may divide into two somewhat dis-

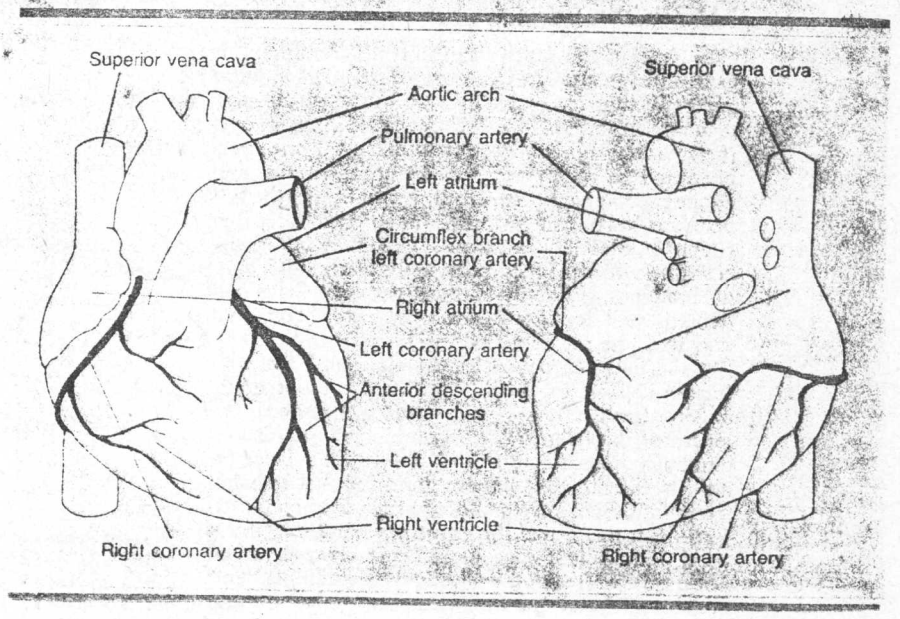

FIGURE 1–4. Major coronary arteries and their branches.

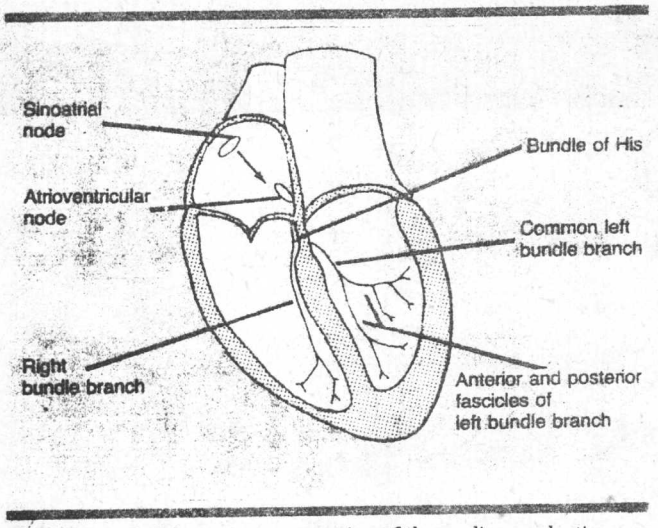

FIGURE 1–5. Schematic representation of the cardiac conduction system.

tinct pathways that travel toward the anterolateral (left anterior fascicle) and posteromedial (left posterior fascicle) papillary muscles. The left posterior fascicle is larger and more diffuse than the anterior fascicle and usually has a more reliable vascular supply than either the left anterior fascicle or the right bundle branch. The left and right bundle branches progressively divide into tiny Purkinje fibers that arborize and finally make intimate contact with ventricular muscle tissue.

MICROSCOPIC ANATOMY

In general, two functional cell types are present in cardiac tissue: those responsible for electrical impulse generation and transmission and those responsible for mechanical contraction. Nodal cells are thought to be the source of normal impulse formation in the sinus node and are richly innervated with adrenergic and cholinergic nerve fibers. Like the sinus node, the AV node and His bundle regions are innervated with a rich supply of cholinergic and adrenergic fibers. Purkinje cells are large clear cells found in the His bundle, bundle branches, and their arborizations. They have particularly well-developed end-to-end connections that may facilitate rapid longitudinal conduction.

