Review

Coronary Artery Blood Flow: Physiologic and Pathophysiologic Regulation

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Summary: Acute myocardial ischemia, which results from a significant imbalance between myocardial oxygen demands and myocardial oxygen supply, occurs in as many as six million persons with atherosclerotic coronary artery disease in the United States. Accordingly, a clear understanding of the physiologic and pathophysiologic factors that influence coronary artery blood flow is important to the clinician and provides the basis for the judicious use of medications for the treatment of patients with atherosclerotic coronary artery disease. This review discusses the endothelial, metabolic, myogenic, and neurohumoral mechanisms of coronary blood flow regulation and the interaction of the different mechanisms in the regulation of coronary blood flow. The importance of nitric oxide in coronary blood flow regulation is emphasized. We also discuss the common clinical problems of hyperlipidemia and coronary atherosclerosis, coronary artery spasm, and systemic arterial hypertension that result in coronary artery endothelial dysfunction, the impaired production and increased inactivation of nitric oxide, and impairment in coronary blood flow regulation. This information is important to clinicians because more than forty million people in the United States have atherosclerotic or hypertensive heart disease and therefore are at risk for significant myocardial complications due to impairment of coronary blood flow regulation.

Key words: coronary blood flow, regulation of coronary blood flow, autoregulation, vascular endothelium, nitric oxide, adenosine, hyperlipidemia, atherosclerosis

Introduction

In the normal heart, an increase in myocardial oxygen demand causes an increase in coronary artery blood flow and oxygen delivery. In contrast, in the presence of obstructive coronary artery disease, increases in myocardial oxygen demand are not matched by increases in coronary artery blood flow. This imbalance between oxygen demand and supply results in acute myocardial ischemia. Therefore, a clear understanding of the physiologic factors that influence myocardial oxygen requirements and coronary blood flow is important to the clinician and provides the basis for the judicious use of medications for the treatment of patients with obstructive coronary artery disease.

The major determinants of myocardial oxygen demand are myocardial tension, myocardial contractility, and heart rate (Table I).¹ Myocardial tension is directly determined by left ventricular systolic pressure and ventricular radius, and is inversely proportional to ventricular wall thickness, as defined by the Law of LaPlace.¹ Ventricular afterload, or impedance, determines the magnitude of ventricular systolic pressure generation, whereas preload, or ventricular volume at end-diastole, affects ventricular radius.² In the normal heart, an increase in myocardial tension, contractility, or heart rate results in an increase in oxygen demand which is matched by an increase in coronary artery blood flow and oxygen delivery.³ The relationship between coronary blood flow and myocardial oxygen demand in the normal heart is linear over a broad range of coronary blood flows from 10 to approximately 600 ml/min/100g of myocardial tissue (Fig. 1).^{3,4}

The increase in coronary blood flow that occurs with augmented myocardial oxygen demands is regulated by changes in the diameter, and consequently the vascular resistance, of the coronary arteries. The major epicardial coronary arteries and their principal branches serve as conductance vessels and, in the absence of coronary arterial disease, contribute only about 5% to total coronary vascular resistance.⁵ In contrast, intramyocardial coronary arterioles are responsible for the majority of coronary vascular resistance.⁶ Coronary arterioles <300 μ m in diameter contribute 95% and arterioles <100 μ m in diameter contribute more than 50% of the total coronary arterial resistance.⁷

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TABLE I Determinants of myocardial oxygen demand

Major
Myocardial tension
Myocardial contractility
Heart rate
Minor
External work (pressure times stroke volume)
Basal myocardial metabolism
Electrical and chemical activation of contraction

Increases in coronary arterial oxygen extraction also occur with increases in myocardial oxygen demand but represent only a limited compensatory mechanism because myocardial arterial oxygen extraction is normally about 75%.^{8,9} Consequently, little additional oxygen can be extracted from arterial blood by the myocardium.

Changes in coronary vascular resistance with increases in myocardial oxygen demand are primarily controlled by endothelial, metabolic, myogenic, and neurohumoral mechanisms (Table II). This review discusses each mechanism of coronary blood flow regulation and the interaction of the different mechanisms to decrease coronary vascular resistance when the demand for oxygen by the heart increases. In addition, the effects of obstructive coronary disease, which modify the response of the coronary vessels to each regulatory mechanism, are discussed. This information is important because approximately 28 million Americans have obstructive coronary artery disease.¹⁰ In these patients, the coronary arteries cannot dilate in response to the increases in oxygen demand, and acute myocardial ischemia can occur.

Endothelial and Metabolic Regulation of Coronary Blood Flow

Coronary artery dilation caused by vasoactive substances constitutes the primary mechanism by which increases in myocardial demand are matched by increases in blood flow.

