Regulation of Coronary Blood Flow

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Abstract

The heart is uniquely responsible for providing its own blood supply through the coronary circulation. Regulation of coronary blood flow is quite complex and, after over 100 years of dedicated research, is understood to be dictated through multiple mechanisms that include extravascular compressive forces (tissue pressure), coronary perfusion pressure, myogenic, local metabolic, endothelial as well as neural and hormonal influences. While each of these determinants can have profound influence over myocardial perfusion, largely through effects on end-effector ion channels, these mechanisms collectively modulate coronary vascular resistance and act to ensure that the myocardial requirements for oxygen and substrates are adequately provided by the coronary circulation. The purpose of this series of *Comprehensive Physiology* is to highlight current knowledge regarding the physiologic regulation of coronary blood flow, with emphasis on functional anatomy and the interplay between the physical and biological determinants of myocardial oxygen delivery.

Overview

The heart is one of the first organs to which we are conceptually exposed as children. We are taught, from an early age, that the heart itself is essential to life and that each cardiac cycle (heart beat) is the source of blood pumping through our body. What is often left undescribed and unappreciated is the nature of blood flow to the heart as opposed to through the heart. Despite being continuously filled with blood throughout the entirety of one's life, blood within the chambers of the heart does not significantly contribute to the viability, maintenance and/or function of cardiac tissue in either large animals or humans. Rather, a separate and specialized circulation, the coronary circulation, provides the myocardium with oxygen and substrates to ensure normal function and viability of the heart. Owing to the limited anaerobic capacity of the heart (49, 119, 733), coronary vascular resistance is continuously regulated to deliver sufficient quantities of oxygen to meet any change in the demand of surrounding myocardial tissue. The specifics of this metabolism-perfusion matching are unique in the coronary circulation because of the continuous pumping and high

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work load of the heart. Based on the requirements for operating a constantly functioning contractile machine, the heart demonstrates the highest per gram oxygen consumption of any organ (~50–100 μL O_2/min/g) and, as such, extracts ~70% to 80% of delivered oxygen even under resting conditions (coronary venous PO_2 ~18–20 mmHg) (270,331,918), unlike skeletal muscle which utilizes only ~30% to 40% of delivered oxygen at rest (venous PO_2 ~40 mmHg) (788, 789). This high extraction percentage results in a system that is almost completely dependent on delivery of blood to the tissue as enhancements to extraction are rather limited. Therefore, for this entirely essential organ to undergo the necessary processes to remain normal and compatible with survival, coronary vascular tone must be constantly modulated to ensure adequate myocardial perfusion.

Regulation of coronary blood flow is understood to be dictated through multiple mechanisms including extravascular compressive forces (tissue pressure), coronary perfusion pressure, myogenic, local metabolic, endothelial as well as neural and hormonal influences. Together, these mechanisms govern coronary flow and act to ensure an overall balance between myocardial oxygen delivery (supply) and metabolism (demand) (Fig. 1) (16, 270, 331, 918, 919, 922). This point is evident in examination of coronary responses to a variety of physiologic perturbations including alterations in metabolism, perfusion pressure, arterial oxygen content, and/or a transient coronary artery occlusion. These well-established phenomena clearly illustrate the tight coupling between coronary blood flow and myocardial oxygen consumption (MVO_2) in response to exercise (i.e., functional hyperemia, Fig. 2A) (94), the relative maintenance of coronary flow over a wide range of perfusion pressures (i.e., pressure-flow autoregulation, Fig. 2B) (96), the marked increase in coronary flow in response to hypoxemia (458,670,958) and anemia (323,905) (Fig. 2C), and the repayment of "oxygen-debt" incurred following the interruption of myocardial oxygen delivery (i.e., reactive hyperemia, Fig. 2D) (97).

The purpose of this *Comprehensive Physiology* article is to highlight current knowledge regarding the physiologic regulation of myocardial perfusion, with emphasis on functional anatomy, extravascular compression and transmural flow distribution, and the interplay of mechanisms known to influence the regulation of coronary blood flow. For a historic review of developments in our understanding of coronary physiology, readers are encouraged to study the prior reviews of Gregg (396), Berne (87), Feigl (331), Chilian and Marcus (167), Hoffman and Spaan (481), Westerhof (967), Duncker and Bache (270), Beyer and Gutterman (100), Tomanek (913), and Tune (918).

Coronary Anatomy

The first description of the blood vessels of the heart is credited to the French anatomist Raymond de Vieussens who published *Nouvelles decouvertes sur le Coeur* ("New discoveries of the heart") in 1706. His observations were expanded in 1715 in his publication of *Treatise of the Heart* where he described not only the coronary vessels, but the pericardium and muscle fibers of the heart (627). This work has been heralded as one of the most important discussions on the anatomic basis of heart disease. These initial descriptions have been followed by over 300 years of subsequent research that has led to a great deal of understanding regarding the anatomy of the coronary circulation and the physiologic

regulation of this critically important vascular bed. To appreciate how blood flow to the myocardium is regulated, it is essential to appreciate the basic anatomical arrangement of the coronary vascular tree (76).

Coronary arterial vascular structure

Detailed descriptions of the anatomical basis of blood supply to the myocardium can be found in early works by Gross (408), Wearn (962, 963), and Belt (76). They classically describe that subsequent to the first main branch of the aorta, the human heart gives rise to two main coronary arteries via coronary ostia located within the sinuses of Valsalva. The left posterior sinus is the origin of the left main coronary artery which in turn is the progenitor to the left anterior descending (LAD) and circumflex coronary arteries. Between these two major, epicardial coronary arteries, the majority of left ventricular blood delivery occurs. Typically, the circumflex artery tracks along a horizontal plane to the left, in the anterior atrioventricular groove, giving rise to obtuse marginal branches along its length. This main coronary artery and its associated marginals are responsible for delivery of blood to the left atrium as well as the lateral wall of the left ventricle. The sister to the circumflex artery is the LAD. Contrary to the horizontal path of the circumflex, the LAD runs vertically from base to apex of the heart along the anterior interventricular groove. Along its length, the LAD gives rise to numerous diagonals as well as septal branches which supply the anterior surface of the left ventricle as well as the anterior portion of the left bundle branch, the mid-portion of the right bundle branch, and the anterior septal myocardium with blood (Fig. 3) (918).

The right ventricle predominately receives blood independent of either the LAD or circumflex arteries. Blood delivery to the right heart is instead provided by blood flow originating in the anterior aortic sinus and emerging on the anterior surface of the heart in the form of the right coronary artery (RCA). The RCA follows a horizontal course along the atrioventricular groove, similar to the circumflex though directionally opposite. Along its length, the RCA gives rise to numerous acute marginal branches that are responsible for providing delivery of blood to the right atrium and right ventricular free wall (76, 396, 398).