Atrial and ventricular myocardial cells, the contractile cells of the heart, contain numerous cross-banded bundles termed myofibrils that traverse the length of the fiber. Myofibrils are composed of longitudinally repeating sarcomeres (Fig. 1–6). Thick filaments composed of myosin constitute the A band, while thin filaments composed primarily of actin extend from the Z line through the I band into the A band, ending at the edges of the central H zone, which is the central area of the A band where thin filaments are absent. Thick and thin filaments overlap in the A band, and interaction between the thick and thin filaments provides the force for contraction of the heart.

The surface membrane of the cell is termed the sarcolemma, and adjacent myocardial cells are connected end to end by a thickened portion of the sarcolemma termed the intercalated disc. Near the Z lines of the sarcolemma are wide invaginations called the T system that traverse the cell. Not continuous with the T system is the sarcoplasmic reticulum that surrounds each myofibril and participates in the excitation of the muscle. When the sarcolemma is depolarized electrically, the impulse conducts through the T system to cause calcium release from the sarcoplasmic reticulum and therefore activates the myofibrils to contract. The thick fibers in the myofibrils are composed of myosin molecules that have the ability to split ATP and interact with the thin actin filaments when activated by calcium. Regulatory proteins, troponin and tropomyosin, inhibit the interaction of actin and myosin unless a calcium-troponin complex is present, which then allows the actin-

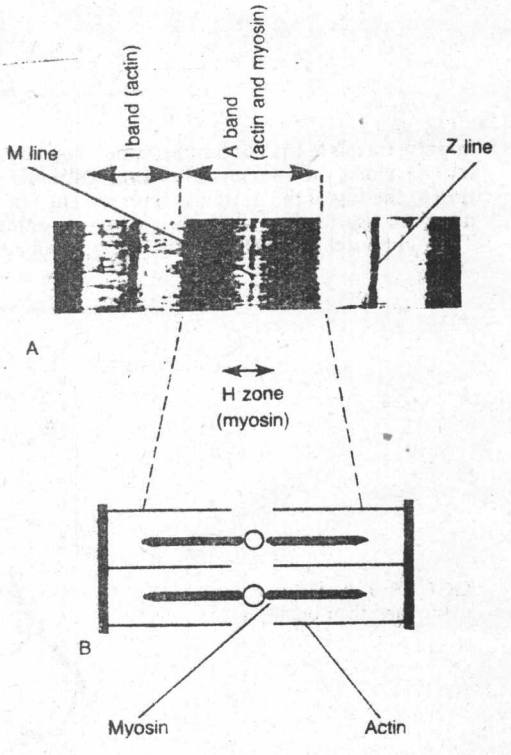

FIGURE 1–6. A, A sarcomere as it appears under the electron microscope. B, Schematic of the location and interaction of actin and myosin (see text).

myosin interaction to proceed. The sarcolemma possesses the ability to control the flux of various ions (especially sodium, potassium, and calcium) into and out of the cell via specific ionic channels located within the membrane. The selective permeability of the membrane establishes ionic gradients and the electrical forces that create and maintain the resting transmembrane potential and generate the action potential (see Chapter 9).

CARDIAC DEVELOPMENT

Congenital heart disease results from altered embryonic development or failure of the rudimentary portion of a structure ever to be formed. Abnormal development of one structure in turn may hinder the development of another portion of the circulatory system (for example, abnormal development of the mitral valve may lead to abnormal formation of the left ventricle).

The fetus' circulation essentially places the pulmonary and systemic systems in parallel rather than in series as in the adult. Oxygenated blood from the umbilical vein passes into the portal venous system and subsequently into the inferior vena cava and is shunted preferentially across the patent foramen ovale to the left heart to perfuse the coronary arteries, head, and upper trunk. Blood returning from the upper portions of the body arrives at the right atrium via the superior vena cava, and most proceeds through the tricuspid valve to the right ventricle and pulmonary artery. However, only a small proportion of this blood goes into the pulmonary arterial tree; most is shunted via the patent ductus arteriosus to the descending aorta. Note that many congenital lesions that cause intracardiac shunts (for example, tetralogy of Fallot) or markedly abnormal cardiac outflow (for example, transposition of the great arteries) would not cause any difficulty during fetal development.

At birth the pulmonary vascular resistance decreases markedly owing to the inflation of the lungs and the increase in oxygen tension to which the pulmonary vessels are exposed. Systemic vascular resistance rises when the umbilical cord is clamped, removing the low-resistance placental circulation. Left atrial pressure rises, which in turn closes the foramen ovale. The increase in arterial P_{O_2} along with alterations in prostaglandins causes the ductus arteriosus to close functionally within 10 to 15 hours. Many congenital heart lesions may not become apparent until cyanosis develops after closure of the foramen ovale or ductus arteriosus.

