CHAPTER 5
NORMAL PHYSIOLOGY OF THE CARDIOVASCULAR SYSTEM

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The principal function of the cardiovascular system is to deliver oxygen and nutrients to metabolizing tissues and remove carbon dioxide and wastes from these tissues. This is accomplished by means of two specialized circulations in series: a low-resistance pulmonary and a high-resistance systemic circulation driven by specialized muscle pumps, the right and left heart (each in turn composed of a thin-walled atrium and thicker-walled ventricle), respectively. Although cardiovascular physiology can be understood at a number of hierarchical levels, the complex interplay among the intrinsic properties of the cardiomyocytes and isolated muscle, chamber mechanics, and their modulation by variable cardiac-loading conditions and neurohormonal and renal compensatory mechanisms determines the integrated performance of the cardiovascular system. Accordingly, cardiovascular physiology will be examined at cellular, isolated muscle, and organ (isolated heart and integrated systems) levels.

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Excitation: The Action Potential

The rhythmic beating of the heart distinguishes it from all other organs. The normal heartbeat is initiated by a complex flow of electrical signals called action potentials. The action potential results from highly coordinated, sequential changes in ion conductances through gated sarcolemmal membrane channels (Fig. 5–1).

Increases in transmembrane potential from a resting value of ~80 to ~90 mV to approximately +30 mV (depolarization) represents phase 0 (the rapid upstroke) of the action potential and results primarily from a sudden increase in sodium (Na+) permeability; this permits a large inward current of Na+ ions to flow down an electrochemical gradient by means of voltage- and time-dependent fast Na+ channels. The upstroke is caused by a regenerative process: that is, depolarization leads to Na+ influx, which leads to further depolarization. The rapid opening of the activation gates for the fast Na+ channel is immediately followed by a slower closing of inactivation gates, which interrupts the influx of Na+ into the cell. The membrane must be fully repolarized for inactivation gates to reopen and conduct another action potential, a process called recovery.

Phase I (the notch) is the initial rapid repolarization phase of the action potential, which is carried by potassium (K+) and to a lesser extent, chloride (Cl–) ion conductance. Phase II of the action potential is unique to cardiac muscle; this plateau phase results from a balance of inward calcium (Ca2+) and outward K+ currents. The slow inward (L-type) Ca2+ channel is activated at threshold potentials above ~50 mV, is maximal at approximately 0 to 10 mV, peaks rapidly, and inactivates slowly. Some Na+ channels remain active and carry a late Na+ current throughout the action potential plateau; increased activity of this channel contributes to the abnormal repolarization and increased intracellular calcium in heart failure and ischemic heart disease. Phase III is the final rapid repolarization that restores resting potential and is caused by inactivation of the Ca2+ current and an increase in the outward K+ current. Several ionic K+ pumps contribute to the plateau and repolarization: (1) the inwardly rectifying K+ current (I\(_{\text{IR}}\)), a K+ conductance that generates the resting potential, turns off during phase 0 and is inactive until repolarization begins—it also generates a small outward current late in repolarization; (2) the transient outward K+ current (I\(_{\text{to}}\)), responsible for the initial phase I repolarization; and (3) the delayed outward K+ current (I\(_{\text{K}}\)), the primary current responsible for initiating final repolarization and turns on slowly at the final phase of the action potential. After repolarization, the Na+ K+ adenosine triphosphatase (ATPase) pump extrudes accumulated intracellular Na+ and pumps extracellular K+ into the cell. Ionic balance across the sarcolemmal membrane is also maintained by the action of a sodium–calcium exchanger.

All myocardial cells are excitable: that is, when adequately stimulated, they can generate an action potential. However, only specialized cells are capable of reaching threshold potential and firing without such an outside stimulus (automaticity). Phase IV of the action potential represents the slow, spontaneous diastolic depolarization responsible for the property of automaticity. Normally, action potentials reach threshold potential and depolarize spontaneously and rhythmically only in the primary pacemaker of the heart, the sinoatrial (SA) node. However, cells in other areas (atrial cells near the ostium of the coronary sinus,
the distal atrioventricular [AV] node, and the His-Purkinje fibers) are capable of automaticity when not suppressed by the faster firing of the SA node. The slope and maximal diastolic potential of the pacemaker potential and the threshold potential determine the rate of impulse formation; the former is modulated by the autonomic nervous system (sympathetic stimulation increasing the slope of the pacemaker potential and accelerating the rate of firing, and parasympathetic stimulation producing the opposite effects). Several ionic currents, specific for the site of impulse genesis, can be involved in the pacemaker current. In the SA node, an inward Ca\(^{2+}\) current and an outward delayed K\(^{+}\) current that is activated during the plateau and deactivated during phase IV contribute to depolarization. The "funny" current (pacemaker current; \(I_{F}\)), which slowly activates on hyperpolarization, is a critical determinant of the slope of diastolic depolarization and is therefore a key regulator of pacemaker activity.\(^3\) The T-type Ca\(^{2+}\) channel is present in the developing heart and adult atrium (and ventricular myocytes from hypertrophied and failing hearts), plays a role in the cardiac pacemaker current, and is involved in release of Ca\(^{2+}\) from internal stores.

Effective cell-to-cell communication is essential for rapid, uniform conduction of action potentials and a resultant effective, synchronized myocardial contraction. The organized distribution of local currents that comprise the depolarization wave flow from cell to cell by means of gap junctions. These clusters of transmembrane channels connect the plasma membranes of adjacent myocytes and form low-resistance pathways.\(^4,5\) These channels are composed of two connexons; each connexon is a hexamer of connexins, members of a multigene family of conserved proteins.

**EXCITATION–CONTRACTION COUPLING**

The cascade of biological processes that begins with the cardiac action potential and ends with myocyte contraction and relaxation defines cardiac excitation–contraction (E–C) coupling (Fig. 5–2). The E–C coupling is intimately related to calcium homeostasis, myofilament calcium sensitivity, and functions of cytoskeletal and sarcomeric proteins.

![Figure 5-1](image1.png)


![Figure 5-2](image2.png)

**FIGURE 5–2.** Major components of excitation–contraction coupling (E–C coupling). Influx of calcium is predominantly through the L-type calcium channel. The arrow through the channel denotes the amount of activator calcium and is an index of the E–C coupling gain. The relative magnitudes of calcium release, reuptake, and efflux are denoted by the arrow widths. The resultant calcium transient and muscle twitch are shown in the lower left of the cell. Ca\(^{2+}\), calcium; Na\(^{+}\), sodium; RyR2, ryanodine receptor; SERCA2, sarcoplasmic-endoplasmic reticulum calcium ATPase; SR, sarcoplasmic reticulum. Adapted from Scoote M, Poole-Wilson PA, Williams AJ, et al. The therapeutic potential of new insights into myocardial excitation-contraction coupling. Heart. 2003; 89(4):371-376.
and forms the biophysical underpinnings of the inotropic state of the heart.\textsuperscript{13,14} Because E–C coupling is a direct manifestation of myocyte calcium handling, an understanding of the calcium transient and calcium homeostasis is essential.

The calcium transient is initiated in response to sarcoplasmic depolarization by extracellular calcium (Ca\textsuperscript{2+}) influx through voltage-dependent L-type Ca\textsuperscript{2+} channels, which instigate the release of stored Ca\textsuperscript{2+} from the cardiomycocyte endoplasmic reticulum, sarcoplasmic reticulum (SR), via spatially proximate Ca\textsuperscript{2+} release channels (ryanodine receptor 2 [RyR2]).

This latter step, fittingly termed calcium-induced calcium release (CICR), amplifies the amount of calcium available for myofilament binding and force generating actin–myosin cross-bridges. Relaxation results from closure of the release channels, resequestration of Ca\textsuperscript{2+} by the sarcoplasmic endoplasmic reticulum Ca\textsuperscript{2+}–ATPase (SERCA2), and cross-bridge dissolution. To maintain steady-state calcium homeostasis, the amount of Ca\textsuperscript{2+} entering the cell with each contraction must be removed before the subsequent contraction. To this end, the Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger (NCX) acting in the forward mode competes with SERCA2 for Ca\textsuperscript{2+} and pumps [Ca\textsuperscript{2+}], into the extracellular space.

The magnitude of the [Ca\textsuperscript{2+}] transient modulates the force developed by myofilaments, and factors that modify calcium cycling and/or Ca\textsuperscript{2+} sensitivity of myofilaments can alter significantly the force and extent of myocyte contraction. The determinants of the cardiac myocyte [Ca\textsuperscript{2+}] transient are as follows. Factors responsible for the [Ca\textsuperscript{2+}] transient amplitude include (1) the calcium current (I\textsubscript{ca}), primarily caused by Ca\textsuperscript{2+} influx through the L-type Ca\textsuperscript{2+} channel, but in small part caused by reverse mode NCX; (2) SR [Ca\textsuperscript{2+}], content, which determines the amount of releasable calcium; (3) the efficiency of E–C coupling, or the gain (ie, the amount of calcium released by the SR for the calcium current, Δ[Ca\textsuperscript{2+}]/I\textsubscript{ca}); and (4) intracellular Ca\textsuperscript{2+} buffers. The decline of the [Ca\textsuperscript{2+}] transient is caused by (1) Ca\textsuperscript{2+} reuptake into SR by SERCA2 (a process modulated by a phosphorylatable regulatory protein termed phospholamban); (2) Ca\textsuperscript{2+} extrusion from the cell by the NCX; (3) Ca\textsuperscript{2+} extrusion from the cell by the sarcoslemmal Ca\textsuperscript{2+}–ATPase; (4) Ca\textsuperscript{2+} accumulation by mitochondria; and (5) Ca\textsuperscript{2+} binding to intracellular buffers (including fluorescent indicators that are used in experimental systems to measure the transient).\textsuperscript{13,14}

Calcium sparks (localized [Ca\textsuperscript{2+}] transients) are the elementary SR Ca\textsuperscript{2+} release events that trigger E–C coupling in heart muscle.\textsuperscript{13} The basis for the generally accepted local control theory of E–C coupling is that Ca\textsuperscript{2+} sparks are triggered by a local [Ca\textsuperscript{2+}], established in the region of the RyR2s by the opening of a single L-type Ca\textsuperscript{2+} channel. The amplitude of Ca\textsuperscript{2+} sparks is determined by SR Ca\textsuperscript{2+} load and gating properties of the RyR2. Although the exact nature and origin of Ca\textsuperscript{2+} sparks are not completely understood, the prevailing view is that the global [Ca\textsuperscript{2+}] transient is produced by the temporal and spatial summation of a large number of Ca\textsuperscript{2+} sparks.\textsuperscript{13,14} The mechanisms responsible for terminating sparks are not clear, but proteins accessory to the RyR2 (eg, sorcin [FKB12]) have been suggested as playing a key role.\textsuperscript{13,14}

Components of Excitation–Contraction Coupling

**Sarcoplasma** The sarcoplasma is the site where calcium enters and leaves the cell through a distribution of ion channels, transporters, and pumps. The T-tubules are invaginations of the sarcoplasma and glycosyl myocyte and are both longitudinal and oblique in their orientation; this system forms a permeability barrier between the cytosol and the extracellular space.\textsuperscript{13} The membranous surface areas are tissue (atrial cells have poorly developed T-tubules) and species specific. T-tubules play a complex regulatory role in the calcium transient; for example, the L\textsubscript{ca} is more sensitive to βAR stimulation and intracellular Ca\textsuperscript{2+} at the T-tubules than at the surface membrane.\textsuperscript{13} The structural specialization of the sarcoplasma include (1) SR coupling in the form of dyads by means of the T-tubule; (2) caveolae, which are invaginations of the sarcoplasma that increase surface area and form a scaffold for signaling molecules such as nitric oxide (NO) synthase and protein kinase C (PKC); and (3) the intercalated disk, which takes the form of a gap junction, intermediate junction, or desmosome. Ankyrins are sarcolemmal adaptor proteins that are implicated in the proper expression and membrane localization of ion channels, transporters, dystrophin, and other proteins.

