CHAPTER OUTLINE

**VASCULAR RESISTANCE**
- Intrinsic and Extrinsic Vasomotor Control
- Role of the Endothelium
- Role of Metabolism and Autoregulation
- Flow-Induced Dilation
- Neurohumoral Influence on Microcirculation
- Intrinsic Myogenic Tone
- Impact of Extravascular and Humoral Forces on the Microcirculation
- Role of Venules in Vascular Resistance

**ENDOTHELIAL FACTORS IN VASCULAR GROWTH AND RESPONSE TO INJURY**

**EFFECT OF DISEASE STATES ON CORONARY CIRCULATION**

**PULMONARY VASCULAR PHYSIOLOGY**

**IMPROVING MYOCARDIAL PERFUSION**
- Angiogenesis
- Challenges and Future Directions

SUMMARY

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Myocardial and pulmonary perfusion is regulated by a complex array of influences intrinsic and extrinsic to the vasculature. Surgical decisions are generally based on the anatomy of large arteries, where the presence of obstructive lesions and vasomotor state of these vessels can affect myocardial, pulmonary, or other organ perfusion. Under normal circumstances, the microcirculation actually plays a more significant role in the regulation of blood flow. A basic understanding of vascular tone and vasomotor regulation, and the influence of various disease states, is necessary to optimize patient care. Over the past four decades, a great deal has been learned, and this has promoted the understanding of blood vessel regulation and organ perfusion in healthy and in diseased states.

The blood vessel wall is organized in three layers: the intima, media, and adventitia. The innermost, or intimal, layer is made of endothelial cells. Initially, the endothelium was thought to serve mainly as a barrier to the diffusion of macromolecules, but it is now known that the endothelium plays a pivotal role in vascular function, regulation of vascular tone, and control of local blood flow. The medial layer surrounds this intimal endothelial layer, and it is composed of a variable number of smooth muscle cells. Smooth muscle cells also control vascular tone via humoral vasoactive factors, neural mediators, or local paracrine factors (Fig. 48-1). The outermost, adventitial, layer surrounds these vascular smooth muscle cells and provides structural integrity to the blood vessel, particularly larger arteries.

The classification of microvessels based on structural characteristics is rather arbitrary, and there is a lack of uniformity in the definitions of microvascular segments such as small arteries, arterioles, and venules. Furthermore, the transition between these segments is gradual, and there is no clear demarcation between them. In general, microvessels are defined as vessels less than 300 µm in internal diameter. Capillaries are the smallest blood vessels, defined as vessels whose walls are composed of only endothelial tubes. The microvessels through which blood flows toward capillaries are arterial microvessels, and those that drain from capillaries are venous microvessels. Arterial microvessels usually have three coats: (1) a thin tunica intima; (2) a relatively thick tunica media, composed of one to several layers of smooth muscle cells disposed circumferentially; and (3) tunica adventitia, composed of fibrous elements and fibroblasts. Venous microvessels collect the blood from capillaries and have thinner vascular walls than arterial microvessels do. Venules (50 µm in diameter) do not possess smooth muscle cell layers. Smaller venules are composed of only endothelial cells and pericytes. Venules are highly permeable and have an important role in nutrient exchange.

The regulation of myocardial perfusion depends on many intrinsic and extrinsic factors that might be affected by atherosclerotic lesions. In the coronary circulation, it has been shown that vasomotor regulation of vessels, in addition to the actual anatomy, plays an important role in coronary perfusion and operative decision making. Blood flow is also largely dependent on the resistance generated by the microcirculation. Although early studies on vasomotor regulation consisted of indirect assessments using measurements of flow and calculations of resistance, recent investigations into the properties of the intact coronary circulation have yielded much information, as have modern methods of analysis for interpretation of physiologic data.
The microcirculation possesses unique features that allow it to respond to the dynamic changes in nutrient requirements and to interact with surrounding tissue. It is important to note that although the various vascular beds in the body possess many similarities, there are also subtle differences. This chapter will discuss regulation of vascular tone, with an emphasis on coronary and pulmonary circulation, and will review the physiologic and molecular basis of recent advances in ischemic cardiac disease.

VASCULAR RESISTANCE

An understanding of vascular resistance is important, because these resistance vessels cause pressure losses and are responsible for regulation of perfusion. Initially, it was thought that the precapillary arterioles were responsible for vascular resistance, with little resistance involvement by the vessels larger than 25 to 50 μm in diameter. However, subsequent work revealed that over half of total vascular resistance is caused by vessels with diameters larger than 100 μm, even including vessels up to 300 μm. Contrary to previous belief, the venous circulation, under conditions of vasodilation, may account for up to 30% of vascular resistance. Figure 48-2 shows that after vasodilation with dipyridamole, larger arteries and veins assume a greater role in resistance. Similarly, ischemia results in a significant redistribution of vascular...
vasomotor tone is critically involved in organ perfusion. Vascular responses to endogenous substances are summarized in Figure 48-4. All these factors have an especially significant role in the setting of microvascular tone.2

Based on in vitro observations, Jones and colleagues12 found that larger arterioles are more sensitive to shear stress than myogenic factors, whereas small microvessels are more sensitive to metabolic factors. They organized arterial microvessels into three microdomains as governed by distinct forms of regulation based on vessel size: (1) small arterioles (<50 µm), most sensitive to metabolic mediators; (2) intermediate arterioles (50 to 80 µm), most sensitive to myogenic mechanisms; and (3) large arterioles (80 to 150 µm), most sensitive to flow-induced dilation. Undoubtedly, there is overlap among these three components; however, this model provides a framework for understanding the regulation of microvessels.

