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By contrast, two-dimensional and Doppler echocardiography (Chap. 248) are indicated in patients with loud systolic murmurs (grades ≥III/ VI), especially those that are holosystolic or late systolic, and in most patients with diastolic or continuous murmurs. ■ ■PITFALLS IN CARDIOVASCULAR MEDICINE Increasing subspecialization in internal medicine and the perfection of advanced diagnostic techniques in cardiology can lead to several undesirable consequences. Examples include the following:

1. Failure by the noncardiologist to recognize important cardiac mani festations of systemic illnesses. For example, the presence of mitral stenosis, patent foramen ovale, and/or transient atrial arrhythmia should be considered in a patient with stroke, or the presence of pulmonary hypertension and cor pulmonale should be considered in a patient with scleroderma or Raynaud’s syndrome. A cardiovas cular examination should be carried out to identify and estimate the severity of the cardiovascular involvement that accompanies many noncardiac disorders.
2. Failure by the cardiologist to recognize underlying systemic disor ders in patients with heart disease. For example, hyperthyroidism should be considered in an elderly patient with atrial fibrillation and unexplained heart failure, and Lyme disease should be considered in a patient with unexplained (fluctuating) atrioventricular block. A cardiovascular abnormality may provide the clue critical to the rec ognition of some systemic disorders. For example, an unexplained pericardial effusion may provide an early clue to the diagnosis of tuberculosis or a neoplasm.
3. Overreliance on and overutilization of laboratory tests, particularly invasive techniques, for the evaluation of the cardiovascular sys tem. Cardiac catheterization and coronary arteriography (Chap. 249) provide precise diagnostic information that may be crucial in developing a therapeutic plan in patients with known or suspected CAD. Although a great deal of attention has been directed to these examinations, it is important to recognize that they serve to supple ment, not supplant, a careful examination carried out with clinical and noninvasive techniques. A coronary arteriogram should not be performed in lieu of a careful history in patients with chest pain sus pected of having ischemic heart disease. Although coronary arteri ography may establish whether the coronary arteries

are obstructed and to what extent, the results of the procedure by themselves often do not provide a definitive answer to the question of whether a patient's symptom of chest discomfort is attributable to coronary atherosclerosis and whether or not revascularization is indicated. Despite the value of invasive tests in certain circumstances, they entail some small risk to the patient, involve discomfort and substantial cost, and place a strain on medical facilities. Therefore, they should be carried out only if the results can be expected to modify the patient's management. ■ ■DISEASE PREVENTION AND MANAGEMENT The prevention of heart disease, especially of CAD, is one of the most important tasks of primary health care givers as well as cardiologists. Prevention begins with risk assessment, followed by attention to life style, such as achieving optimal weight, physical activity, and smoking cessation, and then aggressive treatment of all abnormal risk factors, such as hypertension, hyperlipidemia, and diabetes mellitus (Chap. 415). After a complete diagnosis has been established in patients with known heart disease, a number of management options are usually available. Several examples may be used to demonstrate some of the principles of cardiovascular therapeutics:

4. In the absence of evidence of heart disease, the patient should be clearly informed of this assessment and not be asked to return at intervals for repeated examinations. If there is no evidence of dis ease, such continued attention may lead to the patient's developing inappropriate concern about the possibility of heart disease.
5. If there is no evidence of cardiovascular disease but the patient has one or more risk factors for the development of ischemic heart

disease (Chap. 284), a plan for their reduction should be developed and the patient should be retested at intervals to assess compliance and efficacy in risk reduction. 3. Asymptomatic or mildly symptomatic patients with valvular heart

disease that is anatomically severe should be evaluated periodically, every 6–12 months, by clinical and noninvasive examinations. Early signs of deterioration of ventricular function may signify the need for surgical treatment before the development of disabling symp toms, irreversible myocardial damage, and excessive surgical risk (Chap. 272). 4. In patients with CAD (Chap. 284), available practice guidelines CHAPTER 244 Basic Biology of the Cardiovascular System should be considered in the decision on the form of treatment (medical, percutaneous coronary intervention, or surgical revas cularization). Mechanical revascularization may be employed too frequently in the United States and too infrequently in Eastern Europe and developing nations. The mere presence of angina pectoris and/or the demonstration of critical coronary arterial nar rowing at angiography should not reflexively evoke a decision to treat the patient by revascularization. Instead, these interventions should be limited to patients with CAD in whom revascularizа tion has been shown to improve the natural history (e.g., acute coronary syndrome or multivessel CAD with left ventricular dysfunction). ■ ■FURTHER READING Tsao CW et al: Heart disease and stroke statistics—2023 update: A report from the American Heart Association. Circulation 147:e93, 2023. Joseph Loscalzo, John F. Keaney, Jr.,

Calum A. MacRae

Basic Biology of the Cardiovascular System DEVELOPMENTAL BIOLOGY OF THE CARDIOVASCULAR SYSTEM The heart forms early during embryogenesis (Fig. 244-1), circulating blood, nutrients,

molecular signals, and oxygen to the other developing organs while continuing to grow and undergo complex morphoge netic changes. Early cardiac progenitors arise within crescent-shaped fields of lateral splanchnic mesoderm under the influence of mul tiple cues and migrate to the midline to form the linear heart tube: a single layer of endocardium and a single layer of spontaneously beating cardiomyocytes. The simple linear heart tube undergoes chamber specification and asymmetric looping, coordinated with longitudinal and concentric growth of different regions of the heart tube, to produce the presump tive atria and ventricles. Cells continue to migrate into the heart at both ends from additional heart fields in pharyngeal mesoderm as looping and growth occur. These cells exhibit distinctive gene expression (e.g., Islet-1) and distinctive physiology (e.g., calcium handling), contribut ing to discrete areas of the adult heart, including the right atrium and the right ventricle. These different embryonic origins of cells within the right and left ventricles correlate with distinctive single-cell RNA sequencing profiles decades later and help explain why some forms of congenital and adult cardiac diseases affect different regions of the heart. After looping and chamber formation, a series of morphogenetic events divide the left side from the right side of the heart, separate the