**Sarcoplasmic Reticulum** The SR is an intracellular membrane-bounded compartment comprised of terminal, longitudinal, and corbular components (Fig. 5–3). The free walls of the terminal cisternae are apposed to the walls of the T-tubules and form the dyadic cleft; the RyR2 receptors are located in the walls of the terminal cisternae (feet) and face the dyadic cleft. Longitudinal SR is fairly homogenous and contains primarily the SR Ca\textsuperscript{2+}–ATPase proteins, SERCA2, and the associated phosphoprotein phospholamban. In its dephosphorylated state, phospholamban is an endogenous inhibitor of SERCA2. Phosphorylation by PKA (at amino acid serine 16) and calcium-calmodulin kinase II (CaMKII) (at threonine 17) lowers the Michaelis constant (K\textsubscript{m}) of sarcoplasmic endoplasmic reticulum calcium ATPase (SERCA) and results in enhanced calcium uptake. SR calcium is transported from the tubular lumen of the SR to the terminal cisternae, where it is stored mostly bound to calsequestrin, a low-affinity, high-capacity, calcium-binding protein. Calsequestrin forms a complex with the proteins junctin, triadin, and RyR2. Junctional SR does not come into contact with the sarcoplasma; corbular SR is a form of junctional SR that contains calsequestrin and RyR2 but is not coupled to the well-recognized calcium-cycling events.\textsuperscript{13,14}

**Myofilaments** Myofilaments comprise the contractile machinery of the cell and occupy 45% to 60% of the ventricular myocyte volume (Fig. 5–4). The fundamental unit of the myofilament is the sarcomere,
bounded by Z lines on each end, from which the thin actin filaments extend toward the center. At the center of the thick myosin filament is the M line, where the thick filaments are interconnected by M protein and myosin. Titin runs from the M line to the Z line in association with myosin and myosin-binding protein C (MyBP-C); this large structural sarcomeric protein acts as a scaffold for myosin deposition, stabilizes the thick filament, functions as a molecular spring, and plays a critical role in determining the passive stiffness of the heart. Changes in titin stiffness occur during cardiac development and disease states through shifts in the relative expression of the compliant N2BA and stiff N2B titin isoforms. Acute changes in titin stiffness (and as a result, diastolic ventricular function) is produced by PKC and PKG-mediated phosphorylation of an I band–specific domain of titin. The functions of MyBP-C are not entirely clear; it may play a role in regulation of contraction by limiting the reach of myosin heads toward the thin filament. It may also play a prominent role in myofilament calcium sensitivity, cross-bridge cycling rate, and length-dependent activation. Mutations in the MyBP-C gene are responsible for a significant proportion of familial hypertrophic cardiomyopathy. The Z lines are the sites of anchor for cytoskeletal intermediate filaments and actin filaments at the intercalated disks and focal adhesions. The two major structural complexes involved in the connections between sarcomeric proteins and the extracellular matrix (ECM) are the membrane-spanning integrin complex and the dystrophin complex, which links actin to laminin and collagen.

**Myosin** The myosin molecule consists of two heavy chains with a globular head, a long α-helical tail, and four myosin light chains (Fig. 5–5). The myosin head forms cross-bridges with the thin actin filament through an actin-binding domain. Transduction of chemical to mechanical energy and work is the function of myosin ATPase, located in the myosin heads. Myosin heavy chain exists as two isoforms, α (fast ATPase and cross-bridge formation) and β (slow ATPase and cross-bridge formation). In higher mammals, including humans, the β-myosin isoform predominates, but in small mammals, such as mice and rats, the α form is dominant. The most accepted model of energy transduction is the sliding filament theory based on the formation and dissociation of cross-bridges between the myosin head and the thin filament that transition through different energetic states. Two myosin light chains (the alkali or essential light chain [MLC1] and the phosphorylatable or regulatory light chain [MLC2]), are associated with each myosin head and confer stability to the thick filament. Phosphorylation of the myofilament regulatory protein troponin modulates the activity of myosin ATPase. Although phosphorylation of MLC2 by myosin light-chain kinase (MLCK) is critical for smooth muscle cell contraction (see the following section), its physiological significance in cardiac muscle (increased calcium sensitivity and rate of force development) is controversial.

**Thin Filaments** The backbone of thin filament is helical double-stranded actin. Tropomyosin is a long, flexible, double-stranded (largely α-helix) protein that lies in the groove between the actin strands and inhibits the interaction between actin and myosin (see Fig. 5–5). The troponin complex is composed of a calcium-binding subunit, troponin C (TnC); an inhibitory subunit that binds to actin, troponin I (TnI); and a

![FIGURE 5–4. Electron micrograph (A) and schematic diagram (B) of a sarcomere. The darker staining regions that flank the sarcomere are the Z lines. Myosin-containing thick filaments are in the center of the sarcomere and interact with actin-containing thin filaments by way of myosin heads that protrude from the thick filaments. Thin-filament regulatory proteins, the troponin and tropomyosin, provide calcium regulation of the actin–myosin interface. Thin filaments are anchored to the Z line, which is enriched in proteins such as α-actinin and Cap Z. (Right) Membrane complexes that concentrate over Z lines. Myosin-containing thick filaments are in the center of the sarcomere and interact with actin-containing thin filaments by way of myosin heads that protrude from the thick filaments. Thin-filament regulatory proteins, the troponin and tropomyosin, provide calcium regulation of the actin–myosin interface. Thin filaments are anchored to the Z line, which is enriched in proteins such as α-actinin and Cap Z. Reproduced from McNally E. The cytoskeleton. In: Walsh RA, ed. Molecular Mechanisms of Cardiac Hypertrophy and Failure. London, UK: Taylor and Francis; 2005:309-321.](image1)

tropomyosin-binding subunit, troponin T (TnT), which is attached to tropomyosin. In the resting state, when [Ca\(^{2+}\)] is low, calcium-binding sites of TnC are unoccupied, and TnI preferentially binds to actin; this favors a configuration in which the troponin–tropomyosin complex sterically hinders myosin–actin interaction. In this configuration, cross-bridges are in both detached and weakly attached non–force-producing states. When [Ca\(^{2+}\)] rises, calcium binds to the calcium-specific sites on TnC and strengthens the interaction of TnC and TnI; TnI then dissociates from actin, and a conformational change removes the steric hindrance to myosin–actin interaction. Strong binding of actin to myosin begins when the actin–myosin inhibition is relieved. Binding Ca\(^{2+}\) to troponin causes the process of cross-bridge formation to spread down the actin filament, and by means of ATP hydrolysis, transitions are made from detached or weakly bound states to force-producing states. Release of conformational energy leads to rotation of the myosin head that propels the thin filament along the thick filament. Usually the systolic [Ca\(^{2+}\)], only submaximally activates muscle; the steep relation between [Ca\(^{2+}\)] and tension is thought to result from both nearest neighbor interaction and strong actin–myosin binding, which allows for contractile reserve with modest changes in [Ca\(^{2+}\)]. Although this is the most accepted model, other potential explanations exist; all models incorporate the concept that myofilaments are dynamically involved in their state of activation and not simply subject to passive changes in [Ca\(^{2+}\)]. A simplified mechanical model of cross-bridge formation is presented in Fig. 5–6.

Mitochondria Mitochondria comprise approximately 35% of ventricular myocyte volume and according to their cellular location are designated as either subsarcolemmal or interstitial. Mitochondria are the sites of oxidative phosphorylation and ATP generation. Although they have the capacity to buffer large amounts of Ca\(^{2+}\) and are a potential source of activator calcium, classical teaching is that their contribution to E–C coupling is minimal in view of the short time constants involved; variation in mitochondrial Ca\(^{2+}\) during a twitch is imperceptible and thus plays a very minor role in beat-to-beat changes in calcium homeostasis. However, the kinetics of mitochondrial Ca\(^{2+}\) uptake during E–C coupling have recently become controversial. Nevertheless, slower increases in mitochondrial Ca\(^{2+}\) content are important with respect to mitochondrial function and energetics; for example, the matrix enzymes pyruvate dehydrogenase, nicotinamide adenine dinucleotide–dependent isocitrate dehydrogenase, and α-ketoglutarate dehydrogenase are activated by low [Ca\(^{2+}\)]. In addition, the ability to accumulate large amounts of Ca\(^{2+}\) under pathological conditions (eg, ischemia) can help protect against myocyte Ca\(^{2+}\) overload; however, Ca\(^{2+}\) accumulation by mitochondria ultimately slows ATP production.

### ROLE OF NITRIC OXIDE

NO is produced by the myocardium and regulates cardiac function through both vascular-dependent and -independent effects. In terms of vascular-dependent effects, NO acts as a peripheral vasodilator and reduces afterload, thereby changing pressure–volume (P–V) and force–tension relationships, and ultimately increasing stroke volume. Although these issues are discussed later in the chapter, this section focuses on the vascular-independent effects of NO. NO has a modest positive inotropic effect on basal contractility in isolated myocytes and the isolated perfused heart but a negative inotropic effect in vivo, possibly because of nitrosylation of ion channels responsible for E–C coupling (eg, L-type channel, RyR2). The negative inotropic effects on β-adrenergic stimulated contractility are greater and less controversial and can comprise a critical component of negative feedback over contractile reserve. NO’s positive effects on relaxation or lusitropy (and in part, for negative inotropic effects) are likely to be caused by cyclic 3’, 5’-guanosine monophosphate (cGMP)-mediated reduction in myofilament Ca\(^{2+}\) sensitivity. Finally, mitochondrial NO reduces maximal venous oxygen (MVO\(_{2}\)) consumption and increases mechanical efficiency (stroke work/MVO\(_{2}\)), suggesting that NO regulates energy production as well influencing consumption. The effects of NO on E–C coupling are confusing and controversial because of the presence of three nitric oxide synthase (NOS) isozymes that are spatially localized to highly controlled microdomains and linked to disparate signaling pathways and effectors. For example, NOS type III (NOS3) is compartmentalized to the sarcolemmal and T-tubule caveolae, associated with the L-type channel, inactivated by the scaffolding protein caveolin-3, and activated by Ca\(^{2+}\)/calmodulin and Akt phosphorylation. NOS3 produces its negative inotropic and positive lusitropic effects by means of cGMP activation. In contrast, NOS type I (NOS1), which is also activated by Ca\(^{2+}\)/calmodulin and can be inactivated by caveolin-3, is localized to cardiac SR and is involved with calcium homeostasis. NOS1 increases the open probability of the cardiac RyR2 channel.

![FIGURE 5–6. A mechanical model of the cross-bridge cycle. A. Detached cross-bridge. B. Cross-bridge before developing force. C. Attached cross-bridge developing force stored in the elastic component. D. Cross-bridge rotated and translated so the filaments slide relative to one another. Each step in the cycle can be related to energetically different chemical states. Reproduced from Bers DM. Excitation-Contraction Coupling and Cardiac Contractile Force. 2nd ed. Norwell, MA: Kluwer Academic Publishers, 2001.](image-url)
and modulates β-adrenergic mechanics, calcium transients, and the force–frequency relationship, although the mechanisms are still under investigation. 24 Nevertheless, accumulating data suggest that NO plays an important role in E–C coupling vis-à-vis modulation of Ca2+ channel activity, myofilament Ca2+ sensitivity, and mitochondrial respiration. 25

■ NON–STEADY–STATE EXCITATION–CONTRACTION COUPLING

Heart rate dependence of cardiac contractility reflects basic cycling kinetics of calcium and is critically dependent on SR function. Processes related to force–interval behavior (eg, mechanical restitution, force–frequency, postextrasystolic potentiation [PESP]) are important insofar as they represent fundamental physiological control mechanisms, they are used as indices of myocardial function, and they play a role in the response to exercise and the development and maintenance of heart failure. Non–steady–state aspects of E–C coupling provide the basis for these phenomena.

Mechanical restitution is the relative refractory period that immediately follows a contraction and is usually explained by the recovery of the RyR2 receptors (because ICa and SR Ca2+ content recover rapidly). 26 Mechanical restitution is the basis for PESP, the strong contraction following a weaker extrasystole, because lower [Ca2+] on the extrasystole results in increased ICa (less Ca2+-induced inactivation of the L-channel), less Ca2+ efflux from NCX, and increased SR Ca2+ loading on the postextrasystolic beat. The result is a greater amount of released Ca2+ and therefore a stronger contraction. In the intact heart, the effect of changing preload (and the impact on Frank-Starling and calcium sensitivity) is an important additional mechanism. PESP contributes to the beat-to-beat variability of the pulse in atrial fibrillation. Mechanical alternans, the alternating contraction amplitude at a constant heart rate that is seen in heart failure, is explained by a similar interplay of RyR2 refractoriness (which is increased in heart failure), ICa in-activation, NCX competition, and SR Ca2+ load. 27,28

The relationship between pacing rate and force (force–frequency relationship) can be understood similarly by these non–steady–state phenomena. Increased pacing rate overcomes the encroachment on mechanical restitution and produces an increase in force because of rate-dependent increases in ICa, Ito (which results in less Ca2+ efflux by the NCX), diastolic [Ca2+]i (less time for efflux and greater influx/second), releasable SR Ca2+ content, and fractional SR Ca2+ release. 29,30 A phenomenon similar to the force–frequency relationship is observed when the effects of heart rate on the time constant of isovolumic relaxation are examined. Thus, similar to the effect on contraction, relaxation is augmented at higher rates of stimulation.