Jones and colleagues12 hypothesized that the longitudinal disposition of these three microdomains enables integrated adjustment of flow conductance in the face of various influences, such as increased metabolism or a reduction in perfusion pressure. For example, dilation of small arterioles by augmented metabolism produces a decrease in luminal pressure in upstream microvessels, leading to the dilation of intermediate arterioles by decreasing the myogenic tone. These microvascular dilations could also produce an increase in shear stress and result in enhanced flow-induced dilation in large arterioles. As a result, all sizes, or domains, of arterial microvessels dilate in response to the metabolic stimulation. The marked longitudinal heterogeneity of microvascular responses may be at least partly explained by this microdomain hypothesis.

The redistribution of microvascular resistance can change the myogenic tone in each microvascular segment because the luminal pressure in a certain vascular segment is determined by the systemic pressure and the upstream distribution of vascular resistance. For example, when resistance is shifted upstream by the dilation of small arterioles, the luminal pressure in the upstream microvessels decreases, resulting in myogenic dilation. Changes in the venular pressure caused by the resistance redistribution can also affect the capacity for substance exchange and lead to edema formation.

In the coronary circulation, pressure losses also occur as vessels course from the epicardium through the myocardium11; this is accentuated further in the setting of cardiac hypertrophy. Such a phenomenon is particularly relevant clinically, as it in part explains the propensity of the subendocardium to develop ischemia in hypertrophied hearts (Fig. 48-3). The hypertrophied pathologic state causes a decrease in the perfusion pressure of the subendocardium, predisposing it to ischemia and infarction.11

**REGULATION OF VASCULAR TONE**

**Intrinsic and Extrinsic Vasomotor Control**

Vasomotor tone is influenced by the intrinsic properties of the vessel wall, by local innervation, and by substances from surrounding parenchymal tissue. This regulation of vascular tone is critically involved in organ perfusion. Vascular responses to endogenous substances are summarized in Figure 48-4. All these factors have an especially significant role in the setting of microvascular tone.2

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**FIGURE 48-3** Transmural losses of coronary perfusion pressure in normal and hypertrophied hearts. Pressures were measured using micropuncture–servo null techniques in hearts perfused via the left main coronary artery at 100 mm Hg. (Adapted from Fujii M, Nuno DW, Lamping KG, et al: Effect of hypertension and hypertrophy on coronary microvascular pressure. Circ Res 71:120–126, 1992.)
Endothelial cells have both metabolic and synthetic functions. Through the secretion of a large variety of mediators, these cells are able to influence cellular function throughout the body. LDL, Low-density lipoprotein; MHC, major histocompatibility complex. (Adapted from Galley HF, Webster NR: Physiology of the endothelium. Br J Anaesth 93:105–113, 2004.)

**FIGURE 48-4** Factors that influence microvascular tone. ADP, Adenosine diphosphate; BK, Ca2+–activated K+; CGRP, calcitonin gene-related peptide; ET, endothelin; 5HT, 5-hydroxytryptamine (serotonin); NPY, neuropeptide Y; TXA2, thromboxane A2. (Adapted from Komaru T, Kanatsuka H, Shirato K: Coronary microcirculation: physiology and pharmacology. Pharmacol Ther 86:217–261, 2000.)

**FIGURE 48-5** Endothelial cells have both metabolic and synthetic functions. Through the secretion of a large variety of mediators, these cells are able to influence cellular function throughout the body. LDL, Low-density lipoprotein; MHC, major histocompatibility complex. (Adapted from Galley HF, Webster NR: Physiology of the endothelium. Br J Anaesth 93:105–113, 2004.)

**Role of the Endothelium**

The endothelium plays a pivotal role in vasomotor tone regulation. Many substances affect tone via endothelium-mediated mechanisms. Endothelial cells also release several substances that affect coronary resistance, including vasodilators such as nitric oxide (NO•), prostaglandins, and vasoconstrictors including angiotensin converting enzyme endothelin, and reactive oxygen species (summarized in Fig. 48-3). As the major regulatory molecule, NO• is produced by a constitutively expressed enzyme known as endothelial nitric oxide synthase.
(eNOS or NOS-3). NO• is formed as a result of a series of electron transfers from reduced nicotinamide adenine dinucleotide phosphate (i.e., NADPH) to flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) on the reductase domain, and electron transfer to a prosthetic heme group in the oxygenase domain. When heme reduction occurs, arginine is catalyzed to citrulline and NO•. The NO• formed diffuses to underlying vascular smooth muscle, where its actions include stimulation of soluble guanylate cyclase, increasing the level of cyclic guanosine monophosphate (cGMP) and prompting vasodilation via activation of cGMP-dependent protein kinase. Although binding of calcium and calmodulin is a prerequisite for activity of eNOS, other events, such as phosphorylation, membrane binding, binding of eNOS with heat-shock protein 90, and association with the integral membrane protein caveolin can also modulate NOS activity. In addition, NO• can undergo reactions with thiol-containing compounds to form biologically active nitrosothiols. It is likely that the most important pathway involves activation of soluble guanylate cyclase, which catalyzes the formation of cGMP from guanosine triphosphate. The cGMP serves as an allosteric regulator of the enzyme cGMP-dependent protein kinase, which phosphorylates contractile proteins and ion channels, decreasing intracellular calcium and the sensitivity of contractile proteins to intracellular calcium. The binding of NO• to cytochrome oxidase in the mitochondria alters oxygen consumption and in turn can affect oxygen demand. Similarly, receptors for atrial natriuretic peptide and brain natriuretic peptide are also the particulate forms of guanylate cyclases, and these signal vasodilation via similar pathways. NO• is also released in response to sodium nitroprusside and organic nitrates.