An additional epicardial coronary artery, the posterior descending coronary artery (PDA), is a highly conserved coronary architectural structure in all humans, but its origin is somewhat variable. In instances where the RCA is long enough to cross the acute margin of the heart, the PDA emerges as a distinct vascular flow source manifested as a ~90° turn into the posterior atrioventricular groove. This is true of ~90% of the human population. In the remaining 10% of the population, the origin of the PDA is the circumflex coronary artery. Whether the PDA derives from the RCA (right) or circumflex (left) establishes whether a heart is so called right dominant or left dominant (respectively). Regardless of the PDA's source, the vessel itself traces a path perpendicular to either the RCA or circumflex, along the posterior interventricular groove supplying blood to the surrounding myocardium from its origin to the apex. Septal branches from the PDA descend and supply the posterior third of the interventricular septum as well as the atrioventricular node.

Overall, perfusion of the heart is typically strictly limited to the distribution of the feed vessel supplying blood to that region of the myocardium. This point is clearly illustrated by

intracoronary administration of dye which demonstrates a sharp delineation between perfusion territories (see Fig. 5). However, there is evidence for a microvascular network of anastomoses along the interface of coronary arterial perfusion territories; that is, redundantly supplied border zone that aids in perfusion of the outer boundaries if flow through the alternate artery is impaired (182, 183, 771).

The heart itself is unique in that its blood is supplied in an outside-in fashion. In other words, blood is delivered via epicardial coronary arteries that further divide and penetrate into the myocardium. Elegant visualization and how disease can influence this distinctive arrangement was provided by the work of Estes et al. in 1966 (Fig. 4) (321). It is important to consider that this anatomical arrangement assigns an obligatory role of these large, superficial epicardial coronary arteries to perfuse all layers of the myocardium. The superficial divisions of the epicardial coronaries diminish in diameter as they course across the surface of the heart like a crown; which actually gives rise to the term "coronary" that is derived from the Latin *coronarius*, meaning "of a crown." As the internal diameter reaches ~1 to 3 mm, these coronaries feed tributaries that are oriented perpendicular to the surface of the heart (321). Descending tributaries (~400–1500 μm in diameter) continue transmurally through the outer epicardium and into the inner endocardium. Coronary arteries that exceed an ~0.5 mm thickness receive blood supply from the vasa vasorum externa, which is a specialized microvasculature within the adventitia. Recent data support a link between the expansion of the vasa vasorum with neointimal formation and the progression of atherosclerotic disease (179,596,597,695).

Consistent with other vascular beds, the major site of vascular resistance (and therefore flow control) exists in microvascular beds of vessels with individual diameters less than 100 μm (168). Myocardial arterioles ultimately supply myocardial capillary beds which constitute an extremely dense network (~3000–4000 capillaries/mm^2) (962) wherein intercapillary distances are less than 20 μm (62,193,455,909) (Fig. 4). Detailed morphometric analyses of the coronary vasculature have been elegantly outlined in the prior work of Bassingthwaighte (61,62,142,414,904) and Kassab and Fung (543, 544, 546–549, 551). Unlike other highly metabolic tissues such as skeletal muscle, which show capillary densities of ~600 capillaries/mm^2 (828), the contribution of capillary recruitment to alterations in metabolic demand is less well established in the heart. The prevailing belief is that, due to the continuously high metabolic demand of the heart, very little capillary reserve exists thereby making recruitment contributions secondary to other mechanisms in matching metabolic demand with nutrient/oxygen supply. However, data from Honig and colleagues suggest that up to 25% of capillaries are not perfused in normal rat heart and that recruitment of these capillaries could help maintain functional intercapillary diffusion distances relatively constant in response to stress or disease states such as hypertrophy (456, 457, 488, 489).

Coronary venous structure

Subsequent to nutrient/gas exchange, the coronary vasculature must return deoxygenated, nutrient poor blood back to the systemic circulation. This is accomplished via a venous vascular network that parallels epicardial coronary arteries (see Fig. 3) (869). In normal anatomy, anterior surface drainage is facilitated by the interventricular vein which is

immediately adjacent to the LAD in the interventricular groove. Virtually all drainage from the anterior interventricular vein is derived from the LAD perfusion territory (711, 954). This drainage system continues into the great cardiac vein which courses along the anterior atrioventricular groove parallel to the circumflex artery. Both major veins drain into the coronary sinus located in the posterior atrioventricular groove. Accordingly, venous blood within the coronary sinus is supplied by both the anterior (LAD) and posterior (circumflex) perfusion territories (196,711,796,954). Approximately 55% of the coronary arterial blood supply is returned to the sinus via these two anterior sources. Additionally, ~35% of cardiac venous drainage returns directly into the right atrium by means of the anterior cardiac veins. The former system accomplishes the majority of return for the left ventricle, whereas the latter system facilitates venous return for the right ventricle. This leaves a 10% deficit in return which is accomplished by the Thebesian veins (963). Initially identified in 1706 by Vieussens, Thebesian veins were largely overlooked for centuries to such an extent that often, textbooks would illustrate the inner surfaces of cardiac chambers as completely avascular. However, studies by Wearn in the 1920s and 1930s determined that Thebesian openings existed in both atrial and ventricular chambers although they were significantly more numerous in the ventricles (963). Since that time, these vessels have been shown to play a minor role in coronary venous return by allowing for venous drainage directly into the left ventricular cavity. Anatomical evidence for the presence of coronary venous valves has also been documented and appears to vary by age, gender, and species (11, 12, 741). While these valves could possibly hinder interventional access to the coronary venous system (11), their functional relevance appears to be modest as it is entirely possible to retroperfuse the heart via the coronary venous system (550, 724).

Coronary collaterals

When considering coronary anatomy, it is important to acknowledge the presence of innate collateral vessels (natural bypasses) which provide anastomotic connections between arteries without an intervening capillary bed (Fig. 5) (574, 835). These vessels provide an alternate path for oxygen-rich blood between regional myocardial perfusion territories, typically to ischemic myocardium secondary to coronary stenosis. Such anastomoses within the coronary circulation were described as early as 1670s by Lower in both normal and pathologic hearts (838). Work by Schlesinger and others in the 1930s and 1940s revealed the prominent development of these connections in the presence of obstructive coronary disease (105,827,838). Detailed studies by Baroldi et al. in the 1950s followed by other later investigations have nicely demonstrated the presence at birth of mostly corkscrew-shaped collaterals in normal human hearts with lengths ranging from 1 to 2 cm up to 4 to 5 cm and luminal diameters of 20 to 350 μm (54–56,104,394,837,937,938). Two types of collateral vessels have been described as either connecting branches of the same coronary vessels (intracoronary collaterals) or connections between branches of different coronary vessels (intercoronary collaterals). The presence of intra-coronary collaterals is approximately five times more frequent, have median diameters of ~95 μm, with the density of connections highest in the subendocardium (937). Conventionally, functional collateral vessels stem from outward remodeling of preexisting connections (arteriogenesis) (359–362, 835, 938, 939); however, there is also evidence to support the de novo formation of vessels (angiogenesis) (175,431,649–652,772,932). Importantly, the presence of well-developed collaterals exerts

protective effects on perfusion, electro-physiologic abnormalities, contractile function, degree of infarction, and overall mortality (42, 429, 658–660). For more detailed information regarding the coronary collateral circulation, readers are referred to recent reviews by Duncker and Bache (270), Schaper et al. (835, 836, 939), Teuissen et al. (906), Chilian et al. (176,322,1012), Spaan and Siebes (874,931), Zimarino et al. (1022), and Stoller and Seiler (887).