Neural folds Early heart-forming regions Pericardial coelom Foregut Forming heart PART 6 Disorders of the Cardiovascular System A B First heart field Second heart field LV RV C D E F FIGURE 244-1 A. Schematic depiction of a transverse section through an early embryo depicts the bilateral regions where early heart tubes form. B. The bilateral heart tubes subsequently migrate to the midline and fuse to form the linear heart tube. C. At the early cardiac crescent stage of embryonic development, cardiac precursors include a primary heart field fated to form the linear heart tube and a second heart field fated to add myocardium to the inflow and outflow poles of the heart. D. Second heart field cells populate the pharyngeal region before subsequently migrating to the maturing heart. E. Large portions of the right ventricle and outflow tract and some cells within the atria derive from the second heart field. F. The aortic arch arteries form as symmetric sets of vessels that then remodel under the influence of the neural crest to form the asymmetric mature vasculature. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. atria from the ventricles, and fashion the aorta and pulmonary artery from the truncus arteriosus. Cardiac valves form between the atria and the ventricles and between the ventricles and the outflow vessels. Early in development, myocardial cells secrete an extracellular matrix rich in hyaluronic acid, or “cardiac jelly,” which accumulates within the endocardial cushions, precursors of the valves. Signals from overlying myocardial cells trigger migration, invasion, and phenotypic changes in underlying endocardial cells, an epithelial-mesenchymal transfor mation, that then invade and populate the endocardial cushion matrix. Mesenchymal cells then proliferate and form the mature valve leaflets. The great vessels form as a series of symmetric bilateral aortic arch arteries that remodel asymmetrically to define the mature central vasculature. Migrating neural crest cells from the dorsal neural tube orchestrate this process and are necessary for aortic arch remodeling and septation of the truncus arteriosus. Smooth-muscle cells within the tunica media of the aortic arch, the ductus arteriosus, and the carotid arteries all derive from neural crest. By contrast, smooth muscle within the descending aorta arises from lateral plate mesoderm, and smooth muscle of the proximal outflow tract arises from the second heart field. Neural crest cells are sensitive to both vitamin A and folic acid, and congenital heart diseases involving abnormal remodeling of the aortic arch arteries are observed with maternal deficiencies of these vitamins. Shared embryonic origins of different cardiovascular cell types lead to

syndromic associations between various congenital heart diseases and a range of extracardiac abnormalities. Coronary artery formation requires the addition of yet another cell popula tion to the embryonic heart. Epicardial cells arise in the proepicardial organ, a derivative of the septum transversum, which also contributes to the fibrous portion of the diaphragm and to the liver. Proepicardial cells contribute smooth muscle to the coronary arteries and are required for proper coronary patterning. Other cell types within the heart (e.g., fibroblasts) also can arise from the proepicardium. The cardiac conduction system, which generates and propagates electri cal impulses, differentiates from car diomyocyte precursors. The conduction system is composed of slow-conducting (proximal) components, such as the sinoatrial (SA) and atrioventricular (AV) nodes, as well as fast-conducting (distal) components, including the His bundle, bundle branches, and Purkinje fibers. Precursors within the sinus venosus give rise to the SA node, whereas those within the AV canal mature into hetero geneous cell types that compose the AV node. Decremental conduction through the AV node delays electrical impulses between atria and ventricles, enabling sequential antegrade contraction. The AV node also reduces the transmission of higher impulse rates to the vulner able ventricle, whereas the distal con duction system rapidly propagates each impulse throughout the ventricles. The conduction system is composed of com plex and heterogeneous cell populations with distinct gap junction proteins and ion channels that define the particular local electrical properties. Developmen tal defects in the conduction system can lead to clinical electrophysiologic disorders, such as congenital heart block or pre-excitation (WolffParkinson-White syndrome) (Chap. 256). RA LA RV LV ■ ■ORIGIN OF VASCULAR CELLS Smooth-muscle cells are of varied origin. Some upper-body arterial smooth-muscle cells derive from the neural crest, whereas lower-body arteries develop smooth-muscle cells from neighboring mesodermal structures. Embryonic endothelial progenitor cells are derived from mesoderm. In adults, resident vascular or bone marrow–derived endothelial progenitors may aid repair of damaged or aging arteries. Bone marrow clonality, increasingly prevalent in aging, may impart significant clonality to endothelial cell populations. Vascular stem cells resident in the vessel wall may give rise to some smooth-muscle cells in injured or atheromatous arteries. THE BLOOD VESSEL ■ ■VASCULAR ULTRASTRUCTURE Blood vessels participate in disease biology as well as physiologic function in virtually every organ system. The smallest blood vessels—capillaries—consist of a monolayer of endothelial cells on a basement membrane adjacent to a discontinuous layer of smooth-musclelike cells known as pericytes (Fig. 244-2A). Arteries typically have

A. Capillary B. Vein C. Small muscular artery Pericyte Endothelial cell D. Large muscular artery Internal elastic lamina External elastic lamina Adventitia FIGURE 244-2 Schematics of the structures of various types of blood vessels. A. Capillaries consist of an endothelial tube in contact with a discontinuous population of pericytes. B. Veins typically have thin medias and thicker adventitias. C. A small muscular artery features a prominent tunica media. D. Larger muscular arteries have a prominent media with smooth-muscle cells embedded in a complex extracellular matrix. E. Larger elastic arteries have cylindrical layers of elastic tissue alternating with concentric rings of smooth-muscle cells as well as vasa vasorum to facilitate tissue blood supply. a trilaminar structure (Fig. 244-2B–E). The intima consists of a monolayer of endothelial cells continuous with those of the capil laries. The middle layer, or tunica media, consists of a syncytium of smooth-muscle cells that in veins are much sparser than in arteries (Fig. 244-2B). The outer layer, or adventitia, consists of extracellular matrix with fibroblasts, mast cells, and nerve terminals. Larger arteries require nourishment of the tunica media that is accomplished via their own vasculature,

the vasa vasorum (Fig. 244-2E). Arterioles are small muscular arteries (Fig. 244-2C) that regulate blood pressure and flow through arterial beds. Medium-size muscular arteries also contain prominent smooth-muscle layers (Fig. 244-2D) that participate in atherogenesis. Larger elastic arteries have a highly structured tunica media with concentric bands of smooth-muscle cells, interspersed with strata of elastin-rich extracellular matrix (Fig. 244-2E). Larger arteries form an internal elastic lamina between intima and media while an external elastic lamina partitions the media from sur rounding adventitia. ■ ■VASCULAR CELL BIOLOGY Endothelial Cell The endothelium forms the interface between tissues and the blood compartment, regulating the passage of mol ecules and cells. This function of endothelial cells as a selectively permeable barrier fails in vascular diseases, including atherosclerosis, hypertension, and renal disease, as well as in pulmonary edema, sepsis, and other situations exhibiting “capillary leak.” The endothelium also participates in the local regulation of vascular tone and blood flow. Endogenous endothelium-derived substances, such as prostacyclin, endothelium-derived hyperpolarizing factor, nitric oxide (NO), and hydrogen peroxide (H2O2), provide tonic stimu lation of endothelial homeostatic properties under physiologic condi tions in vivo (Table 244-1). Impaired production or excess catabolism of these substances can mediate dysfunctional properties of the endo thelium. A major homeostatic influence on the endothelium is laminar blood flow, and the measurement of flow-mediated dilatation directly assesses endothelial vasodilator function in humans (Fig. 244-3).