**Figure 48-6** Signal transduction pathways for the vascular responses to agonists. Nitric oxide (NO), prostaglandin I2 (PGI2), and endothelium-derived hyperpolarizing factor (EDHF) are important for the cross-talk between the endothelium and the vascular smooth muscle. AC, Adenylyl cyclase; COX, cyclooxygenase; Cyt P450, cytochrome P450; DG, diacylglycerol; eNOS, endothelial nitric oxide synthase; Gi, Gi-protein; Gq, Gq protein; PCS, prostacyclin synthase; PI, phosphatidylinositol 4-phosphate; PIP2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PLAC, phospholipase A; PLC, phospholipase C; R, receptors; TK, tyrosine kinase; VGCC, voltage-gated Ca2+ channel. (Adapted from Komaru T, Kanatsuka H, Shirato K. Coronary microcirculation: physiology and pharmacology. Pharmacol Ther 86:217–261, 2000.)
Although NO• is the major regulator of vascular tone, there are other factors that modulate endothelium-dependent vascular tone in coronary, pulmonary, and peripheral circulations. Endothelium-derived hyperpolarizing factor (EDHF) is an example. The endothelium-dependent hyperpolarization of vascular smooth muscle is mediated by the opening of a calcium-dependent potassium channel, leading to K⁺ exit from the cell. When the vascular smooth muscle is hyperpolarized, voltage-sensitive calcium channels are closed, leading to a reduction in intracellular calcium. The role of the various EDHFs probably varies depending on the vessel size, the species, and the vascular bed under consideration. It is likely that several EDHFs exist, but current evidence suggests that hydrogen peroxide and epoxyeicosatrienoic acid, a cytochrome p450 metabolite of arachidonic acid, play major roles. Hydrogen peroxide is formed by the mitochondria in response to shear stress and acetylcholine. The hydrogen peroxide not only opens large conductance potassium channels; it also activates protein kinase G, causing oxidation and dimerization. Prostacyclin (PGI₂) causes relaxation of endothelial cells is prostacyclin. There is substantial interaction between NO•, EDHF, and prostacyclin. A major stimulus for release of these factors is shear stress, or the tangential force of fluid as it flows over the endothelium, resulting in flow-dependent vasodilation. Interestingly, the importance of NO• seems to decline and the role of the EDHF increases as blood vessels decrease in size. In addition, the production of EDHF may increase when NO• is low. The interaction of endothelial cells with vascular smooth muscle cells and the intermediates involved is outlined in Figure 48-7.

**Figure 48-7** Role of the increase in cytosolic calcium concentration in the release of endothelium-derived relaxing factors (EDRF). Endothelial receptor activation induces an influx of calcium into the cytoplasm of the endothelial cell. After interaction with calmodulin, NO-synthase and cyclooxygenase are activated, leading to the release of endothelium-derived hyperpolarizing factor (EDHF). NO causes relaxation by activating the formation of cyclic GMP (cGMP) from GTP. EDHF causes hyperpolarization and relaxation by opening K⁺ channels. Prostacyclin (PGI₂) causes relaxation by activating adenylate cyclase (AC), which leads to the formation of cyclic AMP (cAMP). Any increase in cytosolic calcium (including that induced by the calcium ionophore A23187) causes the release of relaxing factors. When agonists activate the endothelial cells, an increase in inositol phosphate may contribute to the increase in cytoplasmic Ca²⁺ by releasing it from the sarcoplasmic reticulum (SR). (Adapted with permission from Vanhoutte PM, Boulanger CM, Vidal M, et al: Endothelium-derived mediators and the renin-angiotensin system. In Robertson JS, Nichols MG, editors: The renin-angiotensin system, London, 1993, Gower Medical.)
extract additional oxygen to meet increased demand is limited because myocardial oxygen extraction is already near its maximal threshold under resting conditions. To account for this limitation, coronary flow rises in response to increased myocardial oxygen requirements.

Flow-Induced Dilation

Flow-induced dilation is a ubiquitous phenomenon of blood vessels in various organs of animals, including humans. Flow-induced dilation plays important physiologic roles by: (1) protecting the vessel wall against friction induced injury, (2) preventing vascular steal phenomenon by dilating upstream vessels when there is focal hyperemia, (3) reducing the heterogeneity of flow distribution, and (4) buffering the pressure distribution in response to rapid pressure changes.