Extravascular Compression and Transmural Flow Distribution

Coronary flow patterns

Few physiologic processes typify the concept of bulk flow better than blood flow. Bulk flow, defined as movement resulting from a pressure gradient, can be mathematically described in the vascular system as a correlate to Ohm's Law ($\text{Flow} = \frac{\Delta \text{Pressure}}{\text{Resistance}}$). In other words, flow is directly proportional to the magnitude of the pressure gradient (arterial – venous) across the vascular tree and inversely proportional to the overall resistance of the vascular network. Keep in mind that pressure itself is the difference between transmural expansive pressures forcing outward against the vascular wall and compressive tissue pressures counteracting that expansion. In the majority of organs, the compressive tissue force is constant and therefore is considered to make only a minimal yet consistent contribution to the pressure gradient. However, the periodicity of contractions in the heart and tremendous compressive forces of the myocardium result in a more complex pattern of flow in the coronary vascular system.

Coronary vascular flow is best described as phasic flow in that the compressive forces of systole counteract the driving force for flow in the coronary circulation and, therefore, the majority of anterograde blood flow to the left ventricle occurs during diastole (Fig. 6). Alternatively, much of the forward flow during systole is used to fill the upstream coronary compliance, while flow through coronary capillaries is relatively constant throughout the cardiac cycle (331,481,967). Indeed, these myocardial compressive forces are so great during systole that the coronary circulation can undergo transient periods of retrograde blood flow (see example tracing in Fig. 27). This effect was first documented in independent studies by Anrep (13) and Gregg (400) in the early 1930s. Subsequent studies of the same era attributed this phasic flow pattern to obstruction of the coronary ostia during systole by the opening of the aortic valve (738, 765). However, this hypothesis has been extensively discredited by anatomical studies highlighting that the ostia are located too far from the aortic valve for leaflets to serve as an obstruction. Further refutation can be found in phasic flow patterns documented in countless *in vivo* cannulated artery preparations wherein blood is supplied via a bypass circuit thereby removing any contribution of the aortic valve to flow behavior (331,863). Evidence of an alternative origin to phasic flow patterns additionally exists in the physiology of the heart itself in that right ventricular coronary blood flow is not significantly diminished during vascular contraction but rather shows a pattern of flow that is elevated during periods of high aortic pressure (i.e., systole) and diminished during periods of lower aortic pressure (i.e., diastole) (Fig. 6) (395, 628). This behavior is consistent with the nature of the ventricular myocardial layers themselves (612, 794, 889–891). The much thicker and more contractile left ventricle generates far greater extravascular compressive

force than does the right ventricle (44, 45, 481, 967), resulting in an inversion of flow patterns between right and left sides of the heart. Counterintuitively, the phasic nature of left ventricular blood flow does not result in lower absolute flow values when compared to the right side of the heart. In a typical adult heart, baseline/resting left coronary blood flow typically ranges between ~0.5 and 1.0 mL/min/g (270, 331, 918, 919). In contrast, right ventricular blood flow averages only ~0.3 to 0.6 mL/min/g (441, 697, 1006, 1026). This phenomenon is explained by underlying differences in the rate of MVO_2 (i.e., oxidative metabolism) between the left ventricle (~50–100 μL O_2/min/g) versus right ventricle (~30–50 μL O_2/min/g) (270,276,387,918,919) and highlights how exquisitely dependent myocardial perfusion is on myocardial metabolism.

Myocardial-coronary interaction

As previously indicated, the extravascular compressive forces of the heart can have a significant impact on phasic and bulk flows within the coronary circulation (453,545,673,869,870). The consequence of forceful ventricular contraction was first reported by Scaramucci in 1695 when he observed that the heart could limit its own blood supply through systolic myocardial compressive forces (834). Based on this initial observation and numerous validating studies, it has been established that coronary venous pressures are not an accurate factor to consider when determining the overall driving force for flow (73,265,331,481,967). Whereas in other, non-compressible tissues, the arterial to venous difference holds as the determinants for the pressure gradient (i.e., for Ohm's law), intramyocardial tissue pressures during systole must be accounted for when assessing the pressure gradient across the coronary vascular tree (259, 263–265). This phenomenon was given a metaphorical moniker, a "vascular waterfall," by Downey and Kirk in 1975 who stated that flow is dependent on the magnitude of the difference between arterial pressure and tissue pressure; that is, flow is determined by the driving force (arterial pressure) and the highest downstream force that the driving force must overcome (tissue pressure) (265). Thus, in principle small coronary arteries behave much like that of a Starling resistor (570) wherein chamber pressure limits flow by narrowing a collapsible tube (192, 485, 631, 632, 973). The "waterfall" metaphor relates to the notion that flow over the falls is determined by the elevation between the origin of the waterfall (tissue pressure) and the highest point upstream (arterial pressure); that is, the overall height of the waterfall (i.e., arterial-venous pressure gradient) does not actually affect the absolute flow of the waterfall (Fig. 7) (253, 260, 265, 318, 968, 1011).

An extension of the vascular waterfall concept is the "intramyocardial pump." First proposed by Spaan and colleagues, the intramyocardial pumping action of the heart explains the phenomenon of retrograde coronary arterial flow and concurrent increases in venous outflow observed during systole (871–873). Described in brief, the heart has a large microvascular compliance that results in high intravascular blood volumes which reportedly range from ~0.10 to ~0.25 mL/min/100 g in beating or arrested hearts (174, 481, 532, 533, 951). Intramyocardial blood volume of the right ventricle has been reported to average ~0.07 mL/min/100 g (481). Systolic compression results in bidirectional extrusion of this volume and accounts for increased venous outflow (anterograde) as well as retrograde arterial flow (Fig. 7) (79, 331, 399, 400, 481). Additional hypotheses to explain the coronary effects of

myocardial contraction include recognition of variations in myocardial stiffness during the cardiac cycle (varying elastance model) (583–585), increases in cardiomyocyte diameter during isotonic cardiac contractions (muscle shortening and thickening model) (977), as well as changes in the shape of vascular cross-sections, branching angles, vessel tortuosity (vascular deformation model) (342, 770). As with any physiologic system, it is likely that the true origins and regulation of phasic coronary flow are the result of multiple processes which can only be truly modeled by integrating multiple hypotheses. Indeed, recent data from Kassab and Lanir support that the physical basis of intramyocardial tissue pressure and the pulsatile nature of coronary blood flow is best described through the combined effects of cavity-induced extracellular pressure and shortening-induced intramyocyte pressure (5, 6, 545).