FIG. 1 The relationship between myocardial oxygen consumption and coronary blood flow. Note that over a broad range of coronary blood flows there is a linear relationship between myocardial oxygen consumption and coronary artery blood flow. The filled circles indicate the effects of interventions that increase or decrease myocardial metabolic rate. These interventions include epinephrine or dinitrophenol administration or hemorrhage.

Nitric oxide (NO) and adenosine are the two most extensively investigated vasoactive substances in the regulation of coronary blood flow.

Nitric Oxide

Nitric oxide is the major vasodilator chemical produced by the coronary endothelium. It is continuously released from the coronary endothelium under resting conditions and contributes to the patency of the coronary arteries.¹¹ In addition, NO is also an important determinant of coronary dilation during exercise-induced increases in myocardial oxygen demand.^{12,13}

Nitric oxide is produced in the endothelium from L-arginine by NO-synthase (Fig. 2).¹⁴ Inhibition of NO synthesis produces constriction of coronary vessels and attenuates the

TABLE II Normal major mechanisms of coronary blood flow regulation

Mechanism	Definition	Target coronary segment
Endothelial	Effects of vasoactive substances such as nitric oxide, prostaglandins, endothelium-derived hyperpolarizing factor, and endothelin released from the endothelium on CVR.	Arterioles 80–150 μ m in diameter and arteries
Metabolic	Effects of myocardial metabolites such as adenosine on CVR.	Arterioles 25–100 μ m in diameter
Myogenic	Vascular smooth muscle contraction or relaxation in response to increases or decreases in intraluminal pressure.	Arterioles 50–100 μ m in diameter
Neurohumoral	Effects of neurotransmitters released from sympathetic or parasympathetic nerve fibers and circulating vasoactive agents in plasma on CVR.	Arterioles (α_2 and α_1 receptors), arteries (α_1 receptors), 140–300 μ m arteries (see text)

Abbreviation: CVR = coronary vascular resistance.

FIG. 2 Nitric oxide (NO) is produced in endothelial cells from L-arginine by calcium-calmodulin-dependent NO synthase. Increases in endothelial Ca^{2+} occur following the entrance of Ca^{2+} from the extracellular space and the release of Ca^{2+} from intracellular stores (IP_3 pathway). Smooth muscle relaxation is mediated by an increase in cGMP. Ca-M = calcium-calmodulin kinase, cGMP = cyclic guanosine monophosphate, GTP = guanosine triphosphate, SR = sarcoplasmic reticulum, IP_3 = inositol triphosphate, NO = nitric oxide.

increase in coronary blood flow that normally occurs with increases in myocardial oxygen demands.¹³ Nitric oxide produces coronary dilation by increasing cyclic guanosine monophosphate (cGMP) in vascular smooth muscle cells.¹⁴ Cyclic guanosine monophosphate reduces the affinity of the troponin-tropomyosin complex on actin for calcium and enhances the re-uptake of calcium by the sarcoplasmic reticulum in vascular muscle cells.¹⁴ In this manner, NO causes vascular relaxation. The coronary vessels most responsive to NO are the large epicardial coronary arteries and the 80–300 μm diameter microvessels.^{15–18}

A primary determinant of NO release from the coronary endothelium is pulsatile stress, or “radial strain,” which is the force imposed on the coronary endothelium by flowing blood.^{11, 12, 14, 19–21} Pulsatile arterial blood flow produces continuous endothelial stress through the rhythmic changes in vessel diameter and deformation of the arterial wall.²² Flow-dependent coronary dilation occurs because pulsatile stress results in transient increases in intracellular calcium in the endothelium by activation of the phospholipase C pathway.²³ Increased endothelial cell calcium activates NO synthase which induces synthesis of NO to produce coronary dilation (Fig. 2).⁶ Inhibition of NO synthesis or damage or destruction of the vascular endothelium significantly decreases flow-dependent endothelial dilation.^{15, 16, 24, 25} In contrast, inhibition of prostaglandins, or activation of alpha- or beta-adrenergic receptors, does not affect flow-dependent dilation of the coronary arteries.^{16, 26}

The mechanical activity of the heart also stimulates the release of NO from the coronary endothelium. In this regard, the rhythmic compression of intramyocardial vessels by myocardial contraction produces endothelial pulsatile stress and the continuous release of NO. This contributes to the continuous adjustment of coronary vascular resistance.²⁷

Acetylcholine, bradykinin, adenosine triphosphate (ATP), prostacyclin, serotonin, substance P, histamine, and adenosine diphosphate (ADP) also stimulate the release of NO.^{14, 20, 28} When the endothelium is intact, acetylcholine is a primary chemical mediator of NO release. When the endothelium is damaged or destroyed by coronary artery disease, acetylcholine produces vascular muscle constriction.^{29–34}