The mechanism by which endothelial cells sense flow has been a focus of substantial investigation. Studies by Tzima and colleagues have defined a mechanosensory complex composed of VE-cadherin, the platelet endothelial cell adhesion molecule (PECAM-1), and the vascular endothelial growth factor receptor-2 (VEGFR-2) that is critical in this process. Shear seems to stimulate PECAM-1 and VE-cadherin, which in turn transactivate VEGFR2, leading to downstream signaling events. In contrast to the myogenic response, the endothelium is required for flow-induced dilation. Regulation of flow-mediated vasodilation is controversial, and both NO and prostaglandins have been shown to be involved, at least in porcine coronary arterioles. The exact mechanism of regulation can depend on age, vessel size, and the vascular bed under consideration. A possible flow-induced arteriolar dilation mechanism is summarized in Figure 48-8.

Autoregulation is mediated by the actions of several factors such as NO, EDHF, and adenosine. Removal of a particular factor does not prevent autoregulation, because the other factors seem to take over its function. Adenosine and hydrogen peroxide also cause hyperpolarization of vascular smooth muscle. From the work of Duncker and colleagues, and others, we now know that several factors work together to influence metabolic regulation and autoregulation, leading to adequate regulation of coronary vascular tone despite interruption of any particular pathway.

Neurohumoral Influence on Microcirculation

The coronary arterial system is densely innervated with sympathetic and parasympathetic nerves. Neurotransmitters released from these, and a wide variety of humoral substances, significantly affect the microvascular tone. Neurohumoral factors affect coronary microvascular tone, and together with myogenic, flow-induced, and local metabolic controls, they participate in determining the coronary vascular resistance necessary for oxygen and nutrition supply to the myocardium (see Fig. 48-4).

![FIGURE 48-8](image-url)
p0195 The role of the autonomic sympathetic and parasympathetic nervous systems is important in regulation of coronary perfusion. In vivo, the vascular response to sympathetic stimulation is mediated by both $\alpha$-adrenergic and $\beta$-adrenergic receptors. In the coronary circulation, the predominant receptor subtype is the $\beta$-adrenergic receptor. For example, direct sympathetic nerve stimulation evokes coronary vasodilation and an increase in coronary flow. If $\beta$-adrenergic antagonists are administered, a transient vasoconstriction can be observed. When coronary microvessels are studied in vitro, $\alpha$-adrenergic stimulation has minimal contractile effects. When selective $\alpha_1$-adrenergic stimulation is applied using pharmacologic stimuli, there is rather potent vasoconstriction of all sizes of coronary microvessels, predominantly the result of the release of endothelium-derived nitric oxide ($\text{NO}^\bullet$). $\beta$-Adrenergic stimulation produces a potent relaxation of all coronary arteries, but especially of small-resistance vessels. In addition, $\beta_2$-adrenergic receptor subtype predominates in vessels smaller than 10 $\mu$m in diameter in in vivo studies, whereas a mixed $\beta_1$- and $\beta_2$-adrenergic receptor population regulates vascular resistance in vivo. On the other hand, larger coronary vessels are regulated by a mixed $\beta_1$- and $\beta_2$-adrenergic receptor subtype population. Activation of cholinergic receptors by either vagal stimulation or the infusion of acetylcholine produces uniform vasodilation of coronary vessels. This vasodilation is predominantly mediated by endothelium-derived nitric oxide, although release of endothelium-derived hyperpolarizing factor (EDHF) and release of prostaglandin substances may contribute. The coronary flow increase by vagal stimulation could be blunted by a metabolically mediated flow decrease caused by a decrease in the heart rate and myocardial contractility.

p0200 Other neurotransmitters that act on the coronary circulation include neuropeptide Y, which is mainly released with norpinephrine as a co-transmitter from sympathetic postganglionic nerve terminals upon intense sympathetic activation. Intracoronary application of neuropeptide Y markedly decreases coronary flow, producing myocardial ischemia without large coronary artery constriction. These results point to its potent and specific constrictor effects on coronary microvessels. Substance P, a potent vasodilator whose effect is dependent on the endothelium, is contained in perivascular nerve fibers and sensory ganglia.