MYOCARDIAL METABOLISM

The heart uses ATP, created by metabolism of carbohydrates or fatty acids, to derive energy for contraction and electrical activity. Energy for electrical activity is minimal compared to that required for contraction. Stored energy reserves are scarce, and the heart must continually have a source of energy in order to function. The principal oxidative substrate for ATP production is fatty acid, but if it is not available, a variety of carbohydrates can be used. Myocardial metabolism is aerobic, and a constant supply of oxygen must be available. The heart, unlike skeletal muscle, is unable to acquire an "oxygen debt" because of its inability to utilize anaerobic metabolism.

CIRCULATORY PHYSIOLOGY

The interaction between myosin and actin, coupled with ATP produced by oxidative phosphorylation, is thought to be the basis for the contraction of each myofibril and therefore the contraction of the whole muscle. Each myofibril exhibits a property called contractility (or inotropic state) that represents the ability of the fiber to develop contractile force. The force exhibited by the fiber is influenced not only by its contractile state but also by its initial length, or preload, according to the Starling curve (Fig. 1–7). This concept can be expanded from the single fiber to describe the function of the entire ventricle. Thus, the abscissa, formerly preload or fiber length, becomes left ventricular filling pressure or volume (i.e., the amount of stretch on the myocardial fibers in diastole); and the ordinate, formerly tension, becomes stroke volume or stroke work (i.e., the ability of the heart to generate tension). Note that as diastolic pressure increases, the normal heart is able to increase its stroke volume, up to a point. This relationship is referred to as a ventricular function curve and, given identical states of contractility and afterload (see below), defines the amount of work that a heart is able to perform. Several factors determine left ventricular filling pressure (Table 1–1).

The term afterload describes the "impedance" or resistance against which the heart must contract. Like preload, afterload also can refer either to a single myofibril or to the heart as a whole. The afterload is approximated by the arterial pressure, the major determinant of the impedance to left ventricular contraction. In the intact heart, the afterload deter-

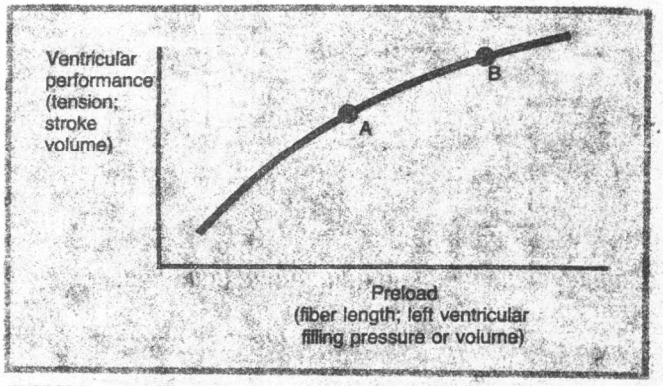

FIGURE 1–7. The normal ventricular function curve. As preload increases from A to B, the curve defines the resultant increase in developed tension or overall cardiac performance.

TABLE 1–1. FACTORS AFFECTING CARDIAC PERFORMANCE

Preload (left ventricular diastolic volume)	Total blood volume	
	Venous tone (sympathetic tone)	
	Body position	
	Intrathoracic and intrapericardial pressure	
	Atrial contraction	
	Pumping action of skeletal muscle	
Afterload (impedance against which the left ventricle must eject blood)	Peripheral vascular resistance	
	Left ventricular volume (preload, wall tension)	
	Physical characteristics of the arterial tree (for example, elasticity of vessels or presence of outflow obstruction)	
Contractility (cardiac performance independent of preload or afterload)	Sympathetic nerve impulses	increased contractility
	Circulating catecholamines	increased contractility
	Digitalis, calcium, other inotropic agents	increased contractility
	Increased heart rate or post-extrasystolic augmentation	increased contractility
	Anoxia, acidosis	decreased contractility
	Pharmacological depression	decreased contractility
	Loss of myocardium	decreased contractility
	Intrinsic depression	decreased contractility
Heart Rate	Autonomic nervous system	
	Temperature, metabolic rate	

mines the amount of blood the heart can pump given a fixed preload and fixed state of contractility; that is, the higher the workload against which the heart must function, the less blood it can eject, and vice versa. Therefore, the ventricular function curve will be shifted up and to the left with decreasing afterload and shifted down and to the right with increasing afterload. Shifts in ventricular function with changes in afterload are minimal in normal ventricles but prominent in failing ventricles.