Nitric oxide also affects the responses of the coronary microcirculation to sympathetic stimulation. In this regard, NO diminishes the vasoconstrictor effects of norepinephrine that occur during stimulation of α_1 - and α_2 -adrenergic receptors in the coronary arteries.^{35, 36} Norepinephrine-induced increases in pulsatile stress cause the release of NO which counteracts alpha-adrenergic vasoconstriction.⁶ In addition, norepinephrine stimulates α_2 -adrenergic receptors in the coronary endothelium, which causes NO release and thereby decreases alpha-adrenergic mediated vasoconstriction.³⁷

Other Vasoactive Substances Released from the Endothelium: Hyperpolarizing Factor, Prostacyclin, and Endothelin

The coronary artery endothelium also releases endothelial-derived hyperpolarizing factor (EDHF).³⁸ In contrast to nitric oxide, EDHF produces vascular smooth muscle relaxation by opening K^+ channels in smooth muscle cells. This allows potassium ions to flow to the extracellular space and increases the electronegativity of the vascular muscle cells.³⁸ The increase in cell electronegativity, or hyperpolarization, increases the threshold for electrical excitation. Hyperpolarization also causes deactivation of cellular voltage-gated calcium channels, a reduction in calcium entry into muscle cells, and therefore vascular smooth muscle relaxation.³⁸

Prostacyclin, a product of the arachidonic acid cascade, is also released from the coronary artery endothelium due to stimulation by thrombin, bradykinin, histamine, adenine nucleotides (ATP and ADP), and thromboxane A_2 .³⁹ In contrast to NO, which causes vasorelaxation through increases in cGMP, prostacyclin produces vascular smooth muscle relaxation through increases in intracellular cyclic adenosine monophosphate (cAMP).⁴⁰ Cyclic AMP facilitates calcium uptake by the sarcoplasmic reticulum in vascular smooth muscle as well as calcium extrusion from the cell to the extracellular space, thereby producing vascular smooth muscle relaxation.^{41, 42}

The coronary endothelium also produces vasoconstrictor substances. The best known is endothelin-1, which contributes to the regulation of vascular tone by exerting a tonic vasoconstrictor effect.^{8, 43} Endothelin-1 release is primarily stimulated by thrombin, angiotensin II, epinephrine, vasopressin, and cytokines such as interleukin-1.⁴⁴ Endothelin-1 produces con-

FIG. 3 Production of adenosine in the heart. ATP = adenosine triphosphate, ADP = adenosine diphosphate, AMP = adenosine monophosphate.

striction of epicardial arteries and also intramyocardial arterioles.⁴⁴ The constrictor effect of endothelin is mediated by activation of endothelin A (ETA) receptors present in vascular muscle.^{44, 45} Endothelin-mediated vasoconstriction is mediated by activation of phospholipase C, which increases intracellular calcium in smooth muscle cells resulting in coronary artery constriction.⁴⁴

Another important vasoactive substance in the regulation of coronary blood flow is adenosine. Adenosine is especially important in metabolic regulation of coronary blood flow when myocardial oxygen demands are not met by myocardial oxygen supply such as commonly occurs during coronary artery obstruction.

Adenosine

When myocardial oxygen demand exceeds oxygen supply, adenosine is produced in myocardial cells from the breakdown of ATP and is released into the interstitial space where it produces coronary arteriolar dilation (Fig. 3).⁴⁶ The myocardial cells take up most of the adenosine from the interstitial space, whereas the metabolites inosine and hypoxanthine escape into the circulation.⁴⁶ Adenosine is the major metabolite that mediates metabolically induced coronary vasodilation during myocardial ischemia.^{47, 48} Small coronary arterioles with diameters <100 μm , which are responsible for $\geq 50\%$ vascular resistance, are the primary target of adenosine-induced coronary artery dilation.^{17, 49}

Adenosine produces coronary artery dilation through stimulation of vascular muscle adenosine A_2 receptors.⁵⁰ Stimulation of these receptors activates adenylyl cyclase to produce cAMP.⁵¹ Increases in cAMP decrease intracellular calcium and the affinity of vascular muscle myosin light chain kinase for calcium, thereby relaxing vascular muscle.^{41, 42}

Myocardial oxygen and carbon dioxide tensions are two additional mediators of the metabolic control of coronary blood flow.⁵² Hypoxia and hypercapnia interact synergistical-

ly to account for approximately 23% of the decreases in coronary vascular resistance that occur during increases in myocardial metabolism.⁵² However, increases in CO_2 and concomitant decreases in pH are primarily involved in the local metabolic regulation of myocardial blood flow by potentiation of other dilator mechanisms such as adenosine.

Myogenic Regulation of Coronary Blood Flow

Myogenic mechanisms regulate coronary blood flow by constricting vascular smooth muscle in response to increases in perfusion pressure and by dilating vascular muscle in response to decreases in coronary perfusion pressure.^{53, 54} As a result of myogenic regulation, flow is maintained relatively constant despite significant changes in perfusion pressure.