Intrinsic Myogenic Tone

p0205 Myogenic contraction is observed when applying luminal pressure to microvessels, which causes development of intrinsic vascular tone, as shown by elevated wall tension or a decrease in vessel diameter. The microcirculation possesses this intrinsic myogenic tone response, which also contributes to maintaining basal vascular tone and autoregulation. Recent evidence has shown that in the microcirculation, fenestrations in the internal elastic lamina allow communications between the endothelium and vascular smooth muscle. Lowering pressure activates endothelial TRPV4 channels in this microdomain, promoting endothelial cell calcium sparklets, vascular smooth muscle hyperpolarization, and vasodilatation. Responses such as these play a critical role in determining the basal tone and in maintaining the intraluminal pressure of the downstream exchange vessels within a physiologic logic. In the myocardium, myogenic responses to increases in pressure are greater in subepicardial microvessels than in vessels from the subendocardium. In addition, myogenic tone can be reduced during inflammatory states when increased expression of inducible nitric oxide synthase (iNOS) causes altered myocardial perfusion. Increases in myogenic tone, which occur during stretch of vascular smooth muscle, are associated with an increase in inositol 1,4,5-trisphosphate, presumably because of activation of phospholipase C. In addition, the myogenic tone mediator 20-HETE produces constriction of vascular smooth muscle by promoting $\text{Ca}^{2+}$-activated $\text{K}^+$ (BK) channel inhibition. This induces depolarization and increases levels of $[\text{Ca}^{2+}]_i$. This effect is most likely caused by activation of L-type $\text{Ca}^{2+}$ channels or the activation of protein kinase C and inhibition of the Na/K-ATPase. Other mediators probably involved in the myogenic tone response include nitric-activated protein kinases and Rho protein. The downstream mediator Rho kinase may modulate myogenic tone by regulation of the actin cytoskeleton. One potential therapeutic agent for treatment of hypertension and coronary spasm is the use of Rho kinase inhibitors. A summary of possible mechanisms of myogenic tone is shown in Figure 48-9.

Impact of Extravascular and Humoral Forces on the Microcirculation

s0050 In the setting of pathologic processes such as ischemia leading to decreased tissue compliance or increased tissue edema, extravascular forces have an especially important role. For example, collateral perfusion is particularly sensitive to changes in heart rate (more frequent extravascular compression) and ventricular diameter (stretch). The coronary circulation is particularly unique in that it is exposed to a large number of extravascular forces produced by contraction of adjacent myocardium and intraventricular pressures. Of relevance to the concept of extravascular forces is the idea that these might collapse coronary vessels under certain circumstances. Of note, flow through the epicardial coronary arteries halted when aortic pressure fell to levels ranging from 25 to 50 mm Hg, raising the possibility that extravascular forces might be sufficiently high to collapse vessels when intraluminal pressures declined to values below this critical value. Flow in the coronary microcirculation continued even when the arterial driving pressure was minimally higher than coronary venous pressure. Based on modeling and various experimental interventions, it has been determined that the decrease of antegrade blood flow in larger upstream vessels is associated with continued forward flow in microvessels and that this is due to capacitance in the coronary circulation. Kanatsuka and colleagues used a floating microscope to visualize epicardial capillaries and were able to show that red cells continued to flow, even after perfusion had stopped in the more proximal vessels. Using this approach, they showed that the pressure at which flow stops in the epicardial coronary...
microvessels was only a few millimeters of mercury higher than right atrial pressure. In addition, when ventricular diastolic pressure is high, vessels deeper in the subendocardium might be made to collapse by pressure transmitted from the ventricular chamber. In contrast, coronary epicardial vessels do not close at any pressure. It therefore seems likely that the concept of “critical closing pressure” is not applicable to all vessels in the coronary circulation.

The response of the coronary microcirculation to humoral agents differs with vessel size and location. Endothelin-1 produces vasoconstriction when administered to the adventitial surfaces of coronary microvessels. The degree of constriction produced by endothelin-1 is inversely related to the size of the vessels. In contrast, when endothelin-1 is administered intra-arterially, vasodilation occurs, presumably via release of NO•. Sero-
tonin constricts vessels less than 100 µm in diameter, whereas it causes vasodilation of smaller arteries. Vaso-
 pressin, on the other hand, produces greater constriction of microvessels less than 100 µm in diameter than it produces in larger microvessels. In the larger epicardial coronary arteries, vasopressin predominantly causes vasodilation.

Role of Venules in Vascular Resistance

Control of vasomotor regulation differs between the venous and arterial microcirculations, and certain reactions to pathologic stimuli occur preferentially on one side of the capillary bed. Therefore, consideration of the venous circulation apart from the arterial circulation is needed. Venules have considerable importance under conditions of vascular dilation, such as during exercise, metabolic stress, or reperfusion after myocardial ischemia. The venous circulation can influence myocardial stiffness and relaxation properties of the heart. Veins also respond differently to agonists and neuronal stimulation compared with arteries in the same vascular bed.

Venules are also the initiating site of neutrophil adherence and transmigration, whereas arterioles seldom manifest these initial changes in the inflammatory response. Ischemia-reperfusion has been determined to cause endothelial dysfunction in veins but, under similar conditions, arterioles appear to be more susceptible to a reduction in endothelium-dependent relaxation than are coronary venules, despite the fact that leukocytes preferentially adhere to venular rather than to arterial endothelial cells. In addition, complement fragment C5a causes

FIGURE 48-9 Schematic illustrations for the possible mechanisms of (A) the myo-
genic constriction and (B) its compensatory mechanisms. DG, Diacylglycerol; 20-HETE, 20-hydroxyeicosatetraenoic acid; IP3, inositol 1,4,5-trisphosphate; PKC, protein kinase C; PLA2, phospholipase A2; PLC, phospholipase C. (Adapted from Komaru T, Kanatsuka H, Shirato K: Coronary microcirculation: physiology and pharmacology. Pharmacol Ther 86:217–261, 2000.)
ENDOTHELIAL FACTORS IN VASCULAR GROWTH AND RESPONSE TO INJURY