■ EXCITATION–TRANScription COUPLING

An emerging concept is that the molecular machinery of E–C coupling is involved in the long-term regulation of gene expression by a process known as excitation–transcription (E–T) coupling. Despite periodic oscillations of [Ca2+]i from 100 nM to 1 μM during E–C coupling, transcription regulatory proteins (eg, NFkB, janus N-terminal kinase [INK], nuclear factor of activated T cells [NFAT]) are calcium activated. The amplitude and duration of the calcium signal; the presence of microdomains and anchoring proteins; and linkages through calmodulin, kinases, and phosphatases are important mechanisms for discriminating important regulatory cues and resolving this apparent paradox. 31 For example, in adult ventricular myocytes, inositol 1,4,5 triphosphate (InsP3) receptors localized to the nuclear envelope are involved in the local control of Ca2+ (so-called reactive signaling) for a CaMKII-mediated activation and regulation of a histone deacetylase. 32 CaMKII regulates proteins involved in calcium transport; ion channels; and cell contraction, metabolism, and proliferation by phosphorylation. Phosphorylation substrates for CaMKII that are involved in modulating contraction–relaxation include phospholamban (PLB), SERCA2a, L-type Ca2+ channels, and the RyR2. 33,34 CaMKII phosphorylates the transcription factor cyclic adenosine monophosphate (cAMP) response element binding, which promotes transcription of c-Fos. 35 In addition, CaMKII has autoregulatory properties that are dependent on the frequency of Ca2+ spikes, a process thought to have a role in neuronal memory. Little is known about in vivo CaMKII activation, but biochemical data suggest that CaMK might be primed to respond to Ca2+ spikes. Thus, calcium–dependent regulation by calmodulin and CaMKII has both acute responses affecting E–C coupling and chronic responses that influence the expression levels of proteins involved in E–C coupling. 36,37 In vascular smooth muscle cells, the L-type channel (via the RhoA/ROK pathway) and the calcineurin/NFAT pathway are involved in the regulation of cell differentiation. 38

■ VASCULAR EXCITATION–CONTRACTION COUPLING

Arterial smooth muscle cells exist in the partially constricted state. The principal determinant of vascular tone is membrane potential, which is achieved through activation of voltage-gated calcium channels. There is a steep relation between [Ca2+] and vascular tone, and therefore membrane potential must be highly regulated to maintain appropriate vascular resistance. The resting smooth muscle cells ranges from –40 to –70 mV, lower than cardiac muscle because of greater Na+ permeability. Thus, the rising phase of the action potential is produced by inward calcium current through the slow L-type Ca2+ channels. Contraction results directly from depolarization-induced Ca2+ influx and indirectly by means of CICR-activation of the contractile apparatus. Relaxation results from lowering cellular Ca2+ via Ca2+ ATPase pumps and hyperpolarization of the cell by activation of K+ channels.

A distinctive feature in smooth muscle is that Ca2+ acts as a second messenger to activate MLCK, which phosphorylates the myosin light chains and produces force. Ca2+ binds to calmodulin, and this complex activates MLCK. Phosphorylation of the 20-kD light chain stimulates actin-activated myosin ATP hydrolysis and contraction. Relaxation occurs when there is dissociation of Ca2+ from calmodulin, inactivation of MLCK, and dephosphorylation of myosin by myosin light-chain phosphatase (Fig. 5–7).

Unlike myocardial cells, both cAMP and cGMP inhibit the activity of the slow Ca2+ channels. Thus, both NO (which increases cGMP) and β-adrenergic agonists (which increase cAMP) are vasodilators. Stimulation of delayed rectifier channels and sarcemmal Ca2+ pumps produce vasodilation. Angiotensin II and α-agonists cause vasostriction by phospholipase C–mediated production of inositol trisphosphate (IP3, which releases Ca2+) and diacylglycerol (DAG), which stimulates PKC phosphorylation of the Ca2+ channel and inhibition of the delayed rectifier channel.

■ PROPERTIES OF MYOCARDIAL CONTRACTION

■ FUNDAMENTALS OF MYOCARDIAL CONTRACTILITY

Fundamental to cardiac muscle function are the relationships between force and muscle length, velocity of shortening, calcium, and heart rate. The maximal force developed at any sarcomere length is determined by the degree of overlap of thick and thin filaments and therefore the number of available cross-bridges. 39 Force increases linearly until a sarcomere length with maximal overlap (–2.2 μm) is achieved
The descending limb of the length–tension relationship is prevented by the strong parallel elastic component in cardiac muscle. The ascending limb of the length–tension relationship is depicted (Fig. 5–8), beyond which force and overlap gradually declines to zero (i.e., the descending limb). The descending limb of the length–tension relationship is prevented by the strong parallel elastic component in cardiac muscle. The ascending limb of the length–tension relationship (equivalent to the Frank-Starling relationship that relates preload to cardiac performance) is also caused by a length-dependent increase in myofilament calcium sensitivity (Fig. 5–9A). This has been explained by enhanced calcium binding to TnC, narrower interfilament gaps at long sarcomere length, and increased SR calcium release and uptake at longer sarcomere lengths.

The relationship between force and velocity of contraction is hyperbolic (Fig. 5–9B); at maximum force (isometric force), shortening cannot occur, and at zero force (ie, unloaded muscle), velocity is at a maximum (V_{max}^*), reflecting the maximum turnover rate of myosin ATPase. Therefore, alterations in the myosin isoform (ie, α, fast; β, slow) such as those seen in response to pressure overload, have an effect on V_{max}^*.

Another fundamental property of cardiac muscle is the force–pCa relation. Shorter sarcomere lengths decrease Ca\(^{2+}\) sensitivity, and caffeine and various inotropic drugs (eg, levosimendan) are potent calcium sensitizers. β-Adrenergic stimulation results in a cAMP-dependent phosphorylation of cardiac TnI and a resultant decrease in myofilament calcium sensitivity; thus, for a positive β-adrenergic receptor (βAR)–inotropic effect, the amplitude of the calcium transient must more than compensate for reduced βAR-mediated myofilament sensitivity.\(^{15,36}\)

The final property relates heart rate to contraction and relaxation. Increasing the heart rate increases contractility; this is related to the Ca\(^{2+}\) capacity and load of the SR. A related phenomenon, frequency-dependent acceleration of relaxation, results from CaMKII phosphorylation of phospholamban (or by some other mechanism that increases SR Ca\(^{2+}\) transport).\(^{33,37}\) CaMKII might be activated by the increased [Ca\(^{2+}\)]i, that occurs with increased stimulation rates; however, the precise mechanisms are unresolved. The physiologic implications for faster relaxation at increased heart rates, when the diastolic filling periods are shortened, are discussed in the following section.

### ISOLATED MUSCLE: MECHANICS OF CONSTITUENT MUSCLE FIBERS

When a strip of heart muscle is attached at both ends so that the length is fixed and then electrically stimulated, the muscle develops force without shortening (Fig. 5–10A). A fundamental property of striated muscle is that the strength of this isometric twitch is dependent on the initial resting muscle length, or preload (Fig. 5–10B). As cardiac muscle is stretched passively, the resting tension rapidly rises and prevents overstretching of the sarcomeres. If additional load is applied before contraction (ie, the preload), stimulation causes contraction with an increased peak tension and rate of tension development (dT/dt). Thus, total tension includes both active and passive tension. The length–tension relationship, which forms the basis for the Frank-Starling relationship, is depicted in Fig. 5–10C. The inotropic state is defined operationally as a change in the rate or extent of force development that occurs independently of the loading conditions. The biophysical basis of the inotropic state includes the subcellular processes that regulate myocyte cytosolic calcium and actin–myosin cross-bridge cycling. In isolated cardiac muscle, changes in the inotropic state are measured by changes in the peak isometric tension and dT/dt at a fixed preload.

If isolated cardiac muscle is allowed to shorten, the contraction is termed isotonic (Fig. 5–10D). Initial muscle length is determined by enhanced calcium binding to TnC, narrower interfilament gaps at long sarcomere length, and increased SR calcium release and uptake at longer sarcomere lengths.\(^{15}\)

The physiologic implications for faster relaxation at increased heart rates, when the diastolic filling periods are shortened, are discussed in the following section.

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**FIGURE 5–7.** The molecular basis of regulation of smooth muscle contraction. Stimulation of muscarinic receptors increases the free 
Ca\(^{2+}\) ions, which bind to calmodulin (CaM) and the Ca\(^{2+}\)-CaM complex subsequently binds to and activates myosin light-chain kinase (MLCK). Phosphorylation of myosin by MLCK stimulates actin-activated myosin-ATP hydrolysis, which produces contraction. Relaxation begins with the cessation of agonist stimulation, resulting in decreased [Ca\(^{2+}\)]i, dissociation of Ca\(^{2+}\) from CaM, inactivation of MLCK because of dissociation of CaM, dephosphorylation of myosin by phosphoprotein phosphatases, and relaxation. Reproduced from Paul R, Henry JA, Ferguson DJC, Solano RJ. Diversity of muscle. In: Sperezakis N, Banks RD, eds. Essentials of Basic Science: Physiology. 2nd ed. Boston, MA: Little, Brown and Company; 1996:217-225.
constant, length–shortening and length–velocity curves (analogous to the length–tension curve seen in isometric muscle) are derived.

The force–velocity curve describes an inverse hyperbolic curve relating afterload and the initial velocity of shortening and can be obtained from a series of variably afterloaded contractions (see Fig. 5–9B). When the afterload is so great that the muscle cannot shorten, the contraction becomes isometric ($P_0$). The velocity of an unloaded contraction ($V_{max}$) is determined by the physicochemical properties unique to cardiac muscle and is therefore considered a measure of the inotropic state. However, because load always exists, $V_{max}$ must be extrapolated from the force–velocity curve. Although changes in preload shift $P_0$ without changing $V_{max}$, a positive inotropic agent increases $V_{max}$ and $P_0$ by means of a parallel upward shift of the force–velocity curve; a negative inotropic agent causes the opposite effect. Similar operational definitions of the inotropic state can be applied to the preloaded isotonic contraction, in that a positive inotropic agent produces an upward shift of the length–shortening and length–velocity curves.

An important property of cardiac muscle is that the isometric passive length–tension curve establishes the limits of tension for an isotonic contraction. In other words, the tension at the end of an isotonic contraction is the same as the tension developed from an isometric contraction at the same resting muscle length.

Besides load and the contractile state, cardiac muscle performance is influenced by the frequency of stimulation. An increase in stimulation frequency causes an increase in tension in isolated cardiac muscle, known as the Bowditch phenomenon.


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Besides load and the contractile state, cardiac muscle performance is influenced by the frequency of stimulation. An increase in stimulation frequency causes an increase in tension in isolated cardiac muscle, known as the Bowditch phenomenon. This is the force–frequency relationship previously described.
CARDIOVASCULAR PHYSIOLOGY

For all the advantages of studying isolated myocytes and muscle fibers, an integrated and more realistic analysis of cardiovascular function regards the left ventricle (LV) as a muscle pump coupled to the systemic and venous circulations. In contrast to isolated cardiac muscle, contraction of the intact LV is auxotonic, in that force increases and decreases during ejection of viscous blood into a viscoelastic arterial system. Moreover, attempts to extrapolate results from isolated muscle to the intact LV are hampered by the complexity of chamber geometry and myocardial fiber orientation, which make it difficult to estimate initial fiber length (preload) and the force opposing LV ejection (afterload). Finally, unlike isolated cardiac muscle, ventricular performance is modulated by neurohumoral influences, right and LV interaction, restraining effects of the pericardium, and atrial function. At the organ level, the preceding events are initiated by the electrical activation of the heart and structured by the sequence of events in a heartbeat, the cardiac cycle.

THE ELECTROCARDIOGRAM

The electrocardiogram (ECG) (Fig. 5–11) records the pattern of electrical activation of the heart on the body surface. Electrical currents generated by differences in potential between depolarized and polarized regions of the heart are conducted through the body, detected by electrodes, and amplified and recorded on calibrated moving paper. The ECG provides important clinical information regarding the electrical orientation of the heart in three-dimensional space, the relative size of the cardiac chambers, and the presence of conduction system defects and provides evidence for a variety of underlying pathologic conditions, such as ischemia, infarction, cardiomyopathy, and hypertrophy.

The SA node is the primary pacemaker of the heart and is located at the junction of the superior vena cava and the right atrium. The action of the SA node is electrically silent, although a measurable conduction time between sinus node discharge and atrial depolarization (denoted by a P wave) can be measured on intracardiac electrograms. Action potentials travel rapidly (1.0–1.5 ms) through the atrial myocardium and generate an atrial contraction. Preferential conduction in specialized bundles of muscle fibers (the internodal tracts of Bachmann, Wenckebach, and Thorel) nearly simultaneously activate the atrial musculature and ensure that the action potential reaches the AV node in a timely fashion. Excitation of the ventricles spreads by means of the AV node and the His-Purkinje system (bundle of His and bundle branches). The impulse travels slowly (0.02–0.05 ms) through the AV node. In contrast, conduction velocity through the Purkinje system is very fast (2.0–4.0 ms). The PR interval includes atrial depolarization, AV nodal conduction, and His-Purkinje activity. Activation of ventricular myocardium (conduction velocity 1.0–2.0 ms) occurs after most of the conduction system is depolarized and is represented by the QRS complex. Ventricular repolarization occurs during the T wave.

The ECG is essentially a voltmeter that measures and records potential differences between pairs of electrodes or leads. Three bipolar leads (I, II, III), three unipolar limb leads (aVR, aVL, aVF), and six precordial leads (V1-V6) record the distribution of the potentials on the frontal and horizontal planes of the heart (see Fig. 5–11). Depolarization and repolarization of the heart results in differences in electrical potential, and the ECG measures these changes in potential over time. The external surface of a depolarized membrane becomes electrically negative relative to quiescent, polarized areas. The direction of the propagated impulse travels from the depolarized to polarized areas. By convention, the direction of the propagation wave toward the positive pole...
of a bipolar lead system or exploring electrode produces an upright deflection and conversely, if the propagation wave is toward the negative pole or away from an exploring electrode, a negative deflection is produced. Depolarization progresses from cell to cell in an orderly fashion from endocardium to epicardium from the apex to base of the heart. In contrast, repolarization does not occur as a propagated wave; nevertheless, it is represented by a single vector that integrates multiple areas of potential difference. Local circuit currents precede the depolarization wavefront, depolarize the adjacent membrane, and bring the membrane to threshold potential; with depolarization, the local circuit currents flow through low-resistance gap junctions (the major component of which is connexin) and depolarize a neighboring cell. Thus, the myocardium functions as a functional syncytium. The ECG is discussed in detail in Chap. 12.