The myogenic mechanism is an intrinsic property of vascular muscle that does not depend on the presence of endothelial substances, neural influences, or vasoactive chemicals in plasma.¹⁵ Myogenic regulation primarily occurs in 50 to 80 μm coronary arterioles that can contribute as much as 50% of the coronary microvascular resistance.^{15, 55} Myogenic constriction or dilation occurs over a greater range of perfusion pressures in subepicardial than in subendocardial arterioles.⁵⁶ In the subendocardium, there is greater dilation of the coronary vessels due to the higher wall tension and, therefore, greater myocardial oxygen demand. Therefore, the vasodilator reserve of these vessels is less compared with that of subepicardial vessels.

Myogenic constriction occurs due to stretch-induced depolarization of vascular smooth muscle cells which results in the activation of nonselective cation channels and subsequent influx of Na^+ , K^+ , and Ca^{2+} ions.⁵⁷ The consequent membrane depolarization of smooth muscle enables the recruitment of voltage-dependent calcium channels that contribute to an increase in intracellular calcium.¹⁶ Stretch of vascular smooth muscle during constriction also increases intracellular calcium through activation of phospholipase C.^{16, 58} The increase in intracellular calcium activates actin-myosin interaction resulting in vascular smooth muscle contraction.

Myogenic vasodilation occurs due to potassium ion efflux via ATP-sensitive potassium channels. A decrease in ATP opens these channels, which allows potassium efflux. Potassium efflux causes hyperpolarization of vascular muscle cells, which increases the threshold for cellular depolarization and decreases cellular excitability.^{59, 60}

The myogenic regulation of coronary blood flow is important since myogenic constriction and dilation occur during autoregulatory responses of the coronary circulation.

Coronary Artery Autoregulation

Autoregulation refers to the intrinsic ability of the heart to maintain myocardial blood flow relatively constant over a wide range of coronary perfusion pressures and is one of the most important mechanisms of coronary flow regulation.⁶¹ Sudden, sustained changes in coronary perfusion pressure result in abrupt and similar directional changes in coronary blood flow (Fig. 4).³ However, the new level of coronary

FIG. 4 Autoregulation of coronary blood flow in the heart. The point where the lines cross represents the normal value for pressure and flow. The broken line indicates the transient increase or decrease in coronary blood flow following an increase or decrease in perfusion pressure, respectively. The solid line represents the return of coronary blood flow toward the steady-state value.

blood flow is transient, and flow returns toward the previous steady state level because of autoregulation. Figure 4 shows plots of transient and steady state flow for different changes in perfusion pressure. The point where the lines cross represents the "normal" steady-state pressure and flow from which perfusion pressure was abruptly increased or decreased.³ The filled symbols indicate the pressure and transient flows immediately after an abrupt increase or decrease from the control mean pressure of 110 mmHg.³ The open symbols indicate the steady-state flows that occurred at each new perfusion pressure. Note that an increase or decrease in perfusion pressure is followed by a transient parallel change in flow. However, due to autoregulation, flow returns to a steady state. The line join-

ing the open symbols illustrates autoregulation that is typically observed in the normal heart.³

In normal subjects, autoregulation maintains the perfusion of the heart at mean aortic pressures as low as 45 mmHg and as high as 150 mmHg.⁶²⁻⁶⁴ If coronary perfusion pressure rises above 150 mmHg or decreases below 45 mmHg, coronary artery blood flow becomes directly dependent on the actual perfusion pressure. Autoregulatory mechanisms predominate in coronary arterioles < 100 to 150 μ m in diameter.^{65, 66} The adjustments in coronary vascular resistance that occur during autoregulation are mediated by endothelial, metabolic, and myogenic mechanisms of coronary flow regulation.⁶⁷

Nitric oxide plays a role in the autoregulation of coronary blood flow.^{62, 68} Inhibition of NO synthesis with N-nitro-L-arginine-methyl ester (L-NAME) raises the lower limit of autoregulation at rest from 45 mmHg to approximately 61 mmHg.⁶² That is, when NO synthesis is impaired, myocardial ischemia occurs at pressures of ≤ 60 mmHg. In contrast, in the presence of NO, myocardial ischemia does not occur until perfusion pressure is < 45 mmHg. Thus, NO inhibition increases the vulnerability of the myocardium to ischemia.⁶²

Neurohumoral Regulation of Coronary Blood Flow

Neurohumoral regulation of blood flow occurs in large coronary arteries as well as in the microcirculation.⁶⁹ However, neurohumoral factors can affect the endothelial, metabolic, and myogenic regulation of coronary blood flow.