Endothelial cells also produce potent vasoconstrictor substances such as endothelin. Excessive production of reactive oxygen species, such as super oxide anion (O2

CHAPTER 244 –), by endothelial or smooth-muscle cells under pathologic conditions (e.g., excessive exposure to angiotensin II) can promote local oxi dative stress and inactivate NO. Vascular smooth-muscle cell Endothelial cells also regulate cel lular traffic through tissues. Normal endothelium exhibits limited interac tion with circulating leukocytes, but bacterial products such as endotoxin or proinflammatory cytokines can induce endothelial cells to express an array of adhesion molecules that selectively bind various classes of leukocytes in different pathologic conditions. The adhesion molecules and chemokines generated during acute bacterial infec tion tend to recruit granulocytes, while in chronic inflammatory diseases such as tuberculosis or atherosclerosis, the adhesion molecules expressed favor monocyte recruitment. Endothelial cell injury participates in the patho physiology of many immune-mediated diseases. For example, complementmediated lysis of endothelial cells con tributes to tissue injury. The foreign histocompatibility complex antigens on endothelial cells in solid-organ allografts can promote allograft arte riopathy, while immune-mediated endothelial injury also plays a role in thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome. Basic Biology of the Cardiovascular System E. Large elastic artery The endothelium also regulates the balance between thrombosis and hemostasis through a highly tuned set of regulatory pathways. For example, inflammatory cytokines, bacterial endotoxin, or angiotensin II can activate endothelial cells to produce substantial quantities of plasminogen activator inhibitor 1 (PAI-1), the major inhibitor of fibri nolysis. Inflammatory stimuli also induce endothelial expression of the potent procoagulant tissue factor, a contributor to disseminated intra vascular coagulation in sepsis; similar effects are observed in hyper glycemia. Thus, in pathologic circumstances, endothelial dysfunction tends to promote local thrombus accumulation rather than combat it. Endothelial cells regulate the growth of subjacent smooth-muscle cells by elaborating heparan sulfate glycosaminoglycans that inhibit smooth-muscle proliferation. In the setting of vascular injury, endo thelium-derived growth factors and chemoattractants (e.g., plateletderived

growth factor) induce the migration and proliferation of vascular smooth-muscle cells. Dysregulation of these growth-stimula tory molecules may promote smooth-muscle accumulation in athero sclerotic lesions. TABLE 244-1 Endothelial Functions in Health and Disease HOMEOSTATIC PROPERTIES DYSFUNCTIONAL PROPERTIES Optimize balance between vasodilation and vasoconstriction Impaired dilation, vasoconstriction Antithrombotic, profibrinolytic Prothrombotic, antifibrinolytic Anti-inflammatory Proinflammatory Antiproliferative Proproliferative Antioxidant Prooxidant Selective permeability Impaired barrier function

 FIGURE 244-3 Assessment of endothelial function in vivo using blood pressure cuff occlusion and release. Upon deflation of the cuff, an ultrasound probe monitors changes in diameter (A) and blood flow (B) of the brachial artery (C). (Reproduced with permission of J. Vita, MD.) Vascular Smooth-Muscle Cell Contraction and relaxation of vascular smooth-muscle cells in muscular arteries determine blood pressure, regional flow, and the afterload experienced by the left ven tricle (see below). Venous tone regulates venous tree capacitance and influences ventricular preload. Smooth-muscle cells in the adult vessel seldom replicate in the absence of arterial injury or inflammatory acti vation, but proliferation and migration of arterial smooth-muscle cells contribute to arterial stenoses in atherosclerosis, arteriolar remodeling in hypertension, and the hyperplastic response of arteries to injury. In the pulmonary circulation, smooth-muscle migration and prolifera tion underlie the vascular pathology that occurs in sustained high-flow

states such as left-to-right shunts in congenital heart disease with resulting pulmonary hypertension. Smooth-muscle cells secrete the bulk of vascular extracellular matrix. Excessive production of collagen and glycosaminoglycans contributes to the remodeling, altered biomechanics, and physiology of arteries affected by hypertension or atherosclerosis. In larger elastic arteries, such as the aorta, the ability to store the kinetic energy of systole promotes tissue perfusion during diastole. Arterial stiffness, associated with aging or disease, increases left ventricular afterload and portends a poor outcome. Like endothelial cells, vascular smooth-muscle cells not only respond to paracrine stimuli from other cells but can themselves serve as a source of such stimuli. For example, proinflammatory stimuli induce smooth-muscle cells to elaborate cytokines and other mediators that drive thrombosis and fibrinolysis as well as proliferation. Vascular Smooth-Muscle Cell Contraction The principal mechanism for vascular smooth-muscle cell contraction is increased cytoplasmic calcium concentration due to transmembrane influx and triggered release from intracellular calcium stores (Fig. 244-4). In vas cular smooth-muscle cells, voltage-dependent L-type calcium channels open with membrane depolarization. Local influx of calcium, termed calcium sparks, can trigger release from intracellular stores, which results in more contraction and increased vessel tone (see below). Opposing currents balance the effects of individual ionic fluxes pro moting homeostasis, which is tightly regulated by neural and metabolic influences. Vasoconstricting agonists also increase intracellular [Ca2+] by vari ous mechanisms including receptor-dependent phospholipase C acti vation producing hydrolysis of phosphatidylinositol 4,5-bisphosphate to generate diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). These membrane lipid derivatives, in turn, activate protein kinase C and increase intracellular [Ca2+]. In addition, IP3 binds specific sarco plasmic reticulum (SR) receptors to increase calcium efflux from this storage pool into the cytoplasm. Vascular smooth-muscle cell contraction depends on myosin light chain phosphorylation that reflects the balance between the activity of relevant kinases and phosphatases. Calcium activates myosin light chain kinase via

calmodulin, augmenting myosin ATPase activity and enhancing contraction. Conversely, myosin light chain phosphatase reduces myosin ATPase activity and contractile force. Other kinase/ phosphorylase combinations result in a complex regulatory network that refines vascular tone and links it to physiologic requirements. Control of Vascular Smooth-Muscle Cell Tone The auto nomic nervous system and endothelial cells modulate vascular smoothmuscle cells through similar convergent pathways. Autonomic neurons enter vessel media and modulate vascular smooth-muscle cell tone in response to baroreceptors and chemoreceptors within the aortic arch or carotid bodies and to thermoreceptors in the skin. Rapidly acting reflex arcs modulated by central inputs respond to multiple sensory inputs as well as emotional stimuli through three neuronal classes: sympathetic, whose principal neurotransmitters are epinephrine and norepinephrine; parasympathetic, whose principal neurotransmit ter is acetylcholine; and nonadrenergic/noncholinergic, which include two subgroups—nitrergic, whose principal neurotransmitter is NO, and peptidergic, whose principal neurotransmitters are substance P, vasoactive intestinal peptide, calcitonin gene-related peptide, and the nonpeptide, adenosine triphosphate (ATP). Each of these neurotransmitters acts through specific receptors on the vascular smooth-muscle cell to modulate intracellular Ca2+ and, consequently, contractile tone. Norepinephrine activates α-adrenergic receptors, and epinephrine activates both α and β receptors. In most blood vessels, norepinephrine activates postjunctional α1 receptors in large arteries and α2 receptors in small arteries and arterioles, lead ing to vasoconstriction. Most blood vessels express β2-adrenergic receptors on their vascular smooth-muscle cells and respond to β agonists by cyclic AMP–dependent relaxation. Acetylcholine released from parasympathetic neurons may bind to muscarinic receptors on either vascular smooth-muscle cells, causing vasoconstriction, or on