THE CARDIAC CYCLE

The cardiac cycle describes pressure, volume, and flow phenomena in the ventricles as a function of time. This cycle is similar for both the LV and right ventricle (RV), although there are differences in timing stemming from differences in the depolarization sequence and the levels of pressure in the pulmonary and systemic circulations. For simplicity the cardiac cycle for the left heart during one beat will be described (Fig. 5–12).

The QRS complex on the surface ECG represents ventricular depolarization. Contraction (systole) begins after an approximately 50-ms delay and results in closure of the mitral valve. The LV contracts isovolumetrically until the ventricular pressure exceeds the systemic pressure; at this time, the aortic valve opens and ventricular ejection occurs. Bulging of the mitral valve into the left atrium during isovolumic contraction causes a slight increase in left atrial pressure (c wave). Shortly after ejection begins, the active state declines, and ventricular pressure begins to decrease. Left atrial pressure rises during ventricular systole (v wave) as blood returns to the left atrium by means of the pulmonary veins. The aortic valve closes when LV pressure falls below aortic pressure; momentum briefly maintains forward flow despite greater aortic than LV pressure. Ventricular pressure then declines exponentially during isovolumic relaxation when both the aortic and mitral valves are closed. This begins ventricular diastole. When ventricular pressure
During ventricular filling, pressure and volume increase. Large arrowheads indicate rapid filling, beginning at the upper left corner of the P–V loop (Fig. 5–13A). Passive filling occurs at a constant pressure, where the ventricle operates on the flat portion of its diastolic P–V line; an isovolumetric contraction (large arrowheads) from varying end-diastolic volumes (preload). Reproduced from Hoit BD, Walsh RA. Determinants of left ventricular performance and cardiac output. Essentials of Physiology. 2nd ed. Boston, MA: Little, Brown and Company, 1996:269–278.

Hand corner of the loop, and end-systole is at the upper left corner of the loop. LV P–V diagrams illustrate the effects of changing preload, afterload, and inotropic state in the intact ventricle (see the following).

A P–V loop can also be described for atrial events. During ventricular ejection, descent of the ventricular base lowers atrial pressure and thus assists in atrial filling. Filling of the atria from the veins results in a v wave on the atrial and venous pressure tracing. When the mitral and tricuspid valves open, blood stored in the atria empties into the ventricles. Atrial contraction, denoted by an a wave on the atrial pressure tracing, actively assists ventricular filling. The resultant atrial P–V diagram has a figure-of-eight configuration with a clockwise V loop, representing passive filling and emptying of the atria, and a counterclockwise A loop, representing active atrial contraction. Thus, the atria function as a reservoir, a conduit for venous flow (during ventricular systole and diastole, respectively), and a booster pump for ventricular filling late in diastole.  

### PRESSURE–VOLUME RELATIONSHIPS IN THE ISOLATED HEART

Isolated, perfused, isovolumically contracting hearts are useful preparations to study preload dependency of ventricular performance (the Frank-Starling relation) and fully relaxed, end-diastolic P–V relationships without the confounding, uncontrolled changes in either neurohumoral activation or coronary perfusion. These preparations are especially well-suited for quantifying end-systolic elastance (stiffness), a relatively load-independent index of ventricular function. The time-varying elastance model of ventricular contraction is based on the experimental observations in which ventricular volume and loading are altered under conditions of unvarying contractility (Fig. 5–14). At any time, t, following the onset of contraction, the relation between pressure (P) and volume (V) is linear according to the relation: P(t) = E(t) – [V(t) – V0], where

\[
\text{E(t)} = E_{\text{es}} + E_{\text{max}}(1 - \frac{V(t)}{V_{\text{es}}})
\]

An alternative time-independent representation of the cardiac cycle is obtained by plotting instantaneous ventricular pressure and volume (Fig. 5–13). During ventricular filling, pressure and volume increase nonlinearly (phase I). The instantaneous slope of the P–V curve during filling (dP/dV) is diastolic stiffness, and its inverse (dV/dP) is compliance. Thus, as chamber volume increases, the ventricle becomes stiffer. In a normal ventricle, operative compliance is high because the ventricle operates on the flat portion of its diastolic P–V curve. During isovolumic contraction (phase II), pressure increases and volume remains constant. During ejection (phase III), pressure rises and falls until the minimum ventricular size is attained. The maximum ratio of pressure to volume (maximal active chamber stiffness or elastance) usually occurs at the end of ejection. Isovolumic relaxation follows (phase IV), and when LV pressure falls below left atrial pressure, ventricular filling begins. Thus, end-diastole is at the lower right
E is the time-varying elastance and \( V_0 \) is the volume at zero pressure or dead volume; this relation becomes progressively steeper until it reaches a maximum at end-systole. Thus, the ventricle behaves like a spring with a stiffness (elastance) that increases during contraction and decreases during relaxation. The slope of the end-systolic P–V relationship, end-systolic elastance (Ees) changes directly as a function of acute changes in contractility without a change in dead volume (\( V'_0 \)). Appropriate changes in Ees are also observed with increases in beating frequency (eg, force–frequency relationships).

The elastance concept has been extended to the study of ventricular mechanooenergetics by proposing that the P–V area (PVA) bounded by the LV P–V loop is a measure of the total mechanical energy of LV contraction.\(^5\) The PVA concept is shown schematically in Fig. 5–15. The total mechanical energy of contraction can be considered to consist of two components: (1) external work, the area enclosed within the P–V loop; and (2) potential energy stored in the ventricular spring at ES; that is, the area between the end-systolic pressure relation on the left and the end-diastolic P–V relation on the right.

The myocardial oxygen consumption (MVO\(_2\))–PVA relationship is obtained by measuring P–V area loops and LV MVO\(_2\) at several steady-states. There is a highly linear correlation (\( r > .98 \)) between LV VO\(_2\)/beat and PVA/beat over a wide range of experimental conditions (see Fig. 5–15, bottom), indicating the accuracy of the PVA as a measure of total mechanical energy. The VO\(_2\) intercept of the VO\(_2\)–PVA relationship is the unloaded VO\(_2\) (PVA–independent VO\(_2\)), which in an isovolumically contracting heart, corresponds to a point at which LV peak pressure is 0 mm Hg (Fig. 5–16). At this point, except for a low level of cross-bridge cycling caused by shape changes, there is neither mechanical energy produced nor energy expended for cross-bridge cycling.\(^5\) The VO\(_2\) under unloaded conditions reflects energy used for E–C coupling and basal metabolism; the latter can be eliminated experimentally by arresting the heart. In this manner, changes in E–C coupling energy consumption have been detected as shifts in the unloaded VO\(_2\). Oxygen consumption used by the contractile apparatus for cross-bridge cycling is PVA-dependent VO\(_2\), which increases linearly and directly with PVA. Because PVA-dependent VO\(_2\) is the energy input and the PVA is the total energy output of the contractile machinery, the inverse slope of the VO\(_2\)–PVA relationship is a dimensionless measure of the thermodynamic efficiency of the contractile machinery. Unlike efficiency expressed as the external work/total VO\(_2\), efficiency expressed by the VO\(_2\)–PVA relationship is relatively insensitive to load. The VO\(_2\)–PVA relationship is sensitive to metabolic changes and impacts the efficiency of ATP production.

### DETERMINANTS OF LEFT VENTRICULAR FUNCTION

#### Measures of Ventricular Performance

Measures of overall ventricular performance typically include cardiac output (the quantity of blood delivered to the circulation, calculated as the stroke volume and heart rate), stroke volume (quantity of blood ejected/beat, which equals the ventricular end-diastolic volume minus the end-systolic volume), and stroke work (the product of pressure and stroke volume, which equals the area bounded by the ventricular PVA and which can be approximated in the clinical setting as \( ((\text{Mean LV systolic – Diastolic pressure}) \times \text{Stroke volume}) / 0.0136 \)). Cardiac output responds to changes in the oxygen requirements of tissues, for example, as occurs with exercise. The extraction of nutrients by tissue can be expressed as the arteriovenous difference across the tissue. According to the Fick principle, the consumption of a particular nutrient (eg, oxygen) by a tissue equals the rate of delivery of that nutrient: that is, the cardiac
output times the arteriovenous difference of that nutrient. Changes in cardiac output necessary to meet the metabolic needs of the tissues can be produced by changes in the stroke volume, heart rate, or both. Changes in stroke volume are mediated by altered loading conditions, inotropic state, and heart rate. Thus, factors that influence the strength of contraction in isolated muscle are the same factors that determine cardiac output. The stroke volume expressed as a function of the end-diastolic volume is the ejection fraction (EF). Thus, EF = (End-diastolic volume – End-systolic volume)/End-diastolic volume.

Preload The influence of preload on measures of ventricular performance defines the LV function curve, known as the Frank-Starling curve. Increasing LV end-diastolic volume increases stroke volume in ejecting beats and increases peak LV pressure in isovolumic beats. The modulation of ventricular performance by changes in preload, termed heterometric regulation, operates on a beat-by-beat basis and is responsible for matching outputs of the right and LVs, as with changes in posture and breathing. The Frank-Starling curve also represents an important compensatory mechanism that maintains LV stroke volume (vis-à-vis increasing LV end-diastolic volume) when LV shortening is impaired, owing either to myocardial contractile dysfunction or to excessive afterload. The atria also exhibit a Frank-Starling curve that becomes clinically important during exercise and when there is resistance to early diastolic LV filling.

Because a representative fiber length (i.e., preload) is difficult to determine in the LV, changes in the myocardial fiber length are estimated from changes in either the LV end-diastolic volume or LV end-diastolic pressure. In the clinical setting, end-diastolic pressure and pulmonary capillary wedge pressure are used frequently as measures of preload. However, the passive P–V relationship, analogous to the passive length–tension curve in isolated muscle, is not linear but exponential. Thus, the ratio of change in LV pressure to volume is greater at higher than at lower LV volumes. Not surprisingly, under certain circumstances, ventricular pressure can inaccurately reflect the ventricular volume. Moreover, changes in ventricular volume can erroneously be inferred from changes in cardiac pressures, which can result only from alterations in ventricular compliance. For example, whereas chronic volume overload can shift the ventricular diastolic pressure relationship rightward so that volume is increased at a normal end-diastolic pressure, chronic pressure overload can shift the diastolic P–V relationship leftward and for the same end-diastolic pressure result in a smaller ventricular volume. Compliance of the LV is affected by pericardial pressure, RV pressure and volume, and coronary artery perfusion (turgor) in addition to changes in the intrinsic elastic properties of the LV.

Afterload Afterload in the intact heart can be considered as the tension in the LV wall that resists ventricular ejection (wall stress during systole) or as the arterial input impedance (the ratio of instantaneous change in pressure to instantaneous change in flow). Although forces within the ventricular wall are difficult to measure, initial estimates of systolic wall stress can be derived from application of the Laplace relationship in which wall tension = (P - r)/2 h, where P refers to pressure, r to ventricular radius, and h to wall thickness. More complex derivations based on various geometric assumptions are used to calculate end-systolic wall stress. Input impedance is a complex function of arterial pressures, elasticity, vessel dimension, and blood viscosity, which requires measurement of instantaneous aortic pressure and flow and is therefore impractical to measure in the clinical setting. Because of its simplicity, aortic pressure is often used as a surrogate for afterload. An increase in afterload causes a decrease in stroke volume and the velocity of LV shortening. The resulting stress–shortening and stress–velocity curves are analogous to those obtained from variably afterloaded isotonic contractions in isolated muscle.

Inotropic State The ideal method of measuring the inotropic state in the intact LV should incorporate the variables of force, length, velocity, and time; be independent of external loading conditions; and relate to physicochemical processes at the sarcomeric level. Because of these constraints, changes in inotropic state are usually defined operationally by shifts of the various ventricular function curves, which, by definition, are independent of loading conditions. For example, a drug with positive inotropic activity (e.g., dobutamine) shifts the Frank-Starling curve (analogous to the length–shortening curve in papillary muscle preparations) upward and to the left, and changes in the stress–shortening relationship (analogous to the force–velocity curve) upward and to the right.

The rate of pressure development in the LV during isovolumic systole (dP/dt max) is used frequently as an index of the inotropic state. Although LV + dP/dt max provides a measure of the rate of tension development and of myocardial contractility, this index is preload dependent, caused in part by length–diameter changes in the filament Ca²⁺ sensitivity. However, LV + dP/dt max is largely independent of afterload, provided that the maximum rate of increase occurs before aortic valve opening. Although changes in the maximal rate of increase of ventricular pressure are highly sensitive to acute changes in contractility and are useful to assess directional changes in inotropic state, absolute dP/dt max is not as useful for assessment of basal contractility as are the ejection phase indices, such as LVEF (stroke volume/end-diastolic volume ×100). Furthermore, dP/dt max cannot be corrected for changes in muscle mass produced by LV hypertrophy, in which case it is best to compare peak stress, which incorporates pressure, volume, mass, and geometry. Because of the direct influence of preload on dP/dt –dP/dt at a common developed pressure (LV systolic minus diastolic pressure) and the slope of the dP/dt end-diastolic volume curve (preload recruitable stroke work; see the following) have been proposed as preload independent indices of the inotropic state.