The large epicardial and intramyocardial coronary arteries are densely innervated by postganglionic sympathetic and parasympathetic nerve fibers.⁷⁰ Therefore, norepinephrine and acetylcholine released from these fibers interact with coronary adrenergic and muscarinic receptors to control coronary vascular resistance.^{70, 71} In addition, other circulating vasoactive substances affect coronary vascular resistance. The effects of these humoral regulators on coronary blood flow are summarized in Table III.⁷²

TABLE III Humoral regulation of coronary blood flow^{6, 78}

Vasoactive agent	Source	Direct effect on vascular smooth muscle	Mechanism
Norepinephrine	Adrenergic nerve fibers	Coronary constriction	Alpha-adrenergic activation
		Coronary dilation	Beta-adrenergic activation
Epinephrine	Adrenal gland and sympathetic nerve fibers	Coronary constriction	Alpha-adrenergic activation
		Coronary dilation	Beta-adrenergic activation
Dopamine	Adrenergic nerve fibers	Coronary dilation	Dopaminergic receptors
Angiotensin	Systemic circulation	Coronary constriction	AT ₁ receptors
Adenosine	Breakdown of ATP	Coronary dilation	A ₂ receptors
Histamine	Mast cells and basophils	Coronary constriction	H ₁ receptors
		Coronary dilation	H ₂ receptors
Prostacyclin	Vascular endothelium	Coronary dilation	Prostacyclin receptors
Thromboxane A ₂	Vascular endothelium and platelets	Coronary constriction	Thromboxane A ₂ receptors
Bradykinin	Vascular endothelium	Coronary dilation	Bradykinin ₂ receptors
Serotonin	Aggregating platelets	Coronary constriction	5 ₁ receptors

Abbreviation: ATP = adenosine triphosphate.

Alpha-adrenergic responses: Humoral as well as neuronal alpha-adrenergic receptor activation results in net coronary artery constriction which increases total coronary vascular resistance by as much as 40%.^{70,73} The coronary artery constriction that occurs during activation of the sympathetic nervous system is mediated by activation of both α_1 and α_2 -adrenergic receptors.^{71,74} The large epicardial coronary arteries contribute < 10% to the increases in coronary vascular resistance that occur during alpha-adrenergic activation.⁷⁵ The dominant site where coronary constriction occurs during sympathetic activation is at the level of the coronary microcirculation.⁷⁶

The distribution of alpha-adrenergic receptors in the coronary vasculature is not uniform. α_1 -adrenergic receptors are abundant in coronary arteries with diameters > 100 μm while α_2 receptors are more common in microvessels < 100 μm in diameter.^{76,77} Activation of α_2 receptors decreases coronary arterial diameter by as much as 24% while activation of α_1 -adrenergic receptors decreases the diameter of coronary arteries by 11%.^{76,77} The magnitude of α_2 vasoconstriction is greater in coronary arterioles due to the greater number of α_2 -receptors found in these vessels.⁷⁷

Beta-adrenergic responses: Beta₁ receptors are primarily located in the large epicardial coronary arteries while beta₂ receptors are located in small coronary arteries and arterioles.^{78,79} Stimulation of these receptors produces coronary artery vasodilation.^{30,80} However, increases in myocardial metabolism as a result of myocardial beta₁ mediated increases in heart rate and myocardial contractility generally mask direct beta receptor-induced coronary artery dilation.³⁰

Cholinergic responses: When the endothelium is intact, acetylcholine produces significant coronary artery dilation as a result of the activation of muscarinic receptors present in the coronary arteries.^{31–33} However, when the endothelium is damaged or destroyed, acetylcholine produces coronary artery constriction.³⁴ M₁, M₂, and M₃ muscarinic receptor subtypes occur in the coronary vessels.^{33,81,82} M₁ and M₂ receptors are abundantly located in the vascular endothelium, while M₃ receptors are found in vascular smooth muscle as well as in the endothelium.^{24,34}

The acetylcholine-mediated increase in coronary artery blood flow is mediated by the release of NO from the coronary endothelium and an increase in cGMP following the activation of endothelial M₁, M₂, and M₃ receptors.^{33,34,81,82} The acetylcholine-mediated coronary vasoconstrictor effect is mediated by direct stimulation of M₃ receptors in vascular muscle.^{34,82,83} The M₃-mediated coronary constriction is due to influx of calcium into the muscle cell as well as to mobilization of intracellular calcium through activation of muscarinic receptor-linked phospholipase C.⁸⁴

Noncholinergic, Nonadrenergic Regulation of Coronary Blood Flow

In addition to norepinephrine and acetylcholine, sympathetic and parasympathetic nerve fibers contain nonadrenergic, noncholinergic neuropeptides such as neuropeptide Y (NPY)

and vasoactive intestinal peptide (VIP). Neuropeptide Y is colocalized with norepinephrine in sympathetic nerve fibers, while VIP is colocalized with acetylcholine in parasympathetic nerve fibers.^{85–87} Neuropeptide Y and VIP containing nerve fibers and receptors are abundant in the coronary arteries of all mammals including humans.^{85–90} Neuropeptide Y and VIP are proposed to play an important role in the regulation of coronary blood flow.^{87,89,91,92}