Nitric oxide inhibits vascular smooth muscle proliferation via apoptosis. Animal models have shown that treatment with 1-nitroarginine methyl ester, an inhibitor of NO• formation, markedly increases neointimal development after vascular injury.55 Local transfection with the eNOS cDNA also reduces the intimal proliferation that follows balloon injury.57 The vascular response to injury is enhanced in mice deficient in eNOS.58 Thus, NO• and cGMP-elevating agents inhibit the growth of fibroblasts and vascular smooth muscle. This effect of NO• on vascular smooth muscle growth is mediated by cGMP and can be mimicked by cGMP analogs such as atrial natriuretic factor.59,60

NO• plays an important role in the process of angiogenesis, and endothelial cells do not seem to be sensitive to the growth-inhibitory effects of NO•. In fact, vascular endothelial growth factor (VEGF)-1 actions during angiogenesis are mediated by NO•. Endothelial cells in the proliferative phase have a sixfold increase in eNOS expression compared with confluent ones, and eNOS knockout mice have little VEGF activity.59 During the vascular injury response, this feed-forward condition promotes vascular growth, because while endothelial cells are proliferating to form new blood vessels, the high levels of NO• promote tube formation. Similarly, in response to the denudation injury, proliferating endothelial cells increase NO• production during the growth period to compensate for the lack of endothelial cells in the denuded area while also decreasing platelet adhesion and vascular smooth muscle proliferation in that same area. Moreover, endothelial progenitor cells (EPCs) from the bone marrow have a role in repair of denuded vessels as well as angiogenesis. Although not completely elucidated, circulating EPCs seem to vary in quantity from one patient to the next. Common risk factors such as diabetes and hypercholesterolemia decrease these cells, whereas lipid-lowering drugs such as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors increase them.

EFFECT OF DISEASE STATES ON CORONARY CIRCULATION

Coronary microvascular homeostasis can be adversely affected in disease states by altering vascular diameter, quantity, or response to humoral factors. The contribution of the endothelium to vascular regulation is particularly vulnerable to pathologies such as atherosclerosis, hyperlipidemia, diabetes, and the aging process. This mechanism is highlighted in Figure 48-11. The mechanisms underlying these abnormal endothelium-dependent responses are most likely multifactorial. Factors responsible include abnormalities of G-protein signaling,
resulting in reduced activation of eNOS in response to endothelial cell receptor activation; an alteration of levels of the critical cofactor for eNOS tetrahydrobiopterin; and an overproduction of asymmetric dimethylarginine, which acts as an antagonist for the eNOS substrate L-arginine. It has been shown that oxidative stress (via increased production of vascular superoxide \( O_2^- \)) is particularly increased in the presence of common risk factors. Such an increase in oxidative stress will cause a reduction in endothelial-dependent vasodilation.

It is accepted that diseases that affect endothelium-dependent vascular dilation affect the coronary microcirculation as well as the larger vessels. Endothelium-dependent vasodilation acetylcholine and bradykinin is dramatically impaired in coronary microvessels from monkeys fed a high-cholesterol diet for 18 months, and sometimes paradoxical constrictions can be observed. Similar findings have been made in other animal models. Subsequent studies performed using in vivo techniques showed that vasoconstriction caused by serotonin and ergonovine (both known to be modulated by the endothelium) is markedly enhanced in the coronary microcirculation of hypercholesterolemic monkeys. These findings are impressive because the coronary microcirculation is spared from the development of overt atherosclerosis. Therefore, in the setting of a risk factor for atherosclerosis, endothelial dysfunction occurs, leading to abnormal vascular responses. In humans with hypercholesterolemia, diminished flow responses to acetylcholine are restored by cholesterol lowering. Similar observations have been made either in humans or in experimental models of hypertension, ischemia-reperfusion, and diabetes. It has been suggested that this endothelial dysfunction plays a role in the development of clinical symptoms despite normal coronary anatomy.

Impaired endothelium-dependent vasodilation has also been linked to increased cardiovascular events. The loss of NO in cardiovascular disease not only leads to a decrease in vasodilation; it also predisposes to atherosclerotic lesion formation and vascular smooth muscle proliferation. NO also has antioxidant properties and prevents adhesion molecule expression by endothelial cells. An example of relevance to the clinical setting is the endothelial changes in the coronary microcirculation after cardioplectic arrest and cardiopulmonary bypass during cardiac surgery. In this setting, endothelial dysfunction persists for some time after cardiopulmonary bypass, and it normalizes thereafter. This result has important clinical implications, because it is common for patients undergoing coronary artery bypass grafting, with seemingly complete coronary revascularization, to exhibit signs of myocardial ischemia during the hours after surgery—most likely caused by endothelial dysfunction.

Collateral vessels in the coronary circulation are particularly important in coronary disease. These allow for normal resting perfusion to a region of the myocardium that is served by an occluded vessel, albeit at a lower perfusion pressure; however, the coronary arterioles nourished by collaterals develop markedly abnormal vascular reactivity—for example, impaired endothelium-dependent vascular relaxations and enhanced constrictions to vasopressin. Possible mechanisms of this impaired microvascular endothelium-dependent relaxation in the collateral-dependent region can involve changes in shear stress, pulsatile flow in the collateral-dependent microvasculature, or intracellular calcium levels. Such changes can cause disturbance in microvascular tone during a disease state.