These findings establish the inextricable link between myocardial compressive forces (extravascular compression of intramyocardial compliance) and coronary blood flow throughout the cardiac cycle. The nature of the physiologic interaction between myocardial contraction and the phasic nature of coronary flow is further complicated by studies in the early 1950s by Rushmer who documented a disparity in compressive forces across the wall of the left ventricle (813). As such it is now well accepted that the greatest degree of vascular compression is found in endocardial layers, with little if any compressive force at the level of the epicardium (17, 20, 44, 561, 677). The phenotypic outcome of this disparity, with regard to blood flow, is that endocardial tissue receives little if any flow during systole as the compressive forces are of sufficient magnitude to exceed the driving force of arterial pressure (264, 561, 994). Thus, the endocardium only truly receives flow during diastole and is therefore extremely dependent on an adequate diastolic filling period to maintain sufficient coronary flow. By contrast, the lack of compressive forces at the epicardial layer allow for perfusion throughout the entire cardiac cycle. Therefore, there is a linear decrease in dependence on diastolic time fraction for the maintenance of coronary flow in the endocardial to epicardial direction. This relationship is schematically depicted in Figure 8 (72). Taken together, these factors dictate that the left ventricle receives ~80% of its blood flow during the diastolic phase of the cardiac cycle (270, 331).

Recognition of the physiologic impact of cardiac contraction on coronary blood flow led to much research and debate regarding the most appropriate means in which to determine the coronary perfusion pressure gradient during diastole. These studies have largely centered around three potential estimates which include: (i) coronary arterial pressure minus intraventricular cavity pressure (148, 200, 202, 203, 257, 308, 781); (ii) coronary arterial pressure minus intramyocardial tissue pressure (75,265,598,742,781); and (iii) coronary arterial pressure minus zero flow pressure (Pzf: systemic pressure at which coronary blood flow ceases during prolonged diastole) (73, 74, 135, 136, 300, 759, 857). Given that intramyocardial tissue pressure is greater in the subendocardium than in the subepicardium (17,20,44,561,677), diastolic arterial pressure minus diastolic intraventricular pressure is only a reasonable estimate of coronary perfusion pressure for the innermost subendocardial layers of the left ventricle (331,481). In 1983, Feigl proposed that the effective diastolic coronary perfusion pressure is best estimated as the smallest gradient between coronary arterial pressure minus intramyocardial tissue pressure, or coronary venous pressure, or

diastolic Pzf (331). Such estimates also apply to the right coronary circulation as well (74, 481).

Transmural flow distribution

Based on higher compressive forces and metabolic requirements of the left ventricular endocardium, it not surprising that a gradient exists for coronary blood flow across the wall of the heart. However, the magnitude of that gradient is relatively modest with reported ratios of endocardial to epicardial (ENDO/EPI) blood flow typically ranging from 1.1 to 1.5 (30, 37, 39, 48, 53, 121, 122, 251, 274, 587, 606, 717, 739, 785, 824,1011). This may seem counterintuitive as the epicardium does not experience the periodic zero flow condition brought on by systolic compression. However, a combination of higher endocardial microvascular density (261,993) and lower endocardial microvascular resistance (165, 173) culminates in slightly higher flows in the endocardium versus epicardium. Studies by the Chilian laboratory highlight that the magnitude of the difference between endocardial and epicardial resistances can be quite extreme. In seminal work to interrogate this question, Chilian demonstrated that at a given arterial pressure in maximally dilated hearts, venular pressures in the endocardium were significantly higher than venular in the epicardium. Thus, the pressure drop (i.e., resistance) across the endocardial microcirculation is markedly lower than that of the epicardial microcirculation (165). These findings support that differences in transmural flow are related to differences in the structural composition of endocardial versus epicardial vessels.

The most direct evidence for a role of extravascular compressive forces in the regulation of transmural flow can be found when comparing studies of maximally dilated beating hearts against maximally dilated arrested hearts. In the setting of the former, ENDO/EPI ratios have been consistently reported to be ~1.0 (261, 274, 787), whereas under conditions of cardiac arrest, where compressive force remains constant, ENDO/EPI ratios are reported to range from 1.4 to 1.6 (257, 261, 992, 993). These disparate findings highlight the interplay between a microvascular structural phenomenon designed to allow for preferential endocardial flow and the periodic extravascular compressive forces of the myocardium to counteract this preferential endocardial flow. The resultant effect of these physiologic influences being the relative normalization of endocardial to epicardial perfusion.

It is important to recognize that the distribution of transmural blood flow is also significantly influenced by the duration of diastole. This effect is clearly evidenced by studies performed by Bache and Cobb who showed that during periods of maximal coronary vasodilation, there is a linear reduction in the ENDO/EPI ratio from 1.0 at 100 beats/min to 0.4 at 250 beats/min (i.e., endocardial flow is inhibited by reductions in diastolic filling time) (26). Other investigators have also corroborated this effect (257, 261, 266). Additional studies also indicate that transmural blood flow is significantly influenced by coronary perfusion pressure, i.e. by a coronary artery stenosis which diminishes distal driving pressures. In 1977, Guyton et al. demonstrated that endocardial blood flow begins to progressively fall as coronary pressure falls below 70 mmHg, whereas epicardial blood flow does not decline until pressures are reduced below 40 mmHg (423). The pressure at which endocardial flow begins to decrease is even higher during exercise, which augments MVO_2, heart rate, and

myocardial tissue pressure (47). Despite this recognition, limitations in endocardial flow (i.e., low ENDO/EPI ratios) are not evident in normal hearts under physiologic conditions across a wide range of heart rates and MVO_2 in either the left (53, 122, 606, 642, 752, 825) or right ventricle (39, 48, 606, 739, 1024). Therefore, under normal physiologic conditions the coronary circulation is able to integrate compressive forces and microvascular resistances in a manner that allows for adequate delivery of substrates to all myocardial layers.