Neuropeptide Y, released endogenously from cardiac sympathetic nerves or administered exogenously, produces concentration-dependent contractions and can increase coronary vascular resistance by as much as 39%.^{87,89,90} The coronary vasoconstrictor effects of NPY are due to the activation of specific NPY receptors present in the coronary arteries.^{81,90,93}

Vasoactive intestinal peptide is colocalized with acetylcholine in postganglionic parasympathetic nerve fibers that innervate the heart.⁸⁵ In the coronary arteries, VIP-containing nerve fibers and VIP receptors are primarily found in the epicardial vessels and, to a lesser extent, in the coronary arterioles.^{85,88,94} Vasoactive intestinal peptide produces dose-dependent relaxation of the coronary arteries. It decreases coronary perfusion pressure by as much as 17%, increases the epicardial coronary artery cross-sectional area by 27%, increases coronary artery blood flow by as much as 62%, and decreases coronary artery vascular resistance by 46%.^{91,92,95,96} Vasoactive intestinal peptide has a direct coronary artery dilator effect that is independent of changes in aortic blood pressure, heart rate, or myocardial contractility.^{91,92}

Interactions between Metabolic, Endothelial, and Myogenic Mechanisms in Coronary Blood Flow Regulation

In the microcirculation, where the majority of coronary vascular resistance is found, metabolic, endothelial (flow-dependent), and myogenic mechanisms act in concert to increase coronary blood flow when myocardial oxygen demands increase (Fig. 5).^{15–17,53} An increase in metabolic demand by the heart preferentially dilates coronary arterioles that are 25–45

FIG. 5 Interaction among metabolic, endothelial, and myogenic mechanisms to increase coronary blood flow following an increase in myocardial oxygen demand. d = diameter.

μm in diameter through the release of vasoactive substances such as adenosine.¹⁷ Dilation of these arterioles decreases vascular resistance and increases flow in upstream 50–80 μm diameter arterioles due to metabolic and, to a lesser extent, myogenic mechanisms. The increases in flow in the small arterioles cause larger arterioles (80–150 μm diameter) and small arteries (140–300 μm diameter) to dilate due to endothelium-dependent flow mediated responses.^{15–17, 53}

When tissue perfusion and myocardial oxygen delivery is adequate, the production of vasodilator metabolites is decreased and the dilation of 25–45 μm diameter arterioles is reduced. As a result of arteriolar constriction and increased perfusion pressure, constriction occurs in intermediate size arterioles (50–80 μm diameter). The resultant increase in arteriolar resistance and decrease in flow thereby reduces the endothelial flow-mediated dilation and returns coronary blood flow to normal.^{15–17, 53} This interaction between the different mechanisms of blood flow regulation allows adequate myocardial perfusion and oxygen delivery in response to increases in myocardial oxygen demand.

Endothelial Dysfunction

Atherosclerotic coronary artery disease is the leading cause of patient morbidity and mortality in the United States. Each year, more than 6 million patients experience acute myocardial ischemia, 1 million patients suffer an acute myocardial infarction, and approximately 25% of these patients die before reaching the hospital.⁹⁷ The most frequent abnormality found in patients with atherosclerotic coronary artery disease is dysfunction of the coronary endothelium.^{98–102}

In normal subjects, NO maintains coronary dilation at rest and during increases in myocardial metabolism, and contributes to flow-induced dilation.^{11–15, 24, 25, 62, 68} Nitric oxide also opposes significant vasoconstriction mediated by endothelin 1, norepinephrine, thromboxane A₂, and serotonin. In contrast, when the coronary endothelium is dysfunctional due to atherosclerotic disease, NO production is substantially reduced. As a consequence, coronary vascular resistance is increased and coronary blood flow does not normally increase during increases in myocardial metabolism because of significant impairment in coronary flow reserve.^{98–110} If the coronary oxygen supply does not meet myocardial oxygen demands, myocardial ischemia occurs.^{107, 111, 112}

In the next sections, we discuss endothelial dysfunction in the presence of atherosclerosis, coronary spasm, and systemic hypertension.