Clinically, patients suffering from ventricular hypertrophy often complain of angina-like symptoms. Animal and human studies have demonstrated that cardiac hypertrophy causes a reduction in the maximal capacity of the coronary circulation to dilate in response to either reactive hyperemia or pharmacologic stimuli. One possible cause for this abnormal response may be a mismatch between the elevated myocardial mass and the relatively reduced coronary microcirculation. Peak flow normalized to myocardial mass may be reduced because of this relative paucity of coronary arterioles, because as the myocardium hypertrophies, the coronary resistance circulation might not increase enough to keep pace with the larger muscle mass. Another possible mechanism of impaired vasodilator responses may be explained by endothelial dysfunction, because many of the diseases associated with myocardial hypertrophy are also associated with a loss of endothelial NO production.

In normal hearts, there is a linear relationship between the diameter of an epicardial coronary artery and the mass of myocardium perfused. Interestingly, epicardial coronary arteries do not enlarge to the same extent as the myocardium hypertrophies, so that for any diameter coronary artery, the amount of myocardium perfused is increased twofold. This phenomenon is particularly
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relevant in the presence of a coronary stenosis, where a small lesion that is otherwise considered minimal becomes flow limiting in a hypertrophic state.

PULMONARY VASCULAR PHYSIOLOGY

The pulmonary vascular response has unique characteristics that distinguish it from other vascular beds. The normal pulmonary circulation is a low-pressure, low-resistance circuit with little or no resting tone. In contrast to the systemic circulation, where neural and humoral mechanisms predominate, the pulmonary circulation is under the control of both active factors that affect vascular smooth muscle tone (e.g., autonomic nerves, humoral factors, gasses), and passive factors (e.g., cardiac output, left atrial pressure, airway pressure).69

In a normal state, unlike systemic arteries, pulmonary arteries have a much thinner smooth muscle layer, which is consistent with a low-pressure system. Small pulmonary arteries are the main effectors of pulmonary vascular resistance, such as hypoxic pulmonary vasoconstriction. In addition, the pulmonary capillary bed and the systemic capillary bed respond differently. Pulmonary veins are similar in structure to pulmonary arteries, but have less smooth muscle and may be regulated differently. Constriction of pulmonary arteries results in elevated pulmonary artery pressure, which increases the pressure on the right side of the heart, whereas constriction of pulmonary veins increases pulmonary capillary pressure, and this could result in pulmonary edema. With disease, the structure of pulmonary vessels can change significantly. With a chronic increase in pulmonary vascular pressure, there is a structural remodeling, with fibrosis, particularly in the intimal layer, and increased size of the smooth muscle layer, which results in a marked alteration in control mechanisms.49

A unique characteristic of the pulmonary circulation is its response to hypoxia. Pulmonary arteries contract when oxygen tension is acutely decreased (Fig. 48-12), unlike systemic vessels, which dilate in response to hypoxia. This phenomenon, called hypoxia-induced pulmonary vasoconstriction (HPV) is an important mechanism that aids in matching ventilation with perfusion by directing blood flow from poorly ventilated regions of the lung to areas with normal or relatively high ventilation.50 Although acute HPV benefits gas exchange and maximizes oxygenation of venous blood in the pulmonary artery, sustained HPV or chronic exposure to hypoxia is a major cause of the elevated pulmonary vascular resistance and pulmonary arterial pressure in patients with pulmonary arterial hypertension associated with hypoxic cardiopulmonary diseases.51 Chronic vasoconstriction leads to vascular remodeling, pulmonary hypertension, and possibly cor pulmonale. Patients with chronic obstructive pulmonary disease, for example, are usually hypoxicemia and may fall into this category. Similarly, pulmonary vasoconstriction presents a challenge in pediatric patients with congenital heart disease, as they are particularly susceptible to developing pulmonary hypertensive crises after cardiac interventions.52 Pulmonary vascular resistance is often increased after lung transplantation.53

Hypoxia is a potent vasoconstrictive stimulus in these patients.54 Although the exact mechanism of HPV remains unclear, many believe that it is related to the inhibition of calcium channels in the pulmonary vascular smooth muscle that leads to contraction.55-57 This hypothesis is supported by increasing evidence that an increase in cytosolic calcium appears to be an important factor in HPV development.58,59 Hypoxia has also been shown to promote membrane depolarization.70 Alternatively, HPV might also be related to the inhibition of secretion of an unknown endogenous mediator that results in vasoconstriction.71 Pulmonary venous hypertension causes pulmonary endothelial dysfunction characterized by reduced bioavailability of NO• and increased formation of vasoconstrictors such as endothelin 1 and thromboxane A2.80-84 Pulmonary venous hypertension may therefore increase pulmonary vasoconstriction and remodeling and cause an increase in pulmonary vascular resistance.82,83 Lung vascular responses may further increase pulmonary arterial pressure in congestive heart failure and augment the risk for right ventricular failure.