Ca2+ NE, ET-1, Ang II VDCC PIP2 G G PLC RhoA Ca2+ “Spark” cAMP DAG IP3R RyrR Plb ATPase IP3 PKC Rho Kinase Caldesmon Calponin FIGURE 244-4 Regulation of vascular smooth-muscle cell calcium concentration and actomyosin ATPase-dependent contraction. AC, adenylyl cyclase; Ang II, angiotensin II; ANP, atrial natriuretic peptide; DAG, diacylglycerol; ET-1, endothelin-1; G, G protein; IP3, inositol 1,4,5-trisphosphate; MLCK, myosin light chain kinase; MLCP, myosin light chain phosphatase; NE, norepinephrine; NO, nitric oxide; pGC, particular guanylyl cyclase; PIP2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; PLC, phospholipase C; sGC, soluble guanylyl cyclase; SR, sarcoplasmic reticulum; VDCC, voltage-dependent calcium channel. Solid lines depict stimulatory interaction, and dashed lines represent inhibition. (Reproduced with permission from B Berk, in Vascular Medicine, 3rd ed. Philadelphia, Saunders, Elsevier; 2006.) endothelial cells, causing NO-dependent vasorelaxation. Nitrergic neurons release NO, which relaxes vascular smooth-muscle cell via the cyclic GMP–dependent and –independent mechanisms outlined, and other peptidergic inputs that regulate vascular tone. For the detailed molecular physiology of the autonomic nervous system, see Chap. 451. The release of endothelial effectors of vascular smooth-muscle cell tone integrates the smooth-muscle response to mechanical (e.g., shear stress, cyclic strain) and biochemical stimuli (purinergic agonists, muscarinic agonists, peptidergic agonists). In addition to these local paracrine modulators, a complex system of circulating modulators ranging from norepinephrine to the natriuretic peptides also modify vascular smooth-muscle cell tone. ■ ■ARTERIOGENESIS AND ANGIOGENESIS Recruitment and growth of blood vessels (arteriogenesis) and new capillaries (angiogenesis) can occur in response to conditions such as chronic hypoxemia and tissue ischemia. Growth factors, including vascular endothelial growth factor (VEGF) and fibroblast growth fac tor

(FGF), can activate a signaling cascade that stimulates endothelial proliferation and tube formation, defined as angiogenesis. Guidance molecules, including members of the semaphorin family of secreted peptides, direct blood vessel patterning by attracting or repelling nascent endothelial tubes. The recruitment and expansion of preexist ing collateral vascular networks in response to a blocked artery, an example of arteriogenesis, can result from selective activation of both growth factors and, perhaps, local or circulating endothelial progenitor cells. True vascular regeneration, or the development of a new blood vessel that includes all three cell layers, normally does not occur in adult mammals, but recent scientific advances might help obviate such limitations.

BetaAgonist ANP NO CHAPTER 244 K+ Ch Na-K ATPase pGC AC GTP ATP sGC SR Basic Biology of the Cardiovascular System cGMP PKG PKA Calcium MLCK MLCP CELLULAR BASIS OF CARDIAC CONTRACTION ■ ■CARDIAC ULTRASTRUCTURE Most of the ventricular mass is composed of cardiomyocytes, normally 60–140 µm in length and 17–25 µm in diameter (Fig. 244-5A). Each cell contains multiple myofibrils that run the length of the cell and are com posed of series of repeating sarcomeres. The cytoplasm between the myo fibrils contains other cell constituents, including a single centrally located nucleus, mitochondria, and the intracellular membrane system, the SR. The sarcomere, the structural and functional unit of contraction, lies between adjacent Z lines, which on transmission electron microscopy are seen as dark repeating bands. The distance between Z lines var ies with the degree of contraction or stretch of the muscle and ranges between 1.6 and 2.2 µm. At the center of the sarcomere is a dark band of constant length (1.5 µm), the A band, which is flanked by two lighter bands, the I bands, which are of variable length. The sarcomere of heart muscle, like that of skeletal muscle, consists of interdigitating thick and thin myofilaments. Thicker filaments, composed principally of the protein myosin, traverse the A band; they are about 10 nm (100 Å) in diameter, with tapered ends. Thinner filaments, composed primarily of actin, course from the Z lines through the I band into the A band; they are ~5 nm (50 Å) in diameter and 1.0 µm in length. Thus, thick and thin filaments overlap only within the (dark) A band, whereas the (light) I band contains only thin filaments. On electron-microscopic examina tion, bridges extend between the thick and thin filaments within the A band; these are myosin heads (see below) bound to actin filaments. ■ ■THE CONTRACTILE PROCESS The sliding filament model for muscle contraction rests on the central observation that both the thick and the thin filaments are constant in

Myofiber PART 6 Disorders of the Cardiovascular System A Na+ Exchange Ca2+ Pump Myofibril e t y c o y M Myofibril Mitochondrion B Myofibril C Diastole Actin Myosin Titin M Z D FIGURE 244-5 A shows the branching myocytes making up the cardiac myofibers. B illustrates the critical role played by the changing [Ca2+] in the myocardial cytosol. Ca2+ ions are schematically shown as entering through the calcium channel that opens in response to the wave of depolarization that travels along the sarcolemma. These Ca2+ ions “trigger” the release of more calcium from the sarcoplasmic reticulum (SR) and thereby initiate a contraction-relaxation cycle. Eventually the small quantity of Ca2+ that has entered the cell leaves predominantly through an Na+/Ca2+ exchanger, with a lesser role for the sarcolemmal Ca2+ pump. The varying actin-myosin overlap is shown for (B) systole, when [Ca2+] is maximal, and (C) diastole, when [Ca2+] is minimal. D. The myosin heads, attached to the thick filaments, interact with the thin actin filaments. (Reproduced with permission from LH Opie: Heart Physiology: From Cell to Circulation, 4th ed. Philadelphia, Lippincott, Williams & Wilkins, 2004.) length during both contraction and relaxation. With activation, the actin filaments are propelled farther into the A band. In this process, the A band remains constant in length, whereas the I band shortens and the Z lines move toward one another.