Heart rate is another determinant of cardiac performance. Even though an increased demand for cardiac output increases contractility and stroke volume via sympathetic nervous system activation, the most important response to sympathetic stimulation serving to increase cardiac output is the rise in heart rate (cardiac output = stroke volume × heart rate). A decrease in the cardiac output or blood pressure increases sympathetic and decreases parasympathetic discharge via baroreceptor mechanisms to increase heart rate. Likewise, an elevated blood pressure will activate the carotid baroreceptors, augment vagal activity, and slow the heart rate.

Four phases of the cardiac cycle can be identified upon initiation of ventricular myocardial contraction (Fig. 1–8). (1) During "isovolumic contraction," the intramyocardial pressure rises with no ejection of blood or change in ventricular volume. (2) When left ventricular pressure reaches that of the aorta, the aortic valve opens and blood is ejected from the contract-

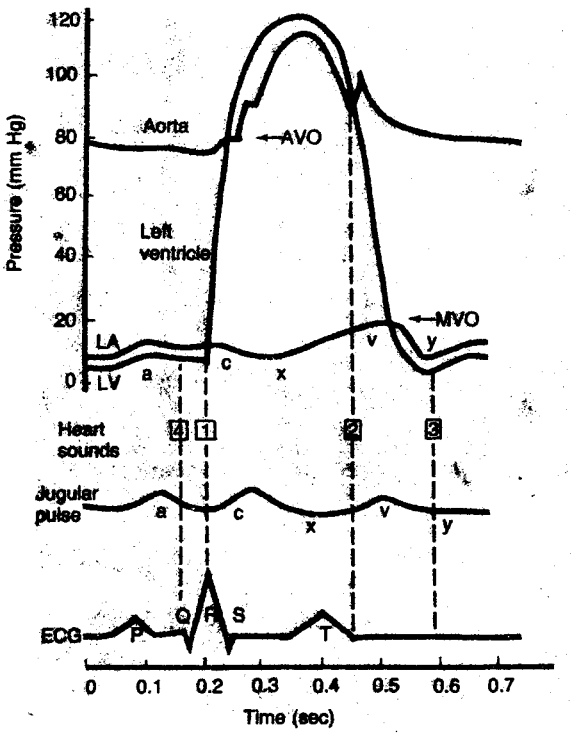

FIGURE 1–8. Simultaneous ECG, pressures obtained from the left atrium, left ventricle, and aorta, and the jugular pulse during one cardiac cycle. For simplification, right-sided heart pressures have been omitted. Normal right atrial pressure closely parallels that of the left atrium, and right ventricular and pulmonary artery pressures time closely with their corresponding left-sided heart counterparts, only being reduced in magnitude. The normal mitral and aortic valve closure precedes tricuspid and pulmonic closure, respectively, whereas valve opening reverses this order. The jugular venous pulse lags behind the right atrial pressure.

During the course of one cardiac cycle, note that the electrical events (ECG) initiate and therefore precede the mechanical (pressure) events and that the latter precede the auscultatory events (heart sounds) they themselves produce. Shortly after the P wave, the atria contract to produce the a wave; a fourth heart sound may succeed the latter. The QRS complex initiates ventricular systole, followed shortly by left ventricular contraction and the rapid build-up of left ventricular (LV) pressure. Almost immediately LV pressure exceeds left atrial (LA) pressure to close the mitral valve and produces the first heart sounds. When LV pressure exceeds aortic pressure, the aortic valve opens (AVO), and when aortic pressure is once again greater than LV pressure, the aortic valve closes to produce the second heart sound and terminate ventricular ejection. The decreasing LV pressure drops below LA pressure to open the mitral valve (MVO), and a period of rapid ventricular filling commences. During this time a third heart sound may be heard. The jugular pulse is explained under the discussion of the venous pulse.

ing ventricle. (3) As the ventricle relaxes and left ventricular pressure decreases, the aortic valve closes, and "isovolumic relaxation" occurs. (4) Upon sufficient decrease in left ventricular pressure, the mitral valve opens and ventricular filling from the atrium occurs. The ventricle fills most rapidly in early diastole and again in late diastole when the atrium contracts. Loss of atrial contraction (e.g., atrial fibrillation or AV dissociation) can impair ventricular filling, especially into a noncompliant ("stiff") vehicle.