Aside from oxygen, agents used as potential therapies for HPV have include inhaled NO•, prostaglandins, endothelin receptor antagonists, protein kinase C inhibitors, and potassium channel activators (Fig. 48-13). Currently, advanced therapies are more likely to include combination treatments, and often incorporate endothelin receptor antagonists or cyclic GMP phosphodiesterase-5 inhibitors.84 Inhaled vasodilators are thought to circumvent potentially deleterious systemic side effects by acting predominantly on the pulmonary circulation (e.g., epoprostenol or the phosphodiesterase-3 inhibitor milrinone).85,86
angiogenic growth factors and gene therapy may enhance endothelium-dependent relaxation, in addition to improving other aspects of cardiac performance. Several animal studies have demonstrated that therapeutic angiogenic interventions, in the setting of chronic ischemia, are associated with an improvement in myocardial perfusion and endothelium-dependent vasodilation in the area supplied by collaterals. These studies used growth factors such as VEGF, fibroblast growth factor (FGF)-1, or FGF-2 placed in the perivascular area. Possible mechanisms through which these factors act include FGF-2- and VEGF-induced release of NO•, which improves collateral perfusion and decreases tissue ischemia. In addition, it has been shown that during periods of chronic ischemia there occurs an upregulation of FGF-2 and VEGF receptors. This finding is consistent with results showing that after administration of growth factors, endothelium-dependent relaxation occurs in the collateral-dependent region, but not in myocardium perfused via the original vessels. In addition, these growth factors can stimulate the release of bone marrow–derived endothelial progenitor cells that promote collateral growth and endothelial function at the treated sites. Unfortunately, clinical trials to date have not demonstrated much benefit with growth factor and gene therapy in patients. Similarly, in clinical trials cell therapy has largely failed to enhance collateral formation to provide sufficient perfusion in the setting of myocardial ischemia. A number of clinical studies have been performed in which patients received bone marrow–derived mononuclear cells or endothelial progenitor cells by infusion several days after myocardial infarction. Other clinical trials have similarly found clinically insignificant benefits or no benefit to cell therapy. These studies demonstrate that cell therapy is safe in the short and long term. Differences in study outcomes are likely related to patient selection, comorbidities, and method of delivery.

**Challenges and Future Directions**

Multiple factors may explain the failure to reproduce the multiple effective preclinical trials with growth factors, genes or cell therapy on vascular regeneration. Patients with end-stage CAD often have significant comorbid conditions, including diabetes and hypercholesterolemia, resulting in aberrant vascular signaling and endothelial dysfunction. These conditions result in hostile local environments with increased oxidative stress and increased expression of anti-angiogenic proteins. Technical issues may contribute to failure in growth factor therapy, including incomplete or nonsustained drug delivery. Similarly, cell-based therapies are fraught with biological and technical failures. Issues include technical failure during injection resulting in “washout,” or “leak out” of cells from injection sites in the heart, lack of homing and incorporation of cells, and cell death. Potential approaches to improve homing and survival of the cells include heat shock treatment and incorporation of bioactive matrices. Another effort to improve functional is the coadministration of growth factors with cell-based therapy. Gene-based therapies may hold the greatest promise for improving angiogenesis and myocardial perfusion, yet are the least studied and most...
poorly understood. Gene-based therapies result in overexpression of survival proteins, use of genetically engineered bone marrow cells, and embryonic stem cells. In addition, investigators have also searched for adjuvant drugs to improve regenerative therapies. Commonly prescribed drugs like statins, cyclo-oxygenase inhibitors, and metformin, as well as naturally occurring substances like resveratrol have demonstrated a number of pleotropic effects in preclinical and clinical studies. The direct and indirect effects of these and other drugs on hyperglycemia, hypercholesterolemia, and oxidative stress can act synergistically with other therapies to improve collateral formation. Despite the overall lack of clinical efficacy to date, the future of regenerative treatments holds much promise. Improvements in treating patient comorbidities along with continued advances in understanding the basic science of angiogenesis, pharmacology, genetic engineering, and more procedure-based interventions will be required to demonstrate successful clinical application of regenerative therapies.

**SUMMARY**

This chapter provided an overview of some of the newer concepts regarding physiological and pathophysiological control of vascular tone. Properties of peripheral vessels cannot be extrapolated to the coronary or pulmonary circulation. Similarly, properties of one size or class of coronary vasoactivity cannot be generalized. Certainly, the technology used in recent studies is dramatically changed from that of older ones. Although we attempted to focus on studies that directly examined the microvasculature using the newer technology (in vitro preparations or in situ observations), it was also important to present classical studies of the intact circulation performed in intact animals or isolated hearts. Newer research questions have necessitated the use of more basic techniques, including cell culture and molecular biological approaches. A more recent development has been the ability to make many in vivo hemodynamic measurements in human subjects in the catheterization laboratory, thus obviating the need and the expenses of flow studies in large animals. As the field of vascular biology grows, we will continue to validate our observations in the intact circulation of our patients and to translate this basic science to the clinical setting.

**REFERENCES**


SECTION 2 ADULT CARDIAC SURGERY