Atherosclerosis

Atherosclerosis causes coronary endothelial dysfunction by significantly reducing NO activity.^{113, 114} Oxidized low-density lipoproteins (LDL) in the coronary endothelium inhibit the release of L-arginine, the precursor of NO, from endothelial stores, decrease the expression of NO synthase (Fig. 2), and increase the breakdown of NO.^{115, 116} Endothelial dysfunction does not result from an inability of the coronary vessels to re-

spond to NO because nitroprusside, an NO donor that is independent of the endothelium, causes dilation of atherosclerotic coronary arteries.¹¹⁷

Dysfunctional coronary endothelium attracts platelets and specific adhesive glycoproteins such as vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and endothelial-leukocyte adhesion molecule.^{102, 118} These glycoproteins allow monocytes and T lymphocytes to attach to the endothelium. In addition, growth-regulatory factors and chemo-attractants released by leukocytes adherent to the endothelium, the dysfunctional endothelium, and by the underlying smooth muscle cells allow monocytes and T lymphocytes to migrate between the endothelial cells into the intima.¹¹⁸ This process is most pronounced at “branch points” or bifurcations of the coronary arteries. Monocyte-derived macrophages accumulate oxidized LDL in the coronary intima, become foam cells, and, together with lymphocytes, form a “fatty streak” in the intima. This is the earliest recognizable lesion of atherosclerosis.¹¹⁸ With further accumulation of oxidized LDL, the fatty streak progresses to a fibrofatty lesion. More advanced atherosclerotic lesions are composed of layers of macrophages, T-lymphocytes, and smooth muscle cells within the intima which, in turn, develop into progressively increasing occlusive atheroma or atherosclerotic plaques.¹¹⁸ Fibrous caps cover the atheromatous plaque. Macrophages, located at the edges of the fibrous cap, can release metalloproteinase enzymes that cause the fibrous cap to become unstable and rupture. If rupture occurs, a sufficient quantity of thrombogenic material is exposed and the coronary artery lumen can become obstructed by thrombus that accumulates within the plaque and also propagates downstream in the coronary artery.

Platelet aggregation on the coronary endothelium also leads to the production and release of thromboxane A₂, a potent vasoconstrictor, which predisposes to coronary spasm and thrombus formation.¹¹⁹ Oxidized LDL in the coronary intima also induces the expression of the vasoconstrictor endothelin and causes endothelial cells and monocytes to express high concentrations of tissue factor which is a potent hemocoagulant.^{120, 121} In contrast to LDL, high-density lipoproteins (HDL) decrease the oxidation of LDL and transfer LDL from peripheral tissues to the liver.¹²⁰

A common manifestation of obstructive coronary artery disease due to atherosclerotic plaque is angina pectoris. Angina pectoris is caused most often by physical or emotional stress which significantly increases myocardial oxygen requirements. However, atherosclerotic coronary arteries have a significantly reduced capacity to dilate in order to increase myocardial blood flow and oxygen supply.^{97, 102} As a consequence, myocardial ischemia, which is manifested clinically by angina pectoris, occurs. The goal of the pharmacologic treatment of angina pectoris is to reduce endothelial dysfunction, increase myocardial oxygen supply, and decrease myocardial oxygen requirements. In this regard, reduction in blood total and LDL cholesterol and increases in HDL cholesterol improve coronary endothelium-dependent dilation.^{120, 122} Administration of antioxidants such as vitamin E in large doses appears to reduce the oxidation of LDL.¹²¹

Furthermore, L-arginine supplementation enhances NO production and is reported to reduce intimal thickening in atherosclerotic arteries.^{98, 113, 123, 124} In addition, short- and long-acting nitroglycerin preparations, which are converted into NO, cause venous and arterial dilation by activating guanylate cyclase, increasing cGMP, and thereby producing vascular muscle relaxation (Fig. 2).^{40, 120} In this regard, nitroglycerin decreases myocardial oxygen requirements by causing venous dilation and decreasing ventricular preload. In addition, nitroglycerin increases coronary flow by causing coronary dilation. Myocardial oxygen requirements are also reduced in patients with angina pectoris by beta-adrenergic receptor blocking agents which decrease myocardial contractility, myocardial wall tension, and heart rate.

Coronary Spasm

Coronary spasm commonly occurs in patients with coronary endothelial dysfunction and plays an important role in the pathogenesis of angina pectoris, variant angina, and acute myocardial infarction.¹²⁵⁻¹²⁷ Thirty-eight percent of patients with angina pectoris at rest and 20% of patients with recent myocardial infarction have coronary artery spasm.¹²⁸ Coronary spasm causes transient reductions of coronary artery blood flow in the absence of increases in myocardial oxygen demands and is associated with electrocardiographic ST-segment elevation or depression indicative of acute myocardial ischemia.¹²⁹ Spasm may occur either at sites of atherosclerotic coronary stenosis or in regions of the coronary vasculature where no stenosis exists. Often intravenous ergonovine maleate, methacholine, histamine, cold-pressor testing, or hyperventilation can induce coronary artery spasm.¹²⁸ Moreover, the response to these provocative tests is markedly increased in patients with hyperlipidemia.¹²⁸