The myosin molecule is a complex, asymmetric protein with a molecular mass of about 500,000 Da; it has a rod-like portion that is about 150 nm (1500 Å) in length with a globular portion (head) at its end. The globular portions of myosin form the bridges to actin and are the site of ATPase activity. In thick myofilaments, composed of ~300 longitudinally stacked myosin molecules, the rod-like segments of myosin assume an orderly, polarized orientation, with outwardly projecting globular heads interacting with actin to generate force and shorten (Fig. 244-5B). Actin has a molecular mass of about 47,000 Da. Thin filaments consist of a double helix of two chains of actin molecules wound about each other on a larger molecule, tropomyosin. A group of regulatory proteins—troponins C, I, and T—localize at regular intervals on this filament (Fig. 244-6). In contrast to myosin, actin lacks intrinsic enzy matic activity but combines reversibly with myosin in the presence of

10 µm Myocyte Ca2+ enters T tubule Ca2+ “trigger” Ca2+ leaves Free Ca2+ SR Contract Relax Systole Z Head 43 nm ATP and Ca2+. Calcium activates the myosin ATPase, which breaks down ATP to supply the energy for contraction (Fig. 244-6). The activ ity of myosin ATPase determines the rate of actomyosin cross-bridge formation and breakdown, and ultimately determines contraction velocity. In relaxed muscle, tropomyosin inhibits this interaction. Titin (Fig. 244-5D) an enormous, flexible, myofibrillar protein, connects myosin to the Z line; its elasticity contributes to the passive mechani cal characteristics of the heart. Dystrophin, a cytoskeletal protein that binds to the dystroglycan complex at membrane adherens junctions, tethers the sarcomere to the cell membrane at these regions of tight coupling to adjacent myocytes. Mutations in multiple sarcomeric and cytoskeletal proteins cause different Mendelian disorders involving the heart and skeletal muscle and also sensitize individuals to toxic cardiomyopathies (e.g., due to alcohol or chemotherapy) and to those caused by other acquired stressors, such as inflammatory or peripar tum cardiomyopathy. During activation of the cardiac myocyte, Ca2+ binds the hetero trimer troponin C, resulting in regulatory conformational changes in tropomyosin and exposing actin cross-bridge interaction sites

ATP Relaxed, energized Relaxed Actin 2. 4. Dissociation of actin and myosin ATP Rigor complex Active complex FIGURE 244-6 Four steps in cardiac muscle contraction and relaxation. In relaxed muscle (upper left), ATP bound to the myosin cross-bridge dissociates the thick and thin filaments. Step 1: Hydrolysis of myosin-bound ATP by the ATPase site on the myosin head transfers the chemical energy of the nucleotide to the activated cross-bridge (upper right). When cytosolic Ca2+ concentration is low, as in relaxed muscle, the reaction cannot proceed because tropomyosin and the troponin complex on the thin filament do not allow the active sites on actin to interact with the cross-bridges. Therefore, even though the cross-bridges are energized, they cannot interact with actin. Step 2: When Ca2+ binding to troponin C has exposed active sites on the thin filament, actin interacts with the myosin cross-bridges to form an active complex (lower right) in which the energy derived from ATP is retained in the actin-bound cross-bridge, whose orientation has not yet shifted. Step 3: The muscle contracts when ADP dissociates from the cross-bridge. This step leads to the formation of the low-energy rigor complex (lower left) in which the chemical energy derived from ATP hydrolysis has been expended to perform mechanical work (the “rowing” motion of the cross-bridge). Step 4: The muscle returns to its resting state, and the cycle ends when a new molecule of ATP binds to the rigor complex and dissociates the cross-bridge from the thin filament. This cycle continues until calcium is dissociated from troponin C in the thin filament, which causes the contractile proteins to return to the resting state with the cross-bridge in the energized state. ADP,

adenosine diphosphate; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase. (Reproduced with permission from AM Katz: Heart failure: Cardiac function and dysfunction, in Atlas of Heart Diseases, 3rd ed, WS Colucci [ed]. Philadelphia, Current Medicine, 2002.) (Fig. 244-6). Repetitive interaction between myosin heads and actin filaments is termed cross-bridge cycling and results in sliding of the actin along the myosin filaments, with muscle shortening and/or the devel opment of tension. The splitting of ATP then dissociates the myosin cross-bridge from actin. In the presence of ATP (Fig. 244-6), actin and myosin filaments bind and dissociate cyclically if sufficient Ca2+ is pres ent; these processes cease when [Ca2+] falls below a critical level, and the troponin-tropomyosin complex once more inhibits actin-myosin interactions (Fig. 244-7). Cytoplasmic [Ca2+] is a principal determinant of the inotropic state of the heart. Most agents that stimulate myocardial contractility (posi tive inotropic stimuli), including digitalis glycosides and β-adrenergic agonists, increase cytoplasmic [Ca2+], triggering cross-bridge cycling. Increased adrenergic neuronal activity stimulates myocardial con tractility through norepinephrine release, activation of β-adrenergic receptors, and, via Gs-stimulated guanine nucleotide-binding proteins, activation of the adenylyl cyclase, which leads to the formation of the intracellular second messenger cyclic AMP from ATP (Fig. 244-7). Cyclic AMP in turn activates protein kinase A (PKA), which phos phorylates sarcolemmal Ca2+ channels, thereby enhancing the influx of Ca2+ into the myocyte. The SR (Fig. 244-8), a complex network of anastomosing intracel lular channels, invests the myofibrils. The transverse tubules, or T sys tem, closely related to the SR, both structurally and functionally, arise as sarcolemmal invaginations that extend into the myofibrillar bundles along the Z lines, i.e., the ends of the sarcomeres. ■ ■CARDIAC ACTIVATION In the inactive state, the cardiomyocyte membrane is electrically polarized; i.e., the interior has a negative charge relative to the outside of the cell, with a transmembrane potential of –80 to –100 mV (Chap. 250). The sarcolemma, which in the resting state is largely impermeable to Na+, and a Na+- and K+-pump energized by ATP extrudes Na+ from the cell and maintains the resting potential. In this resting state, intracellular [K+] is relatively high and [Na+] is far lower;