Myogenic Control and Pressure-Flow Autoregulation

Myogenic control of coronary vascular resistance

Originally described by Bayliss in 1902, the vascular myogenic response is defined as the ability of vascular smooth muscle to constrict in response to an increase in transmural force (i.e., perfusion pressure) (69). By extension, a decrease in intravascular pressure is a followed by a transient diameter collapse followed by dilation (228). Teleologically, this behavior is believed to represent the efforts of the vessel to minimize wall stress; a point supported mathematically by the law of Laplace (wall stress $\propto \frac{\text{Pressure} \times \text{radius}}{\text{wall thickness}}$). Further, this behavior of small arteries and arterioles leads to the maintenance of a certain degree of active force at normal intravascular pressures, that is, basal or myogenic "tone," which allows microvascular resistance to be modulated in either direction by the actions of both vasodilators and vasoconstrictors (224,349,662). The myogenic response is thought to reflect an increase in the activation state of smooth muscle, as opposed to the well-documented length-tension relationship common to essentially all types of mammalian muscle (225). Although vascular smooth muscle is not organized into defined sarcomeres (542), the relationship between active force and optimal length (preload) still holds in the vasculature (434).

While myogenic behavior in the coronary circulation is assumed *in vivo* (171, 541, 783), the majority of evidence for the myogenic phenomena comes from studies in isolated and pressurized microvascular preparations (589–591, 593, 674), where coronary arterioles have been demonstrated to develop an exceptional degree of myogenic tone. This methodology is advantageous in minimizing the number of potential input variables affecting the system, yet there is a notable absence of integrated behaviors as a result. Application of isolated vessel techniques has demonstrated the myogenic nature of arteriolar constriction in that microvascular diameters decrease as intraluminal pressure is increased in incremental steps from ~15 through 100 mmHg in both endothelium-intact and denuded vessels (589–591,593). A classic example of a pressure-induced myogenic response is observed in the tracing published by Kuo et al. in Figure 9 in which a step increase in intraluminal pressure results in an initial increase in arteriolar diameter that is followed by a steady decline to a new steady-state diameter (590). This myogenic constriction is lessened by the onset of flow via a pressure gradient across the vessel. Average arteriolar responses to intraluminal pressures in vessels with and without flow are shown in Figure 9.

Interestingly, myogenic responsiveness is not uniform throughout the coronary vasculature tree as responses have been shown to be the greatest in subepicardial arterioles <100 μm in

diameter, with more modest responses in subendocardial arterioles and small arteries ~400 μm in diameter (590). Based on this relationship between vessel diameter and magnitude of myogenic response, the myogenic response is thought to play a significant role in maintaining basal vascular tone in the resistance vasculature. It is thus within the presence of this "background" vasomotor tone, that nonmyogenic factors bidirectionally influence the regulation of coronary flow as necessary to balance myocardial oxygen delivery with myocardial oxidative metabolism (Fig. 2A). Mechanisms of the coronary myogenic response are discussed in Section "Ion Channels as End Effectors."

Coronary pressure-flow autoregulation

Although the overall physiologic role of the myogenic response remains to be clearly defined, one physiologic phenomenon that has been ascribed to intrinsic myogenic responsiveness is coronary pressure-flow autoregulation (see Fig. 2B) (194, 195, 229, 235, 505, 519, 522, 873). Autoregulatory behavior is characterized as the ability of a vascular bed to maintain blood flow relatively constant across a wide range of perfusion pressures. In other words, this regulatory mechanism acts to preserve myocardial perfusion despite alterations in driving pressure (331, 514, 515). While all tissues have the capacity for autoregulation, to various degrees, the coronary vasculature [much like the cerebral and renal circulation (303, 515, 807)] displays exquisite autoregulatory capacity (84, 201, 252–254, 333, 690, 853). Coronary pressure-flow autoregulation is characterized by relatively constant coronary blood flow with changes in pressure, which is accomplished by comparative changes in microvascular resistance. As such, reductions in perfusion pressure diminish coronary vascular resistance, whereas increases in perfusion pressure elevate coronary vascular resistance (Fig. 10). Accordingly, the range of the autoregulatory response is set by the physiologic limits of microvascular responses to increases in perfusion pressure (resistance plateaus at ~120 mmHg) and decreases in perfusion pressure (resistance plateaus at ~60 mmHg). However, the lower limits of the autoregulatory range have been reported to be as low as ~40 mmHg in conscious instrumented dogs (146). Regardless of the threshold value, it should be recognized that once perfusion pressure is outside of this "window," the coronary vasculature becomes completely dependent on upstream driving pressure (i.e., arterioles respond passively to changes in pressure). Coronary vasodilation in response to reductions in perfusion pressure (e.g., ischemia induced by coronary stenosis) is a critical mechanism that acts to mitigate myocardial injury and infarction (147, 331, 367). As such, coronary vasodilator capacity informs clinical decision making regarding the severity of the stenosis, with indices such as coronary flow reserve (392, 480, 931), fractional flow reserve (762, 974), and index of microcirculatory resistance (1007) typically decreasing as the severity of luminal narrowing increases (513).

Initial characterization of coronary autoregulatory behavior was documented in the 1950s following the development of the cannulated, extracorporeal perfusion circuit, which allowed for coronary pressure to be held constant via a roller pump system (84). Definitive studies of coronary pressure-flow autoregulation were performed by Berne, who demonstrated that this phenomenon occurs rapidly (seconds) in a highly precise manner (84) and Mosher et al. who demonstrated the overall level of pressure-flow autoregulation is directly dependent on the underlying MVO$_2$ (690). Later studies by Guyton et al. established

that although autoregulatory behavior exists transmurally across the left ventricle, the range is significantly lower in the endocardial versus epicardial microcirculation (423); an effect corroborated by numerous additional studies (106, 127, 144, 407, 423, 808, 1006). Autoregulation of right coronary blood flow has also been observed by a number of laboratories; however, the overall autoregulatory capacity is significantly lower in the right versus left coronary circulation (101, 200, 369, 702, 929, 1005, 1006). In particular, direct comparison of pressure-flow autoregulation in conscious, non-cannulated preparations demonstrate that right coronary blood flow decreases ~35% when perfusion pressure is lowered from 80 to 40 mmHg (101) while essentially no change in left coronary blood flow was noted over this same pressure range (146).