The primary cause of coronary vasospasm is focal coronary hyperreactivity that is commonly due to a deficiency in endothelial NO. This is most often caused by hyperlipidemia and coronary atherosclerosis.^{125-127, 130} In patients with vasospasm, the coronary arteries have increased tone at rest. In addition, the coronary arteries are hypersensitive to vasoconstrictor stimuli such as endothelin, thromboxane A₂, and serotonin, and constrict during exposure to cold or exercise.^{127, 129} The coronary concentration of vasoconstrictor agonists is increased in these patients due to coronary endothelial platelet aggregation which releases serotonin and thromboxane A₂. Serotonin is also taken up into the pericoronary sympathetic nerve terminals. When serotonin is released from sympathetic nerves, along with norepinephrine, coronary contraction is significantly augmented.^{130, 131} In addition, the coronary arteries in patients with vasospasm constrict rather than dilate in response to acetylcholine because of coronary endothelial dysfunction.^{127, 129}

Nitroglycerin, which is converted into NO, can reverse coronary spasm. Calcium-channel blocking agents, which decrease calcium entry into vascular muscle cells and therefore facilitate vascular relaxation, are also beneficial in the treatment of patients with recurrent coronary spasm.

Systemic Hypertension

Systemic hypertension results in dysfunction of the coronary endothelium with decreased production of NO synthase and increased inactivation of NO.^{100, 102, 111, 132-135} In hypertensive patients, the intracardiac renin-angiotensin system not only contributes to cardiac and vascular muscle hypertrophy but also produces coronary constriction and increases the production of oxygen-derived free radicals from vascular cells.^{136, 137} Oxygen-derived free radicals scavenge and rapidly inactivate NO, thereby promoting coronary endothelial dysfunction and constriction.^{100, 102} In addition, in the hypertrophied hypertensive heart, increased extravascular myocardial compressive forces and inadequate angiogenesis contribute to the lack of normal coronary dilator responses and impairment in coronary dilatory reserve.¹⁰⁰

Hypertension also accelerates coronary atherosclerosis by causing intimal hyperplasia and hypertrophy of the vascular muscle in the media of the arterial wall.^{138, 139} In addition, the vasoconstrictors angiotensin II, endothelin, vasopressin, and serotonin, which are increased in patients with systemic hypertension, enhance the proliferation of cardiac and vascular muscle and fibroblasts and contribute to perivascular fibrosis of the coronary arterioles.^{100, 111, 132, 135} Collagen, elastin, and glycosaminoglycans also contribute to an increase in coronary vascular wall thickness.^{133, 139} The resultant increase in the vascular wall thickness and "stiffness" leads to a reduced vasodilatory capacity of the coronary vessels and an amplified vasoconstrictive response to contractile agonists.^{130, 133} As a consequence, coronary vascular resistance is significantly increased in patients with systemic hypertension.¹¹¹

Patients with hypertension can have insulin resistance, hyperinsulinemia, and impairment in insulin-induced vasodilation.¹⁴⁰ Insulin resistance contributes to an increase in LDL cholesterol, a decrease in HDL cholesterol, endothelial dysfunction, and an acceleration in coronary atherosclerosis.

As a result of endothelial dysfunction and vascular and cardiac muscle hypertrophy in patients with systemic hypertension, there is impairment in the autoregulation of coronary blood flow and abnormal coronary constrictor responses to acetylcholine. For example, acetylcholine infusion, which dilates coronary arteries in normal individuals, reduces the mean coronary artery diameter by as much as 44% in hypertensive patients.¹³⁵ Moreover, coronary blood flow reserve is depressed by as much as 41% in hypertensive patients.^{100, 111, 133} These abnormalities contribute to ventricular diastolic dysfunction and silent myocardial ischemia in patients with systemic hypertension.

Aggressive medical treatment of systemic hypertension can cause the regression of vascular and cardiac muscle hypertrophy, improve coronary endothelial function, and increase coronary flow reserve.¹⁰⁸ In this regard, research studies indicate that angiotensin-converting enzyme (ACE) inhibitors prevent stimulation of vascular muscle and platelet angiotensin II receptors.¹⁴¹ This blocks vascular muscle cell contractile function and proliferation into the arterial intima and inhibits platelet aggregation. Angiotensin II blockade

also decreases the production of oxygen-derived free radicals that would otherwise inactivate NO. In addition, ACE inhibition of kinase II inhibits bradykinin breakdown; bradykinin is a direct stimulant of NO release from the intact endothelium.¹⁴¹ Thus, ACE inhibitors can promote vasodilatory, antiproliferative, antiaggregatory, and antithrombotic effects.¹⁴¹⁻¹⁴³ Clinical trials are in progress to define precisely the role of angiotensin II-converting enzyme inhibitors and angiotensin receptor blockers in reversing endothelial dysfunction in patients with hypertension and coronary endothelial dysfunction.

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