ADP Pi

1. ATP hydrolysis CHAPTER 244 Actin Formation of active complex Basic Biology of the Cardiovascular System Pi ADP ADP
2.

Product dissociation conversely, extracellular [Na+] is high and [K+] is low. At the same time, extracellular [Ca2+] greatly exceeds free intracellular [Ca2+]. The action potential has four phases (see Fig. 250-1B). Depolariz ing current spreads across the cell membrane, penetrating deeply into the cell via the T tubular system. During the action potential plateau (phase 2), there is a slow inward current through sarcolemmal L-type Ca2+ channels (Fig. 244-8). The absolute quantity of Ca2+ traversing sarcolemmal and T tubular membranes is modest and insufficient to fully activate contraction. However, this initial Ca2+ current, through Ca2+-induced Ca2+ release, triggers substantial Ca2+ release from the SR, inducing contraction. Ca2+ is released from the SR through a Ca2+ release channel, a cardiac isoform of the ryanodine receptor (RyR2). Several regulatory proteins inhibit RyR2 and thus SR Ca2+ release. Inherited disorders or exogenous factors affecting the efficiency or stability of SR Ca2+ han dling can impair contraction, leading to heart failure or to ventricular arrhythmias. The Ca2+ released from the SR diffuses to interact with myofi brillar troponin C (Fig. 244-7), repressing this protein’s inhibition of contraction, and so activating myofilaments to shorten. During repolarization, the activity of the SR Ca2+-ATPase (SERCA2A)

leads to Ca2+ uptake against a concentration gradient into the SR where it complexes with another specialized protein, calsequestrin. The uptake of Ca2+ is ATP (energy)-dependent and lowers cytoplasmic [Ca2+] to a level where actomyosin interaction is inhibited and myocardial relaxation occurs. There is also a sarcolemmal exchange of Ca2+ for Na+ (Fig. 244-8), reducing cytoplasmic [Ca2+]. Additional control of calcium compartmentalization results from cyclic AMP–dependent PKA phosphorylation of the SR protein phospholamban, permit ting SERCA2A activation, increasing SR Ca2+ uptake, and so accelerating relaxation rates, and loading the SR with Ca2+ for subsequent cycles of release and contraction. Thus, the combination of the cell membrane, transverse tubules, and SR, transmitting the action potential, releasing and then re-accumulating Ca2+, controls the cyclic contraction and relaxation of heart muscle.

β - Adrenergic agonist PART 6 Disorders of the Cardiovascular System β γ αs Adenyl cyclase SL GTP β Receptor cAMP Via protein kinase A Metabolic • glycolysis • lipolysis • citrate cycle ADP + Pi + ATP Troponin C Myosin ATPase ADP + Pi Increased

1. rate of contraction
2. peak force
3. rate of relaxation β Force FIGURE 244-7 Signal systems involved in positive inotropic and lusitropic (enhanced relaxation) effects of α-adrenergic stimulation. When the β-adrenergic agonist interacts with the β receptor, a series of G protein–mediated changes leads to activation of adenylyl cyclase and the formation of cyclic adenosine monophosphate (cAMP). The latter acts via protein kinase A to stimulate metabolism (left) and phosphorylate the Ca2+ channel protein (right). The result is an enhanced opening probability of the Ca2+ channel, thereby increasing the inward movement of Ca2+ ions through the sarcolemma (SL) of the T tubule. These Ca2+ ions release more calcium from the sarcoplasmic reticulum (SR) to increase cytosolic Ca2+ and activate troponin C. Ca2+ ions also increase the rate of breakdown of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and inorganic phosphate (Pi). Enhanced myosin ATPase activity explains the increased rate of contraction, with increased activation of troponin C explaining increased peak force development. An increased rate of relaxation results from the ability of cAMP to activate as well the protein phospholamban, situated on the membrane of the SR, that controls the rate of uptake of calcium into the SR. The latter effect explains enhanced relaxation (lusitropic effect). P, phosphorylation; PL, phospholamban; TnI, troponin I. (Reproduced with permission from LH Opie: Heart Physiology: From Cell to Circulation, 4th ed. Philadelphia, Lippincott, Williams & Wilkins, 2004.) Genetic or pharmacologic alterations of any component can disturb any of the functions of this finely tuned system. CONTROL OF CARDIAC PERFORMANCE AND OUTPUT The extent of shortening of heart muscle and, therefore, ventricular stroke volume in the intact heart depends on three major influences: (1) the length of the muscle at the onset of contraction, i.e., the preload; (2) the tension that the muscle must develop during contraction, i.e., the afterload; and (3) muscle contractility, i.e., the extent and velocity of shortening at any given preload and afterload. Table 244-2 lists the major determinants of preload, afterload, and contractility. ■ ■THE ROLE OF MUSCLE LENGTH (PRELOAD) Preload determines sarcomere length at the onset of contraction. Contractile force is optimal at specific sarcomere lengths (~2.2 μm) where both myofilament Ca2+ sensitivity is maximal, and myofilament interactions and activation of contraction are most efficient.

The rela tionship between initial muscle fiber length and the developed force is the basis of Starling’s law of the heart, which states that, within limits,

Ca2+ P Ca2+ + + SR + P Ca2+ + cAMP via Tnl +

-

cAMP via PL

-

Control Time Pattern of contraction the ventricular contraction force depends on the end-diastolic length of the cardiac muscle; in vivo, end-diastolic length relates closely to the ventricular end-diastolic volume. ■ ■CARDIAC PERFORMANCE Ventricular end-diastolic or “filling” pressure can serve as a surrogate for end-diastolic volume. In isolated heart and heart-lung prepara tions, stroke volume varies directly with the end-diastolic fiber length (preload) and inversely with the arterial resistance (afterload), and as the heart fails—i.e., as its contractility declines—it delivers a progressively smaller stroke volume from a normal or even elevated end-diastolic volume. The relation between ventricular end-diastolic pressure and the stroke work of the ventricle (the ventricular func tion curve) provides a working definition of cardiac contractility in the intact organism. An increase in contractility is accompanied by a shift of the ventricular function curve upward and to the left (greater stroke work at any level of ventricular end-diastolic pressure, or lower end-diastolic volume at any level of stroke work), whereas a shift downward and to the right characterizes reduction of contractility (Fig. 244-9).

Na+ pump Plasma membrane Ca2+ pump Na+/Ca2+ exchanger B2 B1 T tubule Cisterna Plasma membrane Ca2+ channel Ca2+- release channel ('foot' protein) A A1 Mitochondria Calsequestrin C E F Z-line Troponin C Thin filament Contractile proteins Thick filament FIGURE 244-8 The Ca2+ fluxes and key structures involved in cardiac excitation-contraction coupling. The arrows denote the direction of Ca2+ fluxes. The thickness of each arrow indicates the magnitude of the calcium flux. Two Ca2+ cycles regulate excitation-contraction coupling and relaxation. The larger cycle is entirely intracellular and involves Ca2+ fluxes into and out of the sarcoplasmic reticulum, as well as Ca2+ binding to and release from troponin C. The smaller extracellular Ca2+ cycle occurs when this cation moves into and out of the cell. The action potential opens plasma membrane Ca2+ channels to allow passive entry of Ca2+ into the cell from the extracellular fluid (arrow A). Only a small portion of the Ca2+ that enters the cell directly activates the contractile proteins (arrow A1). The extracellular cycle is completed when Ca2+ is actively transported back out to the extracellular fluid by way of two plasma membrane fluxes mediated by the sodium-calcium exchanger (arrow B1) and the plasma membrane calcium pump (arrow B2). In the intracellular Ca2+ cycle, passive Ca2+ release occurs through channels in the cisternae (arrow C) and initiates contraction; active Ca2+ uptake by the Ca2+ pump of the sarcotubular network (arrow D) relaxes the heart. Diffusion of Ca2+ within the sarcoplasmic reticulum (arrow G) returns this activator cation to the cisternae, where it is stored in a complex with calsequestrin and other calcium-binding proteins. Ca2+ released from the sarcoplasmic reticulum initiates systole when it binds to troponin C (arrow E). Lowering of cytosolic [Ca2+] by the sarcoplasmic reticulum (SR) causes this ion to dissociate from troponin (arrow F) and relaxes the heart. Ca2+ also may move between mitochondria and cytoplasm (H). (Reproduced with permission from AM Katz: Physiology of the Heart, 4th ed. Philadelphia, Lippincott, Williams & Wilkins, 2005.) ■ ■VENTRICULAR AFTERLOAD In