Mechanisms of coronary autoregulation

Although the coronary pressure-flow autoregulatory response is directionally consistent with a myogenic mechanism, definitive experiments to establish the contribution of myogenic responsiveness to pressure-flow autoregulation *in vivo* are confounded by numerous other pathways (e.g., metabolic and endothelial) with the potential to influence coronary microvascular resistance in response to changes in perfusion pressure. While modeling studies by Spaan and colleagues indicate that a myogenic mechanism is sufficient to achieve coronary pressure-flow autoregulation (194, 195, 873), there is also evidence to support a role for a metabolic as well as an endothelial-dependent component of this response. In particular, support for a metabolic mechanism comes from the observation that coronary autoregulation adjusts to the level of myocardial metabolism (690). Further studies documenting that effective coronary autoregulation is closely coupled to the underlying coronary venous PO_2 (balance between flow and metabolism), as autoregulation is only observed when coronary venous PO_2 is <32 mmHg (255). However, an alternative explanation for these data is simply that effective pressure-flow autoregulation is not observed in artificially dilated preparations; that is, is dependent on underlying myogenic tone. This contention is supported by the loss of autoregulation following the administration of vasodilator agents (23, 252, 459) or following coronary vasodilation secondary to the inhibition of pathways that contribute to the maintenance of baseline vasomotor tone [e.g., L-type Ca^{2+} channels (96)]. Reports that increases in coronary perfusion pressure augment MVO_2 independent of changes in coronary blood flow [i.e., Gregg Effect (18,326,397,530,562,655,801,1005)] have been shown to be quite modest, and if observed, to be mediated by changes in coronary vascular volume in poorly autoregulating preparations (43,106,216,217,260,839). Data from Broten and Feigl indicate that myocardial oxygen and carbon dioxide levels synergistically influence coronary responses at perfusion pressures ranging from 80 to 160 mmHg (123,125). However, efforts to determine specific metabolites that contribute to the coronary autoregulatory response have failed to show any role for proposed putative dilators such as adenosine (256, 285, 438, 577) or other purinergic (adenosine triphosphate, ATP and adenosine diphosphate, ADP) factors (77) (see Section "Metabolic Control of Coronary Blood Flow").

In examining the contribution of coronary endothelium to pressure-flow autoregulation in conscious instrumented dogs, Smith and Canty determined that inhibition of nitric oxide synthase did not influence coronary blood flow within the autoregulatory range, however it

did significantly lower the limits of the autoregulatory response; that is, significantly increased the pressure at which coronary flow becomes pressure dependent from 45 ± 3 to 61 ± 2 mmHg (865) (see Section Endothelial-Dependent Control). These data are consistent with other studies which found that blockade of nitric oxide production moderately reduces (~15%-20%) coronary vasodilation in response to a transient coronary occlusion (i.e., reactive hyperemia) (7, 246, 497). Yada et al. also reported no effect of nitric oxide and H_2O_2 blockade on coronary flow responses to changes in perfusion pressure within the autoregulatory range (998). Data from the Chilian laboratory indicate that these mechanisms collectively modulate coronary responses to changes in perfusion pressure within specific microdomains of the vascular tree in a heterogeneous manner (235,589–593,692). They propose that pressure-mediated responses of the coronary circulation are the manifestation of metabolic (at the arteriolar level) and endothelial (at the small artery level) responses that are reciprocally balanced by a myogenic mechanism within the resistance vasculature (235). This hypothesis is supported by studies in isolated vessels demonstrating that flow-induced dilation significantly abrogates myogenic constriction across a wide range of intraluminal pressures (590). Such a hierarchy has physiologic benefits in that the location and promotion of endothelial-dependent dilation in larger upstream arterioles (>100 μm in diameter) would act to minimize shear stress and preserve vasodilator (metabolic) reserve in smaller downstream arterioles (<100 μm) (520,524,590,592,593,692). Aschematic diagram (Fig. 11) outlines this proposed heterogeneous regulation of coronary vascular resistance in which coronary reserve is locally established predominantly via local metabolic mechanisms and reciprocally balanced by upstream myogenic and flow-sensitive vascular domains (225,692). The interaction of these influences along with extravascular compressive forces and neural input must also be recognized. Convergence of these mechanisms on coronary ion channels is discussed at length below (see Section Ion Channels as End Effectors).

Metabolic Control of Coronary Blood Flow

Balance between coronary blood flow and myocardial metabolism

Metabolic regulation of coronary blood flow relates to the physiologic necessity that, in a highly metabolic tissue such as the heart, it is essential that mechanisms exist to assure that changes in myocardial metabolism (demand) are balanced/matched by concordant and proportional changes in myocardial oxygen delivery (supply) (Fig. 1) (16, 270, 331, 918, 919, 922). This fundamental concept has been recognized for centuries as the Scottish surgeon John Hunter is credited with recognizing that "blood goes where it is needed" in his posthumously published work, *A Treatise on the Blood, Inflammation and Gun-shot Wounds* (published circa 1794). To understand the determinants of the balance between coronary blood flow and myocardial metabolism, one does not have to look past the application of Adolf Fick's equation which was advanced in 1870 and clearly demonstrates that under normal physiologic conditions (assuming myocardial oxygen delivery is not limited) MVO_2 is the product of coronary blood flow and the arterial-venous difference in oxygen content (850). Given that the left ventricle extracts ~70% to 80% of the oxygen delivered in the arterial blood under baseline/resting conditions, it is quite apparent that increases in MVO_2 must be primarily balanced by increases in coronary blood flow(87,119,331). The tight coupling and linear dependence between coronary blood flow

and MVO_2 are illustrated in Figure 12A. The proximity of this normal relationship to the physiologic maximum of 100% oxygen extraction clearly demonstrates how predominantly dependent the left ventricle is on changes in coronary blood flow to ensure adequate oxygen delivery and thus the maintenance of normal cardiac function and output.

Precisely "why" the left ventricle operates within this limited constraint remains a mystery. However, it is important to understand that myocardial oxygen supply/demand balance of the right ventricle is quite different in that its normal resting MVO_2 (30–50 μL O_2/min/g) and coronary blood flow (0.3–0.6 mL/min/g) are lower, which correspond with an overall reduction in myocardial oxygen extraction (~45%; right coronary venous PO_2 ~30 mmHg) (441, 1024, 1025). Seminal work by H. F. Downey and colleagues demonstrated that initial increases in right ventricular MVO_2 are first met by increases in oxygen extraction with little change in coronary flow; that is until venous PO_2 becomes equivalent to that of the left ventricle (i.e., venous PO_2 ~18–20 mmHg) (Fig. 13A) (441, 919, 1025). Assuming that values of coronary venous PO_2 reflect levels of myocardial tissue PO_2 (469, 919), these findings collectively support that mechanisms to invoke metabolic coronary vasodilation are progressively activated as myocardial tissue PO_2 falls below a critical threshold value. The physiologic relevance of this relationship is also supported by the essential observations that pronounced reductions in coronary microvascular resistance are also observed in response to reductions in perfusion pressure (84, 201, 252–254, 333, 690, 853), arterial PO_2 [i.e., hypoxemia; (2,22,89,205,262,376,458,608,645,670,671,708,767, 849, 917, 940, 958)], arterial oxygen content [i.e., anemia; (59, 102, 120, 204, 206–210, 323, 372, 377, 482, 486, 509, 691, 905, 934, 935, 947, 957, 976)], and overt myocardial ischemia (27–29,33,36,97,110,189,246,497,498,730–732) (see Fig. 2). Nevertheless, data from studies of exercise-induced increases in MVO_2 in swine [which display little change in coronary venous PO_2 (270)] and hemodilution-induced anemia (normal arterial PO_2 with progressive increases in coronary venous PO_2 [934, 935]) clearly demonstrate that reductions in tissue oxygen tension are not required for robust coronary vasodilation (Fig. 13B). In other words, other "oxygen sensors" must exist and act to ensure myocardial oxygen delivery is sufficient to meet myocardial requirements for oxidative phosphorylation. Other proposed oxygen sensing mechanisms include erythrocytes (hemoglobin oxygen saturation) (309, 311, 387, 388), endothelium and/or vascular smooth muscle cells (507, 985). Despite over 50 years of extensive research, precisely how coronary vascular resistance is so tightly coupled with myocardial metabolism remains one of (if not) the central questions of coronary physiologists to this day.