End-systolic P–V points from ejecting beats obtained from variably preload or afterloaded contraction fall reasonably close to the isovolumetric P–V line for a given inotropic state (vide supra). Thus, changes in the inotropic state, independent of the loading conditions can be identified by changes in the slope of the end-systolic P–V relationship (Ees). By acutely altering loading conditions (e.g., transient vena caval occlusions or phentolamine boluses), a family of PVAs is obtained (single-beat methods designed for clinical use have been proposed). End-systolic can be defined as end ejection or as the time of maximal elastance (the maximal P–V ratio) during systole. In the normal heart, these two points are closely related in time. In practice, the end-systolic P–V relationship (ESPVR) is constructed by connecting the end-systolic points of each loop; the relationship is relatively linear and defines the properties of the chamber when maximally activated.

However, Ees does have a modest degree of load dependence, likely caused by the load dependence of activation. Moreover, the linear ESPVR is really curvilinear, particularly at the extremes of the contractile state. The effects of nonlinearity are particularly important when the P–V relationship is acquired over a narrow range of pressures and volume. A single slope in the latter instance will not uniquely characterize the ESPVR and therefore the contractile state. In addition, the extrapolated Vp is unlikely to represent dead volume. Finally, Vp is not entirely independent of inotropic state. Thus, more than Ees is needed to compare two contractile states; interpretation must take into account Vp and analysis of covariance, or a multiple linear regression analysis with dummy variables is desirable. Other considerations for the use of P–V relations to characterize contractility are (1) specialized and invasive instruments are necessary for its measurement; (2) methods used to alter load should be free of
inotropic effects; (3) because changes in autonomic tone and heart rate can complicate analysis, loading changes should be as rapid as possible; (4) arrhythmias may occur and complicate the analysis; (5) changes in coronary perfusion pressure that can alter the P–V relationship occur with changes in load; and (6) changes in mass and geometry of the ventricle make changes in the ESPVR ambiguous. In addition to Ees, preload recruitable stroke work (slope of the end-diastolic volume–stroke work relationship) and the slope of the end-diastolic volume–dP/dt relationship are derived as indices of contractility from P–V analysis. Each of these approaches is linear and afterload independent. Preload recruitable stroke work is independent of heart size, and the slope of the end-diastolic volume–dP/dt relationship is more sensitive to inotropic state than is Ees.46

Heart Rate Heart rate is normally determined by the interplay between the intrinsic automaticity of the SA node and the activity of the autonomic nervous system. Increasing heart rate causes a small but measurable increase in the inotropic state through the force–frequency relationship. In addition, heart rate is a major determinant of cardiac output. However, in a normal heart, pacing between heart rates of 60 and 160 beats/min has little effect on cardiac output because the diminished diastolic filling time offsets the modest increase in inotropic state.

### DIASTOLE AND DIASTOLIC FUNCTION

Diastole is the summation of processes by which the heart keeps latent its ability to generate force and shorten, and returns to its precontractile state. Diastolic properties of the ventricle are complex and multifactorially determined and are related to the speed and synchrony of myocardial relaxation and inactivation, loading conditions, viscoelasticity, heart rate, atrial function, and ventricular interaction. Diastole occurs in a series of energy-consuming steps beginning with release of calcium from TnC, detachment of actin–myosin cross-bridges, SERCA2a-induced calcium sequestration into the SR, NCX-induced extrusion of calcium from the cytoplasm, and return of the sarcomere to its resting length. Adequate ATP must be present for these processes to occur at a sufficient rate and extent.

The P–V relationship during early diastole reflects the lusitropic (relaxation) state of the heart, analogous to the inotropic (contraction) state measured during systole. The rate of LV relaxation can be estimated from the maximal rate of pressure decay (−dP/dtmax) and indices (eg, relaxation half-time [RT50]) that are related to the time necessary for ventricular relaxation, but these measurements are highly dependent on the prevailing load of the intact circulation. In contrast, τ, the time constant of LV relaxation during isovolumic relaxation, provides a more accurate, less load-dependent measure of relaxation; τ is shortened by β-adrenergic stimulation (cyclase-dependent phosphorylation of phospholamban and TnI) and prolonged with β-adrenergic antagonists.46 Although several mathematical models of the exponential decay of LV pressure exist, a simple monoexponential model that declines to zero is frequently used: P(t) = Pae−t/τ where P(t) is the LV pressure at any time, t; τ is the relaxation constant; P0 is the LV pressure at the onset of relaxation; and e is the base of the natural logarithm. The natural logarithmic transformation of both sides of the equation yields lnP = −1/τ ln P0. Thus, τ is derived by obtaining the negative of the reciprocal of the slope of lnP(t) versus time, t, from aortic valve closure to mitral valve opening (isovolumetric relaxation). High-fidelity catheter tip micromanometers are necessary for accurate measurement of −dP/dtmax and τ.

In addition to relaxation, the passive viscoelasticity of the ventricle, dependent both on intracellular and extracellular structures, is a major determinant of diastolic function. During contraction, cytoskeletal proteins such as titin and microtubules are deformed by actin–myosin cross-bridge cycling and sarcomere contraction, which act like viscoelastic springs during diastole.44 This reclaimed potential energy constitutes a recoiling force that helps restore the myocardium to its resting configuration. In addition, ECM proteins such as collagen contribute to the establishment of resting force and length.

Chamber stiffness is quantified from the relationship between diastolic LV pressure and volume. LV diastolic pressure can be changed either by a volume-dependent change in operating stiffness (equal to the slope of a tangent drawn to the P–V curve at any point) or by a volume-independent change in the overall chamber stiffness because of a change in properties either intrinsic (eg, hypertrophy) or extrinsic (eg, pericardial) to the ventricle (Fig. 5–17, Table 5–1). Operating stiffness
changes throughout filling, such that stiffness \((dP/dV)\) is less at smaller volumes and greater at larger volumes. Because the diastolic P–V relationship is generally exponential, the relationship between \(dP/dV\) and pressure is linear. The slope of this relationship is called the modulus of chamber stiffness \((k_c)\) and has been used to quantitate chamber stiffness. Thus, when chamber stiffness is increased, the P–V curve shifts to the left, the slope of the \(dP/dt\) versus pressure relationship becomes steeper, and \(k_c\) is increased.

Diastolic chamber stiffness, similar to the systolic chamber stiffness index, \(Ees\), is dependent on both material (myocardial) stiffness and ventricular chamber characteristics (eg, volume, mass). Myocardial stiffness is quantified from the relationship between diastolic LV wall stress \((\sigma)\) and strain \((\varepsilon)\). Strain is the deformation of the muscle produced by an applied force and is expressed as the percent change in length from the unstressed length. At any given strain throughout diastole, myocardial stiffness is equal to the slope \((d\varepsilon/d\sigma)\) of a tangent drawn to the stress–strain curve at that strain. Because the stress–strain relationship is generally exponential, the relationship between \((d\varepsilon/d\sigma)\) and stress is linear. The slope of this relationship is the modulus of myocardial stiffness \((K_m)\) and has been used to quantitate myocardial stiffness. Thus, when myocardial stiffness is increased, the stress–strain relationship shifts to the left, the slope of the \((d\varepsilon/d\sigma)\) versus stress relationship becomes steeper, and \(K_m\) increases.

The end-diastolic P–V relationship (EDPVR) is constructed by connecting the end-diastolic points (lower right hand) of a series of PVAs; the relationship is nonlinear and defines the passive properties of the chamber when it is fully relaxed. The nonlinearity of the EDPVR results from the different types of structural proteins being stretched over the range of pressures and volumes. Thus, at the low end of the relationship, where operative stiffness is low, stiffness is caused by compliant elastin and sarcomeric titin. As volume increases and operative stiffness increases, the slack length of collagen and titin are exceeded, and stretch is resisted. At the other extreme (subphysiologic volumes), negative pressures are required to reduce volume (diastolic suction); however, negative pressures are rarely recorded in vivo, and less stringent criteria to establish the presence of diastolic suction are required. It is important to recall that changes in intrathoracic pressure, pericardial constraint, and ventricular interaction all influence the EDPVR. Analytic limitations similar to the ESPVR are present for the EDPVR; that is, comparisons of EDPVR should account for covariance of the parameters.49

A variety of curve fits for EDPVR using nonlinear regression analysis have been proposed, but single value indices of stiffness, such as the stiffness constant, have met with limited success. Chamber stiffness \((k)\) and myocardial stiffness \((K_m)\) provide load and chamber size-independent parameters of passive chamber and myocardial properties, respectively; however, when comparing hearts of different sizes, a simple approach is to measure the volume at a specified pressure.50

**Ventriculoarterial Coupling**

In isolated muscle, loading conditions represent the force applied to muscle before and after (preload and afterload, respectively) the onset of contraction. In the intact ventricle, preload and afterload are also determined by the volume status of the individual and the characteristics of the arterial and venous circulations (pulmonary and systemic circulations for the RV and LV, respectively). Thus, loading conditions are not only important direct determinants of ventricular performance, but they also function indirectly by coupling the ventricle to the vascular system.

Ventricular contraction transfers blood from the venous to the arterial side of the circulation, and arterial and venous capacitances (the change in volume per change in pressure, \(dV/dP\)) determine the respective pressures that result from the shift in blood volume. These pressures determine the driving force across the peripheral resistance (where resistance equals pressure gradient for flow divided by the cardiac output) and are primarily responsible for venous return to the heart.

The venous return curve describes the inverse relationship between venous pressure and cardiac output (Fig. 5–18A, B). In contrast to convention, the venous return curve plots the independent variable (cardiac output) on the vertical axis and the dependent variable (venous pressure) on the horizontal axis. The \(x\)-intercept is the mean circulatory pressure (ie, that pressure in the vascular system in the absence of cardiac pumping). The mean circulatory pressure is a function of the capacitance of the vascular system and the total blood volume. The plateau of the venous return curve and the \(y\)-intercept represents the maximal obtainable cardiac output as venous pressure is reduced. In the normal heart, cardiac output is limited by venous return, and the operating venous pressure is near the plateau of the venous return curve.

Coupling of the venous system of the heart is graphically represented in Fig. 5–18C. In this analysis, the intersection of the ventricular function (Frank-Starling) curve and the venous return curve represents the steady-state operating values of cardiac output and venous pressure. At this equilibrium point, the ability of the venous system to provide venous return at a given pressure is matched with the ability of the ventricle to pump that venous return when distended to the same pressure.

Increased blood volume and venoconstriction shift the venous function curve upward and to the right, increasing the mean circulatory pressure and the maximal cardiac output (Fig. 5–18D). The venous system contains the major fraction of blood in the vascular system because of the greater capacitance of veins than of arteries. As a result, venoconstriction shifts significant quantities of blood from the peripheral to central circulation. Because arteries contain only a small percentage of the total blood volume, their contractile state does not affect the mean circulatory pressure. Moreover, because venous pressure varies inversely with systemic vascular resistance, arteriolar constriction (increased afterload) shifts the curve downward and to the left without changing the mean circulatory pressure. Conversely, arteriolar dilation shifts the curve upward and to the right. An increased inotropic state shifts the ventricular function curve to the left without significantly altering the venous return curve. Conversely, in chronic heart failure, there is a rightward shift of the ventricular function curve and because of renal salt and water retention, a parallel rightward shift of the vascular function curve. In this way, cardiac output is initially maintained at the expense of increased venous pressure and congestion. If the compensatory mechanisms fail, venous pressure increases further, and cardiac output falls.

Ventriculoarterial coupling can also be expressed in the P–V framework (Fig. 5–19). Arterial properties are represented by effective arterial elastance \((EA)\), which incorporates the mean resistance and pulsatile features of the arterial load. \(EA\) is estimated by \(PES/SV\), where \(PES\) is the end-systolic pressure and \(SV\) is the stroke volume. The \(EA/Ees\) ratio has been used as an index of ventriculoarterial coupling and has been shown to be a critical determinant of pump performance and efficiency. With increases in \(EA\), stroke work initially increases, reaches a plateau, and then decreases. Maximum stroke work occurs when arterial and ventricular properties are equal (ie, when \(EA = Ees\)). Similar changes with increases in \(EA\) occurs with ventricular efficiency, defined as external stroke work \(/\text{MVO}_2/\text{beat}\), and are maximum when...
EA = Ees/2. Therefore, in this conceptual framework, energetically optimal ventriculoarterial coupling exists when the EA/Ees ratio ranges from 0.5 to 1.0.