the intact heart, as ex vivo, the extent and velocity of shortening of ventricular muscle fibers at any level of preload and of myocardial contractility relate inversely to the afterload, i.e., the instantaneous load opposing shortening. In the intact heart, the afterload may be defined as the tension developed in the ventricular wall during ejection. After load is determined by the aortic pressure as well as by the volume of the ventricular cavity and myocardial tissue characteristics including thickness. Laplace's law models the tension of the myocardial fiber as the product of intra-cavitary ventricular pressure and ventricular radius divided by wall thickness. Therefore, at any given aortic pres sure, the afterload on a dilated left ventricle exceeds that on a normalsized ventricle. Conversely, at the same aortic pressure and ventricular diastolic volume, the afterload on a hypertrophied ventricle is lower than that on a normal chamber. Aortic pressure in turn depends on the peripheral vascular resistance, the biomechanics of the arterial tree, and the volume of blood it contains at the onset of ejection. Ventricular afterload finely regulates cardiovascular performance (Fig. 244-10). As noted, elevations in both preload and contractility increase myocardial fiber shortening, whereas increases in afterload reduce it. The extent of myocardial fiber shortening and left ventricular size determine stroke volume. An increase in arterial pressure induced by vasoconstriction, for example, augments afterload, which opposes myocardial fiber shortening, reducing stroke volume.

Plasma membrane Extracellular CHAPTER 244 Intracellular (cytosol) Sarcoplasmic reticulum Basic Biology of the Cardiovascular System Sarcotubular network G Sarcoplasmic reticulum Ca2+ pump D H When myocardial contractility is impaired and the ventricle dilates, afterload rises (Laplace's law) and limits cardiac output. Increased afterload also may result from neural and humoral stimuli that occur in response to a fall in cardiac output. This increased afterload may reduce cardiac output further, thereby increasing ventricular volume and initiating a vicious circle, especially in patients with ischemic heart disease and limited myocardial O2 supply. Treatment with vasodila tors has the opposite effect; when afterload falls, cardiac output rises (Chaps. 266–270). Under normal circumstances, the various influences acting on car diac performance interact in a complex fashion to maintain cardiac output at a level responsive to the requirements of tissue metabolic demands (Fig. 244-10). Interference with a single mechanism may not influence the cardiac output due to homeostatic adjustments. For example, a moderate reduction of blood volume or the loss of the atrial contribution to ventricular contraction can be tolerated without a reduction in resting cardiac output. Under these circumstances, other factors, such as adrenergic neuronal impulses increasing cardiac contractility, heart rate, and venous tone, will serve as compensa tory mechanisms and sustain cardiac output in a normal individual. Ultimately, understanding the complex interactions between so many different phasic variables requires rigorous models to predict relevant outcomes, and led to the early application of systems engineering prin ciples in medicine.

TABLE 244-2 Determinants of Stroke Volume I. Ventricular Preload A. Blood volume B. Distribution of blood volume

1. Body position
2. Intrathoracic pressure
3. Intrapericardial pressure
4. Venous tone

5. Pumping action of skeletal muscles C. Atrial contraction II. Ventricular Afterload PART 6 Disorders of the Cardiovascular System A. Systemic vascular resistance B. Elasticity of arterial tree C. Arterial blood volume D. Ventricular wall tension
6. Ventricular radius
7. Ventricular wall thickness III. Myocardial Contractilitya A. Intramyocardial [Ca2+] ↑↓ B. Cardiac adrenergic nerve activity ↑↓b C. Circulating catecholamines ↑↓b D. Cardiac rate ↑↓b E. Exogenous inotropic agents ↑ F. Myocardial ischemia ↓ G. Myocardial cell death (necrosis, apoptosis, autophagy) ↓ H. Alterations of sarcomeric and cytoskeletal proteins ↓
8. Genetic
9. Hemodynamic overload I. Myocardial fibrosis ↓ J. Chronic overexpression of neurohormones ↓ K. Ventricular remodeling ↓ L. Chronic and/or excessive myocardial hypertrophy ↓ aArrows indicate directional effects of determinants of contractility. bContractility rises initially but later becomes depressed. Maximal activity Normal-exercise

C

Normal-rest Ventricular performance Contractile state of myocardium Walking

B Exercise Heart failure 3′ D Rest A E

Fatal myocardial depression Dyspnea Pulmonary edema Ventricular EDV Stretching of myocardium FIGURE 244-9 The interrelations among influences on ventricular end-diastolic volume (EDV) through stretching of the myocardium and the contractile state of the myocardium. Levels of ventricular EDV associated with filling pressures that result in dyspnea and pulmonary edema are shown on the abscissa. Levels of ventricular performance required when the subject is at rest, while walking, and during maximal activity are designated on the ordinate. The broken lines are the descending limbs of the ventricular-performance curves, which are rarely seen during life but show the level of ventricular performance if end-diastolic volume could be elevated to very high levels. For further explanation, see text. (Reproduced with permission from WS Colucci, and E Braunwald: Pathophysiology of heart failure, in Braunwald’s Heart Disease, 7th ed, Philadelphia: Elsevier, 2005.)