Normal intracardiac pressures are shown in Figure 1–1. Atrial pressure curves are composed of the a wave, which is generated by atrial contraction, and the v wave, which is an early diastolic peak caused by filling of the atrium from the peripheral veins. The x descent follows the a wave and the y descent follows the v wave. A small deflection, the c wave, occurs after the a wave in early systole and probably represents bulging of the tricuspid valve apparatus into the left atrium during early systole. Ventricular pressures are described by a peak systolic pressure and an end-diastolic pressure, which is the ventricular pressure immediately before the onset of systole. Note that the minimum left ventricular pressure occurs in early diastole. Aortic and pulmonary artery pressures are represented by a peak systolic and a minimum diastolic value.

Cardiac output is a measure of the amount of blood flow in liters/minute. The cardiac index is the cardiac output divided by the body surface area and is normally 2.8 to 4.2 L/min/sq m. Cardiac output can be measured by either indicator dilution or the Fick technique (see Chapter 3). The pulmonary and systemic vascular resistances are also important parameters of circulatory function. Resistance is defined as the difference in pressure across a capillary bed divided by the flow across that capillary bed, usually the cardiac output: $[R = (P_1 - P_2)/\text{flow}]$ (Fig. 1–3). For example, the pulmonary vascular resistance is the difference between the mean pulmonary arterial pressure and mean pulmonary venous pressure, divided by the pulmonary blood flow. Similarly, systemic vascular resistance is the difference between mean arterial pressure and mean right atrial pressure, divided by the systemic cardiac output. Note that an increase in arterial pressure may occur without necessarily causing an increase in vascular resistance. For example, if both pulmonary arterial and venous pressures are elevated to the same degree, pulmonary vascular resistance will be unchanged; if pulmonary blood flow and pulmonary arterial pressure increase while pulmonary venous pressure remains the same, resistance will be unchanged.

The most widely used parameter for quantitating overall ventricular function is the ejection fraction, defined as the diastolic volume minus the systolic volume (stroke volume), divided by the diastolic volume: [(DV − SV)/DV]. These volumes may be estimated from either invasive (e.g., left ventriculography) or noninvasive (e.g., echocardiography or radionuclide ventriculography) tests. The ejection fraction may be a useful gross evaluation of ventricular function, but there are situations (for example, when a large left ventricular aneurysm is present) in which the ejection fraction can give a misleading impression of overall ventricular function.

PHYSIOLOGY OF THE CORONARY CIRCULATION

Three major determinants of myocardial oxygen consumption are contractility, heart rate, and wall tension. Myocardial wall tension is directly proportional to the pressure within the ventricular chamber and the radius of the ventricular chamber (Laplace relationship). The myocardial mass is a determinant of wall tension and therefore myocardial oxygen consumption; the larger the muscle mass, the more oxygen needed.

The coronary vascular bed is able to autoregulate, enabling myocardial oxygen and substrate delivery to equal the demand. Coronary vascular resistance is normally determined by the arterioles and is influenced by neural and metabolic factors. Both the sympathetic and parasympathetic nervous systems innervate the coronary arteries. Alpha receptor stimulation causes vasoconstriction while stimulation of the beta-2 receptor as well as the vagus causes vasodilation. Metabolic factors regulate regional perfusion. Several mediators including oxygen, carbon dioxide, and metabolites such as adenosine are probably important. However, when coronary perfusion pressure falls to below 60 to 70 mm Hg, the vessels become maximally dilated and flow depends on perfusion pressure alone, since capability for further autoregulation is lost. The normal coronary vascular bed has a capacity to increase its blood flow four- to five-fold during maximal exercise. Hemodynamic factors that affect coronary perfusion include arterial pressure (especially diastolic pressure, since coronary flow occurs primarily in diastole), the time spent in diastole, and the intraventricular pressure (which exerts tension on the myocardial walls and diminishes coronary flow).

PHYSIOLOGY OF THE SYSTEMIC CIRCULATION

The aortic wall contains elastic fibers that allow it to expand with the expulsion of blood from the left ventricle, somewhat damping the pulse pressure generated and aiding diastolic flow to the coronary arteries with its recoil. The aorta successively branches into smaller and smaller vessels until arterioles, the major determinants of resistance in the systemic circulation, are reached (see Fig. 1–3). The arterioles contain a vascular sphincter that modulates blood flow dependent on regional metabolic needs; for example, acidosis and decreased oxygen tension increase regional perfusion, and vice versa. The capillaries consist of a single endothelial cell layer and allow diffusion of oxygen, nutrients, CO_2, and waste products. The capillaries lead into the venous system, where blood is eventually delivered back to the right atrium. The flow