To understand potential mechanisms responsible for the balance between coronary blood flow and MVO_2, it is essential to appreciate how inhibition of metabolic vasodilation would influence this highly constrained relationship. First, it is apparent from the relationship between coronary blood flow and MVO_2 shown in Figure 12A, that any interruption of the coronary response to increases in metabolism must occur between the normal and the maximal physiologic response of 100% oxygen extraction. Second, given the limited myocardial oxygen extraction reserve, reductions in metabolic coronary vasodilation will not only diminish coronary blood flow, but will also decrease MVO_2 in relative proportion to the overall reduction in myocardial oxygen delivery. Third, if metabolic coronary vasodilation is completely inhibited experimentally, MVO_2 would only increase ~20% to 30% (depending

on the degree of baseline extraction reserve). Taken together, these physiologic confines and consequences significantly complicate interpretation of alterations in the balance between coronary blood flow and myocardial metabolism.

An alternate means in which to assess myocardial oxygen supply/demand balance was proposed by Heyndrickx et al. in 1982 (469). They proposed that changes in coronary venous PO_2 relative to MVO_2 provide an accurate and more sensitive index of the overall balance between myocardial oxygen delivery and metabolism. Data from Berwick et al. are used to illustrate how changes in the balance between coronary blood flow and myocardial metabolism affect the relationship of both coronary blood flow(Fig. 12A) and coronary venous PO_2 (Fig. 12B) relative to exercise-induced increases in MVO_2 in swine (94). As depicted in Figure 12B, coronary venous PO_2 typically falls modestly as MVO_2 increases with exercise (94, 111, 213, 214, 274, 278, 280, 281, 283, 285, 293–295, 388,389,454,483,484,497,559,642,664,669,920,921,923); however, this response can vary with little/no change in swine (94, 111, 281, 663, 664, 667, 669), moderate reductions in humans (454,483,484,563), with the largest decreases typically observed in dogs (32, 274, 276, 282, 283, 285, 424, 920, 921,923–925). These reductions in PO_2 reflect slight increases in oxygen extraction that occur along with elevations in coronary blood flow in response to elevations in MVO_2. As such, if increases in MVO_2 were perfectly matched by increases in coronary blood flow, coronary venous PO_2 would remain constant (relationship would remain completely horizontal). Inhibition of a "tonic vasodilator" influence, defined as a similar reduction in coronary blood flow at rest and during increases in MVO_2, results in a compensatory increase in myocardial oxygen extraction and equivalent reductions in coronary venous PO_2 (270, 276, 918, 919). Accordingly, a tonic metabolic influence has been classically interpreted by a parallel downward shift in the relationship between coronary venous PO_2 and MVO_2. Inhibition of such a mediator may or may not result in an absolute reduction in overall MVO_2 and typically produces minimal if any detectable reduction in the relationship between coronary blood flow and MVO_2 (see "*Tonic*" influence in Fig. 12). An alternative explanation for this scenario was recently posited by Gorman et al. who suggested that a downward parallel shift indicates an inhibition of a negative feedback control mechanism which allows for coronary blood flow to be maintained by an augmented error signal (388). Conversely, the expected result for the inhibition of a factor whose production and contribution to metabolic vasodilation increases in proportion to MVO_2 has characteristically been a steepening of the slope of the relationship between coronary venous PO_2 and MVO_2. The logic here is that the progressive attenuation of the coronary response to increases in MVO_2 is accompanied by increases in oxygen extraction in attempts to meet the myocardial requirements for oxygen (918). This effect is also evident in the relatively modest shift of the coronary blood flow versus MVO_2 relationship downward toward the maximal physiologic response (see "*Metabolic*" influence in Fig. 12). Although these conventional interpretations have been relatively standard for over three decades, alternative interpretations and questions regarding the most appropriate means in which to assess the balance between coronary blood flow and myocardial metabolism continue to generate much debate (270, 271, 388, 460, 917–919).

Proposed mechanisms of local metabolic control

Although there is widespread agreement that locally derived vasodilators play a dominant role in the regulation of microvascular resistance, the precise mechanisms responsible for the inextricably tight coupling of coronary blood flow with myocardial metabolism remain poorly understood (243, 271, 918, 919). It should be recognized upfront that neural (sympathetic) influences play both an indirect and direct role in the regulation of coronary blood flow. These effects occur via activation of vascular adrenergic receptors and through the augmentation of MVO_2 via increases in heart rate and cardiac contractility, respectively. A detailed discussion of adrenergic control of coronary blood flow is provided in the Section Neural Control.

In considering local metabolic control of coronary blood flow it is important to define the experimental findings required to satisfy specific factors as a local "metabolites." The precise criteria defined by Feigl in his classic review of the coronary circulation in 1983 were (331):

1. *The proposed metabolite is released under the appropriate conditions and can be recovered from the tissue under those conditions.*

2. *Artificial infusion of the metabolite into the target tissue should faithfully mimic the physiological response.*

3. *The biochemical apparatus for production of the metabolite is present in the tissue in appropriate locations.*

4. *Mechanisms for inactivation and/or uptake of the metabolite are present in appropriate locations.*

5. *The action of various inhibitors and blocking agents on synthesis, release, target-organ receptor function, or metabolite inactivation should have effects consistent with the hypothesis.*

6. *Quantitative studies should indicate that the amount and time course of metabolite release under physiologic conditions is appropriate to give the indicated effect.*

While many substances fulfill some of these criteria, arguably few if any have fully satisfied all. Summaries of key research findings relating to proposed metabolic vasodilator compounds are provided as follows.

Oxygen and carbon dioxide—As early as the 1920s, oxygen was investigated as a potential signal for regulation of coronary flow. In separate studies, Hilton and Eicholtz (474) and Gremels and Starling (406) demonstrated that coronary flow increases with progressive reductions in arterial PO_2 (hypoxemia), with more pronounced increases as arterial PO_2 falls below 40 mmHg. This increase in coronary flow corresponds with increases in blood pressure, heart rate, and MVO_2 which occur via reflex activation of the sympathetic nervous system (338, 767, 917). This vasodilator response is also accompanied by an increase in myocardial oxygen extraction (decrease in coronary venous PO_2). Evidence of overt myocardial ischemia is observed as arterial PO_2 falls below 30 to 35

mmHg with net myocardial lactate production, ST segment changes, and diminished cardiac contractile function (188, 767, 958).