HEMODYNAMICS

CARDIAC OUTPUT AND BLOOD FLOW

Cardiac output is determined by a relationship analogous to Ohm’s law governing current, voltage, and resistance—that is, cardiac output (Q) increases with an increase in the pressure gradient (P1 – P2) generated by the heart or a decrease in the resistance (R) according to the relationship Q = (P1 – P2)/R. The normal cardiac output at rest is approximately 5 to 6 L/min and can increase approximately five-fold during strenuous exercise (see Fig. 5–19A). The relative distribution of the cardiac output changes dramatically with exercise, such that blood flow to the skin and skeletal muscle increases to constitute as much as 85% of the cardiac output; blood flow to the heart increases three- to five-fold; and the brain receives the same amount as it does at rest, and the renal and splanchnic circulations receive about half of their basal flow. Physical factors, metabolic products, and peptides that operate through autocrine (regulation of cell function by the producing cell), paracrine (regulation of neighboring cells by the producing cell), or endocrine (regulation of distant cells by the producing cell) mechanisms and neural regulation control the relative distribution of regional blood flow.

Blood flow refers to the bulk flow of fluid in the circulation. Blood flow velocity refers to the speed with which blood moves along the circulation in any particular segment and is related directly to blood flow and inversely to cross-sectional area. Thus, blood flow velocity is greatest in the aorta and least in the capillary beds (Fig. 5–20). In the normal circulation, blood flows predominantly in a streamline or laminar pattern. Friction between the blood vessel wall and adjacent laminar pattern resembling a parabola in much of the circulation. The laminar
pattern of blood flow is interrupted and converted to a turbulent flow pattern in the ventricles, at bifurcations in the circulation, and when there is an abrupt change in vessel diameter (eg, from atherosclerosis), which causes blood flow to increase above a critical, dimensionless value (related to cross-sectional area, mean velocity of flow, and kinematic viscosity of the fluid) called the Reynolds number.

**PRESSURE**

As blood courses through the large arteries, systolic pressure increases slightly, and diastolic pressure decreases. Because the decrease in diastolic pressure is greater than the increase in systolic pressure, the pulse pressure (systolic-diastolic) increases gradually, and mean arterial blood pressure (⅓ systolic pressure + ⅔ diastolic pressure) decreases in the systemic arteries as the distance from the heart increases. The arterioles provide the greatest resistance to blood flow in the circulation. Consequently, absolute blood pressure decreases by the greatest amount in the arterioles; in addition, the oscillations of blood pressure are abolished in the arteriolar portion of the systemic circulation. Blood enters the capillaries of the systemic circulation with pressures of approximately 35 mm Hg. As blood flows through the capillaries, the blood pressure decreases to approximately 20 mm Hg, and in the venules, it decreases to approximately 5 mm Hg. Blood pressure decreases further in the large veins and vena cava, so blood returns to the right atrium with an absolute pressure nearly equal to the atmospheric pressure. The RV generates lower pressures than the left (0-30 mm Hg vs 3-120 mm Hg). Similar to the systemic circulation, the arterioles exert the greatest resistance to blood flow; however, pulmonary arterioles do not completely dampen the pressure pulses.

Transformation of the ventricular pressure pulse, with its intermittent flow and large pressure changes, into the peripheral pulse, with its continuous flow and smaller pressure changes is caused by the initial transfer of kinetic to potential energy in the aorta in systole and subsequent reclamation of this stored energy in diastole. The arterial pulse is altered by several factors, including heart rate (increased diastolic pressure with increased heart rate), stroke volume (systolic and pulse pressure increase with increased stroke volume), aortic valve function (increased pulse pressure and decreased diastolic pressure with aortic insufficiency, decreased pulse pressure and a slow rate of increase of pressure with aortic stenosis), arterial compliance (increased pulse pressure and peaked waveform with decreased compliance), and transmission of the pressure wave through the arterial circulation. The latter results from waves reflected at branch points, changes in arterial
compliance, and differential transmission between the high-frequency and low-frequency components of the arterial pressure waveform.

**Resistance**

Total peripheral vascular resistance is the sum of all regional resistances in the systemic circulation that must be overcome by the ejecting LV. This is calculated as Mean aortic—Mean right atrial pressure/Cardiac output for the systemic circulation and as Pulmonary arterial pressure—Pulmonary venous pressure/Cardiac output for the pulmonary circulation. However, the circulation is composed of a number of circuits (eg, coronary, skeletal, and splanchic) arranged in series as well as in parallel. Each circuit provides resistance to blood flow, and the type of circuit determines its contribution to total peripheral resistance. For a circuit that has resistances arranged in series, the total resistance is equal to the sum of component resistances. For resistances connected in parallel, the reciprocal of the total resistance is equal to the sum of the reciprocals of the component resistances. Resistances connected in parallel are more efficient than resistances connected in series because the heart does not have to generate a large driving pressure to perfuse multiple beds. In addition, because arterial pressure is maintained within narrow limits, a marked change in the resistance of one circuit changes only slightly blood flow to other circuits. Thus, when one circuit is eliminated, total resistance and arterial blood pressure increase immediately; the increase is sensed by baroreceptors that mediate changes that cause pressure to return to its original value, maintaining blood flow to other areas of the circulation relatively constant (Fig. 5–21). Although less efficient, series resistance units are sometimes necessary (eg, the portal venous connection between the gastrointestinal tract and liver).

Several factors influence resistance (R) to blood flow. The most important factor is the vessel radius (r), such that 1/r^4, thus, when the radius is halved, resistance increases by a factor of 16. Another factor is viscosity; the energy required to overcome frictional forces necessary for fluid movement is directly related to viscosity. For a homogeneous fluid such as water or plasma at a given temperature, viscosity is constant (ie, it is a Newtonian fluid). At 98.6°F (37°C), the viscosity of plasma is approximately 1.7 times that of water. However, for a suspension solution such as blood, viscosity is not constant, that is, it is non-Newtonian. In large blood vessels, laminar blood flow and the alignment of red blood cells parallel to the axis of motion greatly reduce viscosity. However, as the shear rate increases, the cells fall out of alignment and stack like coins called rouleaux, which increases apparent viscosity. The following factors also affect blood viscosity: temperature; hematocrit; plasma viscosity; red blood cell deformability and aggregation; and protein concentration, mainly through increasing red blood cell aggregation at low shear rates, with a minor effect on plasma viscosity. The relationship between viscosity, length, and vessel radius is quantified by Poiseuille’s law; R = 8

**THE MICROCIRCULATION**

The microcirculation is composed of arterioles, capillaries, and venules. Arterioles range from 10 to 150 μm in diameter and regulate the distribution of blood flow to capillaries (0.5–1.0 μm); small arterioles (metarterioles) can bypass the capillary beds, shunting flow directly into the small venules (10–40 μm). The independent vasoactivity of different-sized arterioles produces blood flow patterns that vary in speed and direction. Although flow in the arterioles is usually continuous, continuous, and unidirectional, capillary flow is highly variable. Capillaries have a single layer of endothelial cells through which oxygen and nutrients diffuse to adjacent tissues. Venules have an endothelial cell layer surrounded by an adventitia and contractile pericytes and are involved in transvascular exchange of fluid and macromolecules across the vascular wall. The larger venules and veins collect and store blood for return to the heart. The cellular and molecular mechanisms that control blood flow in the microcirculation are only beginning to be understood.6–7

Important determinants of capillary exchange through the endothelial cell membrane (diffusion) include (1) the capillary density, which is directly related to the metabolic activity of tissue; (2) lipid solubility of the material to be exchanged; (3) the free diffusion coefficient (small molecules and molecules with very little net electric charge have very high free diffusion coefficients); and (4) the relative concentrations of the material in the blood and the tissue interstitium. Thus, the rate of diffusion for a substance Q moving from the vessel to the interstitial space, dQ/dt, is proportional to the capillary wall area (2πrL), the difference in concentration of the substance (ΔC), which represents the driving force for the movement across the vessel wall, and the permeability (P) which is a function of lipid solubility and the free diffusion coefficient: dQ/dt = (2πrL)(P)(ΔC). Permeability for substances varies by capillary bed (eg, whereas capillaries in the brain restrict the diffusion of almost all solutes, liver capillaries have a very high permeability to large solutes such as albumin). Endothelial transport across restrictive beds is accomplished by other processes such as pinocytosis and vesicular transport. Pores occupy less than 1% of the total capillary surface area; there are more present on the venular than arteriolar end of the capillary system, and therefore lipid-insoluble materials (eg, glucose, small ions) exchange slowly. Thus, whereas lipid-soluble materials are considered flow limited, lipid-insoluble materials (except water) are considered to be relatively limited by diffusion.

The transvascular exchange of water occurs primarily through the bulk flow of water through the pores in the capillary walls (Q_ww), the amount of bulk flow is a function of the difference in hydrostatic
pressure in the vessel (CHP, variable, depending on tissue bed) and interstitium (THP, small but variable), the capillary filtration coefficient (CFC), the plasma colloid osmotic pressure (COP, caused by protein in blood plasma, ~20 mm Hg), and the tissue colloid osmotic pressure (TOP, caused by proteins in the interstitial space, ~4.5 mm Hg). Thus, the net force out of the vessel (filtration) is a hydrostatic force, and the net force into the vessel (reabsorption) is a colloid osmotic force. The effect of these forces on transvascular water flow is described in the Starling equation: \[ Q_{f,0} = CFC[(CHP – THP) – \sigma(COP – TOP)], \] where \( \sigma \) is the reflection coefficient for the movement of proteins across the capillary wall (the inverse of the permeability of the vessel wall to protein). The capillary filtration coefficient is the product of capillary surface area and permeability and is related to number and size of the pores through which water can pass through the vessel. Because the balance of forces is different across the length of a capillary bed, filtration occurs near the arterial end and reabsorption near the venule end of the capillary.

Of these forces, capillary hydrostatic pressure (CHP) is the principal mechanism responsible for transcapillary exchange of water. CHP increases whenever arterial pressure increases, venous pressure increases, venule resistance to flow increases, or arteriolar resistance to flow decreases. Mathematically, \( CHP = (R_v/R_a)P_a + P_v \), where \( R_v/R_a \) is the ratio of venule-to-arteriolar resistance, \( P_a \) is approximately mean arterial pressure, and \( P_v \) is approximately central venous pressure. Capillary pressure is far more sensitive to changes in venous pressure than in arterial pressure. The ratio of venule-to-arteriolar resistance \( (R_v/R_a) \) is approximately 0.1; thus, arterial pressure must increase 10 mm Hg to cause a 1-mm Hg increase in capillary hydrostatic pressure, but a 1-mm Hg increase in venous pressure will cause a similar increase in capillary hydrostatic pressure. Greater filtration than reabsorption produces tissue lymph flow; the total volume of lymph fluid (important in returning plasma proteins that leaked from the microcirculation and transport of chylomicrons) is approximately 3 to 4 L/d.

**SPECIAL CIRCULATIONS**

The relative proportions of cardiac output that perfuses various circulations at rest and with strenuous exercise are summarized in Fig. 5–22. These circulations are discussed below.

**CORONARY CIRCULATION**

Two major coronary arteries arise from the aortic sinuses; subdivide on the epicardial surface of the heart; and give off small, penetrating branches and an extensive network of intramural arteries, arterioles, and capillaries. Contribute to the high oxygen requirements of the myocardium, capillary density is very high (accounting for ~15% of the total cardiac mass), which facilitate the diffusion of nutrients and wastes to and from the cardiomyocytes. Myocardial capillaries feed into a network of intramural venules that drain into large epicardial collecting veins. The majority of the LV venous blood drains into the coronary sinus, which runs along the AV groove and empties into the right atrium. Other drainage is by means of thebesian veins, which drain directly into the right heart, and anterior cardiac veins that empty into the right atrium. Small intramural collateral vessels connect the coronaries and can enlarge after coronary obstruction, providing near-normal flow at rest to the distal segment of the diseased artery. However, the capacity to augment myocardial blood flow during exercise or stress (ie, the coronary reserve) is usually limited in collateral vessels.

**Myocardial Metabolism**

Cardiac muscle metabolism requires sustained oxidative phosphorylation to synthesize the ATP that powers the continuous cycles of E-C coupling and relaxation. A smaller amount of energy (~15%–20%) is needed for electrical excitation and basal housekeeping activities of the cardiomyocyte. Accordingly, myocardial oxygen requirements are high (~8 mL/min/100 g myocardium). During stress or exercise, oxygen requirements increase abruptly. However, unlike skeletal muscle, extraction of oxygen in cardiac muscle is near maximal at rest; therefore, to augment oxygen supply, coronary blood flow must increase.

Compared with other tissues, the myocardium contains a low concentration of high-energy phosphates, given the constant requirement for energy. ATP levels are buffered in the heart by the much larger concentration of phosphocreatine (PCr), which regenerates ATP, by the creatine (Cr) kinase-catalyzed reaction ADP + PCr = ATP + Cr. Regeneration of ATP from PCr can protect the heart from ATP depletion during a mild or brief increase in energy demand, but the heart is fundamentally dependent on continuous resynthesis of mitochondrial ATP.