Venous return Preload Contractility Stroke volume Cardiac output Arterial pressure Heart rate Afterload Peripheral resistance Medullary vasomotor and cardiac centers Carotid and aortic baroreceptors Higher nervous centers FIGURE 244-10 Interactions in the intact circulation of preload, contractility, and afterload in producing stroke volume. Stroke volume combined with heart rate determines cardiac output, which, when combined with peripheral vascular resistance, determines arterial pressure for tissue perfusion. The characteristics of the arterial system also contribute to afterload, an increase that reduces stroke volume. The interaction of these components with carotid and aortic arch baroreceptors provides a feedback mechanism to higher medullary and vasomotor cardiac centers and to higher levels in the central nervous system to effect a modulating influence on heart rate, peripheral vascular resistance, venous return, and contractility. (Reproduced with permission from MR Starling: Physiology of myocardial contraction, in Atlas of Heart Failure: Cardiac Function and Dysfunction, 3rd ed, WS Colucci and E Braunwald

[eds]. Philadelphia: Current Medicine; 2002.) ■ ■EXERCISE The integrated response to exercise illustrates typical interactions among the three determinants of stroke volume: preload, afterload, and contractility (Fig. 244-9). Hyperventilation, the pumping action of the exercising muscles, and venoconstriction during exercise all augment venous return and hence ventricular filling and preload (Table 244-2). Simultaneously, the increase in neuronal and humoral adrenergic stimulation of the myocardium and the tachycardia that occur during exercise combine to augment the myocardial contractility (Fig. 244-9, curves 1 and 2), together elevating stroke volume and stroke work, with little or no change in end-diastolic pressure and volume (Fig. 244-9, points A and B). Vasodilation occurs in the exercising muscles, thus limiting the increase in afterload that otherwise would occur as cardiac output rises to levels as high as five times greater than basal levels dur ing maximal exercise. This vasodilation ultimately allows the achieve ment of elevated cardiac outputs during exercise at arterial pressures only moderately higher than the resting state. ASSESSMENT OF CARDIAC FUNCTION Several techniques can define impaired cardiac function in clinical practice. Cardiac output and stroke volume may decline in the pres ence of heart failure, but these variables are often within normal limits, especially at rest, even late in disease. A more sensitive index of cardiac function is the ejection fraction, i.e., the ratio of stroke volume to end-diastolic volume (normal value = 67 ± 8%), which is frequently depressed in systolic heart failure even when stroke volume is normal. Alternatively, abnormally elevated ventricular end-diastolic volume (normal value = 75 ± 20 mL/m2) or end-systolic volume (normal value = 25 ± 7 mL/m2) signifies left ventricular systolic impairment. Noninvasive techniques, particularly echocardiography, radionu clide scintigraphy, and cardiac magnetic resonance imaging (MRI) (Chap. 248), have great value in the clinical assessment of myocardial function. They provide measurements of end-diastolic and end-systolic volumes, ejection fraction, and systolic shortening rate, and they allow assessment of ventricular filling (see below) as well as regional contrac tion, relaxation, and tissue characterization. The latter measurements

ESPVR afterload LV pressure preload

LV volume FIGURE 244-11 The responses of the left ventricle to increased afterload, increased preload, and increased and reduced contractility are shown in the pressure-volume plane. Left. Effects of increases in preload and afterload on the pressure-volume loop. Because there has been no change in contractility, the end-systolic pressure-volume relationship (ESPVR) is unchanged. With an increase in afterload, stroke volume falls (1 → 2); with an increase in preload, stroke volume rises (1 → 3). Right. With increased myocardial contractility and constant left ventricular end-diastolic volume, the ESPVR moves to the left of the normal line (lower end-systolic volume at any end-systolic pressure) and stroke volume rises (1 → 3). With reduced myocardial contractility, the ESPVR moves to the right; end-systolic volume is increased, and stroke volume falls (1 → 2). have particular importance in ischemic heart disease, as myocardial infarction causes regional myocardial damage. Strong dependence on ventricular loading conditions influences the precision of measurements of cardiac output, ejection fraction, and ventricular volumes as indices of cardiac function. Thus, a depressed ejection fraction and lowered cardiac output may occur in patients with normal ventricular function but reduced preload, as occurs in hypovolemia, or with increased afterload, as occurs in acutely elevated arterial pressure. The end-systolic left ventricular pressure-volume relationship has particular value as an index of ventricular performance as it does not depend on preload and afterload (Fig. 244-11). At any level of myocar dial contractility, left ventricular end-systolic volume varies inversely with end-systolic pressure; as contractility declines,

end-systolic vol ume (at any level of end-systolic pressure) rises. Invasive measurement of end-systolic left ventricular pressure-volume loops adds rigor to research studies of left ventricular function, but these techniques are less pragmatic than the more readily assessed indices obtained in rou tine clinical practice, such as ventricular volumes and ejection fraction. Integrated cardiopulmonary exercise testing with formal analysis of exhaled gases is now more broadly available and can estimate maximal oxygen delivery as an indirect metric of physiologic reserve. Longitu dinal measurements of some aspects of cardiovascular physiology are increasingly feasible with implantable or wearable devices. ■ ■DIASTOLIC FUNCTION Ventricular filling is influenced by several characteristics of the myo cardium including: (1) the extent and speed of myocardial relaxation; and (2) the passive stiffness of the ventricular wall. The former is largely a function of the rate of uptake of Ca2+ by the SR that may be enhanced by adrenergic activation and reduced by ischemia due to limited ATP available for pumping Ca2+ into the SR (see above). For the latter, ventricular stiffness increases with hypertrophy, fibrosis, and conditions that infiltrate the ventricle, such as amyloid, or can result from an extrinsic constraint (e.g., pericardial constriction) (Fig. 244-12). Ventricular filling can be assessed by measuring flow velocity across the mitral valve using Doppler ultrasound. Normally, inflow velocity is more rapid in early diastole than during atrial systole. However, with mild to moderately impaired relaxation, the rate of early diastolic filling declines, as presystolic filling rates rise. With further stiffening, flow is “pseudo-normalized,” as early ventricular filling becomes more rapid with rising left atrial pressure upstream of the left ventricle.

Normal contractility Contractility CHAPTER 244 Contractility LV pressure

Basic Biology of the Cardiovascular System

LV volume ■ ■CARDIAC METABOLISM The heart requires a continuous supply of energy (ATP) not only to drive mechanical contraction, but also to maintain ionic and biochemi cal homeostasis. The development of tension, the frequency of contrac tion, and myocardial contractility levels are the principal determinants of the heart’s energy and oxygen requirements, representing ~15% of that of the entire organism. The heart’s ATP production requires the generation of acetyl coen zyme A that can be derived from (in descending order) free fatty acids (FFAs), glucose, lactate, amino acids, and ketone bodies. Myocardial FFAs derive from circulating FFAs, whereas the cardiomyocyte’s glu cose derives from plasma as well as from myocardial glycogen stores (via glycogenolysis). These two principal sources of acetyl coenzyme Abnormal relaxation Pericardial restraint Left ventricular pressure Chamber dilation Increased chamber stiffness Left ventricular volume FIGURE 244-12 Mechanisms that cause diastolic dysfunction reflected in the pressure-volume relation. The bottom half of the pressure-volume loop is depicted. Solid lines represent normal subjects; broken lines represent patients with diastolic dysfunction. (Reproduced with permission from JD Carroll et al: The differential effects of positive inotropic and vasodilator therapy on diastolic properties in patients with congestive cardiomyopathy. Circulation; 1986; 74: 815.)

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