A variety of substrates are used for myocardial ATP synthesis. Under normal resting conditions, the heart generates 60% to 70% of its ATP from \( \beta \) oxidation of free fatty acids and 30% from metabolism of carbohydrates. Amino acids and ketones are also used as substrates but to much lesser extent. During exercise, the large amount of lactate is oxidized to help keep ATP levels high.
produced by skeletal muscle becomes a major substrate, entering the Krebs cycle after conversion to pyruvate. Oxidation of free fatty acids is inhibited, and carbohydrates become the predominant substrate for energy metabolism; which it is also the case in the failing heart.46,49

Control of Coronary Blood Flow

Resting coronary blood flow is normally between 60 and 90 mL/min/100 g of myocardium and can rapidly increase four- to five-fold during exercise or other conditions requiring augmented flow. The coronary flow rate is determined by the coronary artery perfusion pressure and by the resistance to flow exerted by forces generated within and outside the coronary vascular bed; the complexity of these forces is highlighted by the unexpected finding that the coronary diastolic pressure at the time of zero flow (eg, after a long diastole) is greater than coronary sinus pressure. Control of coronary blood flow is metabolic, mechanical, autonomic, and endothelial. However, the exact local feedback control mechanisms that match coronary blood flow to myocardial oxygen consumption are poorly understood.

Metabolic Control: Autoregulation

A sudden change in aortic pressure is met by a rapid adjustment of coronary vascular resistance so that blood flow remains constant. This autoregulatory phenomenon protects the myocardium from inadequate blood flow owing to a decline in coronary perfusion pressure. Autoregulation at high aortic pressures may attenuate endothelial wall stress and protect the vasculature from damage resulting from elevated coronary distending pressures. The normal coronary vascular bed usually autoregulates over a range of systemic arterial pressures ranging from 60 to 140 mm Hg. Above or below these limits, autoregulation fails, and coronary flow increases or decreases in a linear fashion, with corresponding increases or decreases in aortic pressure, respectively. Autoregulation also occurs in localized areas of the coronary vasculature when a partial obstruction of an artery causes a decrease in the coronary perfusion pressure. The vessel distal to the obstruction dilates, thus normalizing flow by decreasing coronary vascular resistance.

Autoregulatory reserve refers to the maximum degree of vasodilation in the coronary vascular bed and determines the range of decreased perfusion pressures over which myocardial flow can be maintained. Autoregulatory reserve depends on the level of chronic vasodilation in the coronary vasculature as a whole or in any specific region of the heart. If a region of the vascular bed is already vasodilated in an effort to compensate for a localized decrease in coronary perfusion pressure, the capacity to autoregulate during additional reductions in aortic diastolic pressure will be impaired. Thus, the affected area of myocardium becomes vulnerable to transient decreases in aortic pressure. This impairment in autoregulation is the basis for perfusion scans used to diagnose myocardial ischemia.

Autoregulation is mediated by both myogenic (a change in tone in the response to changes in pressure and flow) and metabolic (related to washout of vasoactive metabolites) means. The most compelling evidence suggests that adenosine, a breakdown product of ATP, is a major mediator of autoregulation. Adenosine is a potent vasodilator that is generated continually in myocardial cells from adenosine monophosphate by the action of 5’ nucleotidase located at the inner surface of the cell membrane. Adenosine diffuses freely across the cell membrane, and any decrease in perfusion pressure, by causing an initial decrease in coronary artery flow, leads to a diminished rate of adenosine washout and an increase in local tissue concentration. This in turn results in increased vasodilation and a subsequent increase in the coronary flow rate. Tissue PO2, and the level of other metabolic products in tissue (eg, carbon dioxide), by changing slightly as perfusion pressure increases and decreases, can also directly affect coronary artery tone. In addition, local release of potassium (K+) and adenosine-induced activation of ATP-sensitive K+ channels can also mediate autoregulation in the coronary circulation.

Mechanical Control

The pattern of blood flow to the LV, which receives the greatest proportion of coronary flow, is unique in that arterial flow is markedly decreased during systole because of the intramyocardial pressure generated by contracting myocardial fibers. Thus, most of the coronary flow to the LV occurs during diastole, and coronary perfusion pressure is largely determined by aortic diastolic pressure. Blood flow to the RV myocardium is also phasic, but because the systolic pressure transmitted to the RV myocardium is much lower, the difference between systolic and diastolic flow is less marked.

Several factors affecting blood flow are markedly different in the inner, subendocardial, and outer, subepicardial, layers of myocardium. Systolic compression is greater in the subendocardial layers (mechanical interference with flow in late diastole because of chamber distension may also occur). In the subepicardium, flow is slightly higher in systole than diastole. In the midwall, flow is approximately equal in systole and diastole. Vascular density is increased in the subendocardium so that net flow is augmented despite the almost complete absence of blood flow in the subendocardium during systole. In addition, the intrinsic coronary vascular resistance in subendocardial arteries is lower, so that the ratio of subendocardial to subepicardial flow is approximately 1.1:1. Although this suits the increased oxygen requirements because of increased wall stress and shortening, the lower resting coronary resistance limits the coronary reserve of the subendocardial vessels and makes it more vulnerable to injury if coronary perfusion pressure drops or coronary flow is impeded. Thus, subendocardial injury is common when myocardial oxygen requirements increase, such as with severe hypertension.

Autonomic Control

The autonomic nervous system influences the smooth muscle tone of the coronary arteries, and this modulates coronary flow to some extent, although under normal conditions, its role is overshadowed by metabolic and mechanical influences. The larger epicardial coronary arteries have both α-adrenergic receptors, which mediate vasoconstriction, and β-adrenergic receptors, which mediate vasodilation. Parasympathetic muscarinic coronary vasodilation has also been demonstrated, but its role in regulation of coronary flow is unclear.

Release of norepinephrine during sympathetic stimulation can cause coronary artery vasoconstriction, but this response is normally overridden by metabolic factors because sympathetic stimulation also increases heart rate and contractility, thereby augmenting myocardial oxygen consumption, ATP turnover, and vasodilation by metabolic mechanisms. Although there is a small degree of resting coronary vasoconstrictor tone, the significance of sympathetic innervation of the normal coronary arteries is unclear. Abnormal increases in vasoconstrictor tone have been suggested as a mechanism underlying ischemic heart disease.

Stimulation of β1-adrenergic receptors in the smaller coronary arteries by endogenous circulating catecholamines or by pharmacologic β-agonists results in coronary vasodilation. The extent to which coronary β-receptors contribute to coronary blood flow regulation is difficult to assess because β-stimulation of the myocardium increases oxygen consumption, leading to metabolically mediated vasodilation. However, during exercise, sympathetic β-adrenergic-mediated feed-forward arteriolar vasodilation contributes approximately 25% of the increase in coronary blood flow, and α-adrenergic–mediated
vasoconstriction in medium and large coronary arteries helps maintain blood flow to the vulnerable subendocardium.\(^5\)

**Endothelial Control**

Endothelium-derived relaxing factor (EDRF) is a potent vasodilator that is elaborated by vascular endothelial cells in response to a number of stress signals, such as hypoxia, and ADP accumulation. EDRF release is also stimulated by distending forces in the vascular wall, which can amplify the coronary flow in response to conditions such as exercise when it can be appropriate for both coronary perfusion pressure and flow to increase. This is in contrast to autoregulation, which keeps flow constant during inappropriate changes in coronary perfusion pressure.

Nitric oxide (NO) is the principal EDRF. Reactive hyperemia, myogenic vasodilation, and the vasodilator effects of acetylcholine and bradykinin are mediated by NO. NO-independent vasodilation increases shear stress, which stimulates endothelial NO synthase, generates NO, and prolongs vasodilation.\(^7\)

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**Cerebral Circulation**

The brain cannot survive on anaerobic metabolism; therefore, powerful mechanisms exist to maintain constant cerebral blood flow. Cerebral blood flow is also controlled by autoregulation of blood flow in the face of perfusion pressures ranging from approximately 60 to 150 mm Hg. When arterial blood pressure decreases below 60 mm Hg and cerebral blood flow decreases, brain tissue begins to become ischemic; this elicits a powerful stimulation of the peripheral sympathetic nervous system, resulting in generalized vasoconstriction and an increase in arterial blood pressure. This response is effective down to blood pressures of 15 to 20 mm Hg and is so powerful that blood flow to other areas can decrease to zero in an effort to preserve cerebral blood flow. Myocardial blood flow increases because the intense sympathetic stimulation increases myocardial work (heart rate and contractility).

There is also a positive curvilinear relationship between cerebral blood flow and arterial CO\(_2\) tension, mediated partly through changes in extracellular pH; small increases in arterial blood CO\(_2\) tension above normal values produce large increases in cerebral blood flow. Decreases in CO\(_2\) decrease blood flow. There is also an inverse relationship between arterial O\(_2\) content and cerebral blood flow that helps maintain cerebral O\(_2\) delivery constant.

Although cerebral blood vessels are innervated, neural mechanisms modify cerebral blood flow only weakly and are overpowered by other factors that regulate cerebral blood flow.

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**Skeletal Muscle Circulation**

Blood flow to resting skeletal muscle is relatively low, normally only 3 to 4 mL/min/100 g of muscle. Whereas only 10% of the capillary beds are perfused, this is sufficient to meet the basal metabolic needs of resting muscle. Blood vessels in skeletal muscle are innervated and constrict in response to \(\alpha\)-adrenergic stimulation and dilate in response to \(\beta\)-adrenergic or cholinergic stimulation. Adrenergic and cholinergic vasodilation is largely mediated by endothelial NO.\(^2\) When skeletal muscle is inactive and blood flow is needed in other vascular beds, neural mechanisms constrict muscle vessels to divert blood to the needed areas. When skeletal muscle is active, however, neural influences on blood flow are overridden by powerful local metabolic and vascular control mechanisms. The primary regulators of skeletal muscle blood flow during exercise are metabolic factors. A decrease in oxygen tension and increases in concentration of carbon dioxide, lactic acid, hydrogen ions, and potassium ions directly increase muscle blood flow. As the increase in blood flow washes out these substances, tissue concentrations return to normal. Strenuous exercise can increase blood flow to muscle by as much as 25-fold, to a maximum of approximately 80 mL/min/100 g, and opens previously unperfused capillary beds. With aerobic exercise, blood flow is maintained at a steady level, albeit one higher than normal, commensurate with the increase in metabolic rate. Skeletal muscle can depend on anaerobic metabolism for short periods of time by generating an oxygen debt; at the end of exercise, muscle blood flow remains elevated until the concentration of all effectors return to normal.

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**Integrated Physiology**

Integrated control of the circulation results from both intrinsic (eg, myogenic tone, endothelial function) and extrinsic (eg, autonomic nervous system) mechanisms to the vascular wall.

The cardiac output is delivered to the peripheral tissues by the aorta and large conductance arteries. These vessels have relatively little smooth muscle in their walls and are not significantly affected by the preceding vascular control mechanisms. Importantly, however, they contain mechanoreceptors (the aortic arch and carotid sinus baroreceptors) that initiate circulatory reflexes important in controlling systemic arterial pressure. The elastic tissue of the aorta and its branches converts pulsatile cardiac flow into a continuous, steady-state flow optimal for perfusion of the smaller arteries and arterioles. These smaller vessels are surrounded by layers of smooth muscle cells in direct contact with endothelium on the luminal side and are richly innervated on the adventitial side. Regulatory input from both the endothelium and neural connections together determines the tension in the vascular smooth muscle and the cross-sectional area of the vessel. The effective cross-sectional area in the muscular arteries, arterioles, and venules is the principal determinant of steady-state peripheral resistance.

In contrast to arteries, veins are highly distensible and together with the venules and venous sinuses contain approximately 60% of the blood volume. By regulating the functional cross-sectional area of the venous compartment, blood can be translocated from the venous to the arterial side of the circulation. Thus, an increase in the venomotor tone decreases venous capacitance and redistributes blood volume thereby increasing cardiac output; a decrease in venomotor tone has the opposite effect. Local external pressures (intra-abdominal, intrathoracic) influence the large veins as they return blood to the right heart. Because venous pressures are relatively low and capacitance is large, these external forces can facilitate or inhibit venous return.

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**Autonomic Nervous System**

The autonomic nervous system affects vasomotor tone and cardiac function through its sympathetic and parasympathetic divisions. It also influences systemic volume and peripheral resistance by modulating the release of certain peptide hormones (eg, angiotensin II). Neural control involves assimilation of inputs from the cerebral cortex and specialized sensors (ie, the mechanoreceptors, chemoreceptors, osmoreceptors, and thermoreceptors), integration into several specialized regions of the brain (hypothalamus, pons, medulla), and transmission of efferent nerve activity to the periphery over the sympathetic and parasympathetic pathways. The dynamic balance between these two systems determines the net, integrated response.

The overall organization of the vasomotor area is complex, but there appear to be three functionally overlapping anatomic zones that interact extensively. These are (1) a vasoconstrictor area in the upper anterolateral medulla, (2) a vasodilator area in the lower anterolateral medulla, and (3) a sensory area that integrates the vasoconstrictor and
Baroreceptor areas located bilaterally in the nucleus tractus solitarii of the posterolateral medulla and lower pons. Regions modifying heart rate are located in the thalamus, posterior, and posterolateral regions of the hypothalamus and the dorsal region of the medulla.

Stimulation and withdrawal of sympathetic nervous activity are the most powerful factors controlling the peripheral circulation. In addition to cardiovascular reflex regulation, mechanisms involving central interactions between angiotensin II and NO contribute to sympathetic excitation. Fibers travel either in specific sympathetic nerves, which innervate the viscera and heart or join the paravertebral sympathetic chain and synapse in secondary ganglia that give rise to the spinal nerves that innervate peripheral vessels. The vascular nerves terminate on small arteries, arterioles, venules, and veins and modulate resistance and vascular volume. Cardiac nerves, many of which descend from the stellate ganglia, innervate the atria and ventricles.

Relex sympathetic stimulation causes vasoconstriction by releasing norepinephrine from sympathetic nerve endings. Sympathetic nerve stimulation to a limb increases local vascular resistance and decreases blood flow and capillary pressure; as a result, local interstitial fluid is absorbed, and blood volume is displaced from the limb. In a metabolically active organ, local influences are likely to override the autonomic ones. Although most reflex sympathetic stimulation produces vascular constriction, a subset of fibers originating in the cerebral motor cortex releases acetylcholine rather than norepinephrine. These neurons innervate the vasculature of skeletal muscle and bring about an anticipatory increase in local blood flow before exercise. Sympathetic stimulation of these fibers also releases epinephrine from the adrenal medullae. Unlike norepinephrine, epinephrine stimulates both α and β receptors. The effect of epinephrine is biphasic; at low concentrations, epinephrine produces vasodilation and cardiac stimulation; at higher concentrations, vasoconstriction predominates.

Relex sympathetic stimulation is important because it increases cardiac output necessary during exercise or other forms of stress. These cardiac-stimulating effects of the sympathetic nervous system increase the metabolic requirements of heart muscle. Sympathetically mediated actions are largely responsible for maintaining systemic arterial pressure and vital organ perfusion during hypovolemic states and cardiac dysfunction. The inhibition of sympathetic outflow allows vessels to dilate and respond to local humoral and myogenic stimuli.

The parasympathetic nervous system consists of a cranial division, which supplies the blood vessels of the head and viscera, and a sacral division, which innervates the vessels of the genitalia, bladder, and large intestine. Because these fibers supply only a small percentage of the resistance vessels, the parasympathetic division of the autonomic nervous system plays a minor role in arterial pressure regulation. It does, however, play an important role in modulating the heart rate. Fibers traveling in the vagus nerve innervate the SA and AV nodes and atrial myocardium. Changes in heart rate arise from slower intrinsic rates of depolarization and changes in membrane depolarization secondary to acetylcholine stimulation. When the vagus nerve is stimulated, the heart rate and the force of atrial contraction both decline. These effects, coupled with the development of AV block, can lower cardiac output by as much as 40% to 50%. Effects of vagal stimulation are evident after external massage of the carotid sinus, which stimulates the glossopharyngeal afferent limb of the baroreceptors reflex and modifies efferent parasympathetic outflow.

### Baroreceptor Control

The baroreceptor system consists of the carotid sinus and aortic arch mechanoreceptors, central vasomotor integrating areas, and autonomic efferents. The baroreflex system operates as an open loop with negative feedback and cushions changes in arterial pressure, such as those produced by changes in posture. Under resting conditions, the system is static; however, it can be modified by periodic or transient perturbations, such as respiration or exercise, and therefore is also dynamic. The neural outflow from the vasomotor centers modulates the smooth muscle tone of resistance vessels, the force of myocardial contraction, and the heart rate and thereby buffers changes in systemic arterial pressure. Activation of the baroreceptors by an arterial blood pressure-induced stretch produces an increase in afferent impulses traveling through the vagus and glossopharyngeal nerves. In the central vasomotor centers of the pons and medulla, sympathetic efferent nerve activity to the heart, resistance vessels, and veins is inhibited; parasympathetic outflow to the heart increases. The result is cardiac slowing and a decrease in blood pressure.

The carotid sinus baroreceptor is located at the bifurcation of the common carotid artery. The receptors are located in the adventitia of the sinus wall and are innervated by a branch of the glossopharyngeal nerve, which carries afferent activity to the nucleus tractus solitarii in the medulla. Strain energy density (ie, the force required to bring about an incremental stretch) in the wall of the sinus is linearly related to pressure over a wide range of values from 50 to 250 mm Hg. Over this range, the relationship between deformations produced by an increase in pressure and afferent nerve activity is directly linear. The rate of afferent nerve discharge is largely influenced by the mean arterial pressure and to a lesser extent by pulse pressure. Thus, for a given mean pressure, a narrower pulse pressure decreases afferent activity. Factors that modify the distensibility of the carotid sinus (eg, hypertension, atherosclerosis) also change the relationship between intraluminal pressure and stretch. The ability of baroreceptors to cushion chronic increases in mean arterial pressure is limited by resetting, a rightward shift in the relationship between baroreceptor firing and mean arterial pressure. Baroreflex resetting (in this case closer to threshold) also occurs during exercise, which increases the ability of the reflex to buffer hypertensive stimuli.

Carotid baroreceptor denervation causes an increase in blood pressure variability but not sustained hypertension. The aortic arch baroreflex system is similar to that of the carotid sinus. Nerve endings concentrated at the junction between the adventitia and media of the aortic arch serve as stretch receptors with their afferent impulses traveling in the vagus nerve. The threshold of pressure stimulation for aortic receptors is approximately 90 mm Hg compared with 60 mm Hg for the carotid receptors. Therefore, the carotid sinus is important in modulating blood pressure and heart rate at lower pressures, a feature that may be important for maintaining cerebral perfusion in an upright posture.

### Chemoreceptor Control

Arterial chemoreceptors are located in the carotid arteries and aortic arch in the same regions as baroreceptors. These receptors are composed of excitable cells that release neurotransmitters and activate afferent nerves (type I receptors) and inexcitable cells that function as a sensor for hypoxia and acidosis (type II receptors). The carotid bodies are innervated by a branch of the glossopharyngeal nerve, and the aortic bodies are supplied by a branch of the vagus. Nerve activity is stimulated by decreases in pH or P02 or by an increase in the CO2 tension and temperature. For any given arterial P02, the number of discharges increases at higher P02; conversely, for any given P02, the number of impulses increases with lower P02. The carotid and aortic body chemoreflexes are responsible for reflex systemic arterial hypertension, which is mediated by sympathetic outflow from the vasomotor areas. Increases in heart rate, contractility, and cardiac output are most likely caused by the combined effects of central nervous system hypoxia.
and increased ventilation because chemoreceptor denervation does not abolish the cardiac responses, but lung denervation largely prevents or reverses them. Moreover, carotid chemoreceptor denervation eliminates the ventilatory responses to hypoxia and hypercapnia.

**MECHANORECEPTOR CONTROL**

Mechanoreceptors in the heart possess both vagal and sympathetic afferents. Sensors on the atria and ventricles receive vagal afferents, and sensors on the pulmonary veins and coronary vessels receive sympathetic afferents. However, the cardiac mechanoreceptors are much less involved than are the baroreceptors in the short-term regulation of arterial pressure.

Atrial A and B receptors are located at the venoatrial junctions and have distinct functions. Type A receptors react primarily to heart rate but adapt to long-term changes in atrial volume. Type B receptors increase their discharge during atrial distension. C fibers arise from receptors scattered throughout the atria; these discharge with a low frequency and respond with increased discharge to increase in atrial pressure. The A and B receptors are thought to mediate the increase in heart rate associated with atrial distension (such as can occur with intravenous infusions) known as the Bainbridge reflex. In contrast, activation of atrial C fibers generally produces a vasodepressor effect (bradycardia and peripheral vasodilation).

Ventricular mechanoreceptor afferent discharge decreases periodically with inspiration. Ventricular C fibers are located primarily in the epicardium and discharge more rapidly in response to increase in both systolic and diastolic pressure. They exhibit a sharp threshold, discharging only at high systolic pressures, but progressively increase as diastolic pressures increase from 5 to 20 mm Hg. Ventricular distension can produce a powerful depressor reflex called the Bezold-Jarisch reflex; vagal afferents of this cardiopulmonary reflex are also activated by chemical stimulation (e.g., prostanoids, cytokines, serotonin, and classically, Veratrum alkaloids). The central connections for this reflex are in the nucleus tractus solitarii, which has both sympathetic and parasympathetic synapses. Cardiac C-fiber activation also induces gastric relaxation by means of vagal noncholinergic fibers, which is part of a more generalized activation of the vomiting reflex.

The sympathetic afferents are less well understood than the vagal afferents. Atria and ventricular receptors can affect the release of vasopressin and the renal release of renin by modifying efferent sympathetic outflow. Atrial fibers increase activity with increases in atrial pressure and volume and respond to phasic changes in atrial volume. Ventricular fibers increase their discharge rate when ventricular end-diastolic pressure (via unmyelinated fibers) or systolic pressure (via myelinated fibers) is elevated. Afferents on the coronary vessels discharge more rapidly as blood flow or intracoronary pressures decrease and may be important during myocardial ischemia.

**LOCAL INFLUENCES AND CIRCULATORY CONTROL**

Vascular tone is greatest in the small muscular arteries. The level of tone represents the integration of excitatory and inhibitory pathways of metabolic, endothelial, and neurotransmitter origin. However, vascular smooth muscle constricts in response to pressure or stretch in the absence of the endothelium. The mediator of this myogenic response is uncertain but may be integrins, stretch-activated cation channels, and cytoskeletal proteins. Signaling pathways involved in the myogenic response include phospholipase C/PKC and calmodulin-mediated myosin light-chain phosphorylation. In addition, calcium sensitivity of the contractile proteins is produced by inhibition of myosin light-chain phosphatase, which dephosphorylates and inactivates myosin.

Flexible and precise circulatory control is possible because vascular smooth muscle can change its tension in response to both centrally transmitted signals and local factors. Vasodilators include atrial natriuretic peptide (ANP), kinins, NO, and prostacyclins; vasoconstrictors include thromboxane A2, prostaglandin H2, superoxide anion, endothelins, arginine vasopressin (AVP), and angiotensin II. The endothelium is an important modulator of tone because it releases many of these vasoactive substances. Vasodepressor molecules are released in response to both physical and chemical stimulation. For example, flow-induced shear produces vasodilation and normalization of elevated shear stress.

An important endothelial-derived relaxing factor is the simple gas NO, which is synthesized from L-arginine by NOS. There are three isoforms of NOS that vary in their calcium dependence and type of regulation: neuronal NOS, inducible NOS, and endothelial NOS. As mentioned earlier, these isoforms are spatially localized to highly controlled microdomains and are linked to disparate signaling pathways and effectors. In the vasculature, NO elicits paracrine control by means of vasodilation by the action of cGMP. The endothelium is also the source of substances that initiate smooth muscle contraction.

Angiotensin II is a powerful vasoconstrictor peptide that has endocrine functions crucial to salt and water homeostasis but is also locally produced and plays critical autocrine and paracrine roles in organ perfusion and growth.

The endothelins are a group of peptides cleaved from larger inactive precursors that constrict arterial and venous smooth muscle. Endothelins (and the other G protein–coupled receptor ligands, angiotensin II and α1-adrenergic agonists) function by activating phospholipase, which produces IP3 and DAG; InsP3 releases Ca2+ into the cytoplasm from endoplasmic reticulum stores, and DAG activates PKC. Arterial constriction increases peripheral resistance, and venoconstriction decreases capacitance and increases cardiac preload; the former usually predominates.

ANP is a direct-acting vasodilator that is released in response to atrial stretch, β-adrenergic stimulation, and increased heart rate. ANP stimulates the second messenger, membrane-bound cGMP, to produce arterial and venous dilation. The resultant hemodynamic effects include a dose-dependent decrease in arterial pressure and cardiac output. ANP also blocks the effects of angiotensin II on aldosterone release and lowers angiotensin II level. Although ANP is elevated in heart failure, its effects are offset by the action of potent vasoconstrictors and sodium retention.

Kinins are polypeptide vasodilators that are synthesized and circulate as large, inactive molecules and are locally bioconverted to active moieties. Bradykinin is formed from kallikrein and performs vital roles in inflammation and local circulatory control.

AVP is synthesized in neurons of the hypothalamic nuclei and is released from nerve endings of the neurohypophysis. AVP is also a neurotransmitter found in central regions involved in circulatory control. AVP is important in maintaining arterial pressure in the presence of reduced blood volume and regulates osmolality. AVP modulates volume by inhibiting systemic ANP when arterial and atrial receptors are activated.

Substance P is a neurotransmitter peptide that is widely distributed in the brain and peripheral nervous system. Its cardiovascular regulatory potential is suggested by its relatively high concentration in the vasomotor area, where it may interact with the opioid peptide system. In addition, it is present in the nerves that supply virtually every vascular bed, where its release triggers vasodilation through a specific receptor.

Opioids such as the enkephalins and endorphins are also widely distributed in the brain and spinal cord. Although infusion of these
neurotransmitters produces transient vasodilation, they are thought to cooperate with and modulate the response of other neurotransmitters operating in the same synaptic cleft. They appear to be most involved in the behavioral responses to pain and exercise.

Vasoactive intestinal polypeptide is found in the brain, gut, salivary glands, uterus, and skeletal muscle. It is a potent vasodilator and increases heart rate above that obtained with sympathetic stimulation.

Endocannabinoids are synthesized from membrane phospholipids in cardiovascular tissues and activate specific G protein-coupled cannabinoid CB1 and CB2 receptors, the former resulting in arterial vasodilation and decreased ventricular contractility. Tonic activation of CB1 has been implicated in the genesis of acquired cardiovascular risk factors, and CB2 stimulation is immunomodulatory.

REFERENCES