Hypoxic dilation has been observed in isolated vessels preparations which demonstrate marked relaxation in small arteries and arterioles in response to reductions in PO_2 (138,370,506,508,512,681). Similar findings have also been demonstrated in isolated heart preparations (222, 713, 956). Jackson and Duling proposed that hypoxic vasodilation results from the activation of oxygen sensors in terminal arterioles, capillaries, and venules and that these sensors initiate conducted vasodilator responses from their origin to distant resistance arterioles (506, 508). Studies regarding the role of the endothelium are varied as data support the contribution of nitric oxide to hypoxic vasodilation (511,618,956) with others showing no effect (618,681,910). Although inhibition of nitric oxide synthase significantly diminished coronary responses to hypoxia in conscious dogs, the reductions in coronary flow were directly associated with significant reductions in the rate-pressure product (index of MVO_2) (22). Similarly, inhibition of prostaglandin production by blockade of cyclooxygenase has been shown to diminish hypoxic coronary vasodilation (138, 534, 535, 707, 713, 727, 795). However, this finding is not consistent (609, 618) and evidence for hypoxia-induced release of vasoconstrictor prostaglandins must also be considered (672, 681, 809, 811, 910). Thus, a definitive role of endothelial-derived vasodilators in hypoxic coronary vasodilation has not been clearly established.

The Gutterman laboratory found hypoxic vasodilation of isolated human coronary arterioles to be exceptionally slow (approximately 15 min to peak effect) (681). These findings, in addition to the fact that myocardial tissue oxygenation is relatively maintained during physiologic increases in MVO_2 (142,233,239,243,625,626,841,867), fail to support a prominent role for oxygen itself as a metabolic vasodilator. It is also important to recognize that separation of the direct vascular effects of hypoxia from its potential to augment the production of other vasodilator factors significantly confound interpretation of a role for oxygen as a local metabolic mechanism. In particular, it is well established that myocardial adenosine release increases exponentially with the severity of hypoxia (240–242, 458, 893, 936) and that inhibition of adenosine's action through enzymatic degradation or receptor inhibition significantly diminishes hypoxic coronary vasodilation (~20%–30% at arterial PO_2's <40 mmHg) in isolated hearts (539, 712, 964) and in anesthetized animals *in vivo* (376, 608, 670, 671). Accordingly, it is likely that the effects of oxygen are appreciable, but only under pathophysiologic conditions that are sufficient to produce the onset of ischemia.

Considering that CO_2 is vasoactive and a natural byproduct of cellular respiration, it is intuitive that CO_2 could serve as a signal linking changes in coronary blood flow and myocardial metabolism. Work by Case et al. demonstrated an inverse linear relationship between coronary vascular resistance and increases in coronary venous CO_2 levels (151,152). However, this hypercapnic vasodilation was later attributed to H^+ (acidosis) as normalization of pH with sodium carbonate was shown to abolish coronary responses to increases in plasma PCO_2 (971). Although there is a synergistic effect of combined hypoxia and hypercapnia on coronary blood flow (123, 125), such changes are not associated with physiologic increases in MVO_2 (918, 919). Therefore, it is unlikely that CO_2 is a relevant mediator of metabolic coronary vasodilation.

Potassium—In 1938, Katz and Lindner proposed K^+ as a potential regulator of coronary blood flow, the hypothesis being that there is an increased flux of K^+ across the myocardial membrane (into the interstitial space) during increases in metabolic activity (553). Consistent with this hypothesis, subsequent studies found K^+ to be a vasodilator (131, 267, 373, 701) and myocardial efflux of K^+ to be elevated by tachycardia (374, 375, 411, 751, 897, 975, 986) and myocardial ischemia (150,162,211,375,440,510,751,846). However, the vasodilator action of K^+ has been shown to be transient (131, 373), and higher concentrations of K^+ (typically >20 mmol/L) are known to produce vasoconstriction (875). These discrepant findings appear to be related to the effect of K^+ in setting the basal activity of the Na/K-ATPase (355, 721). Work by the Sparks laboratory demonstrated that K^+ release quickly declines following increases in heart rate in normally oxygenated hearts (699). Thus, while K^+ could play a transient role in initiating metabolic vasodilation, it is improbable that K^+ contributes to steady-state increases in coronary blood flow in response to increases in myocardial metabolism.

Adenosine—The seminal theory regarding local metabolic control of coronary blood flow was proposed by Berne in 1963 (85). The theme of Berne's hypothesis was that myocardial PO_2 is the primary regulated variable in a negative feedback loop in which the potent vasodilator factor adenosine (breakdown production of ATP) is released from the myocardium in proportion to increases in myocardial oxidative metabolism and/or reductions in myocardial oxygenation (86–88,91,92,336). Increasing concentrations of adenosine in the cardiac interstitium subsequently increase coronary blood flow via activation of specific receptors on coronary vascular smooth muscle cells. This increase in blood flow would then act to restore myocardial oxygenation toward normal as a part of a negative feedback control system (Fig. 14).

The hypothesis itself is quite elegant in linking changes in metabolism to flow with a metabolic byproduct which also happens to be a potent coronary vasodilator. Although initial studies by the Berne laboratory and others supported that increases in MVO_2 were accompanied by elevated levels of cardiac adenosine (25, 312–314, 316, 656, 961), subsequent studies have failed to show any significant effect of either enzymatic degradation or receptor inhibition on coronary blood flow responses in dogs (32,923,996), swine (281,664), and humans (293–295) (Fig. 15A). Furthermore, studies to estimate changes in interstitial adenosine concentration indicate that adenosine levels remain below a critical threshold concentration necessary to elicit vasodilation at rest and/or during increases in MVO_2 in the absence and presence of adenosine receptor blockade (586,790,791,883,886,920,921, 923) (Fig. 15B). Therefore, despite the attractiveness of the hypothesis, there is little evidence to support a role for adenosine as a mediator of local metabolic coronary vasodilation under normal physiologic conditions.

Additional studies do however indicate that adenosine contributes to the regulation of coronary blood flow in the setting of myocardial ischemia, as pharmacologic inhibition of adenosine action reduces coronary responses in models of critical coronary stenosis (275,607), transient coronary artery occlusion (97, 356, 1014), and severe hypoxemia (376, 608, 670, 671). Taken together these data indicate that while adenosine is capable of eliciting potent vasodilation, such effects are not physiologically evident unless myocardial

oxygen delivery is compromised (i.e., myocardium is ischemic). These findings also serve to further support the maintenance of myocardial oxygen supply-demand balance within physiologic alterations in MVO_2 (142, 233, 239, 243, 625, 626, 841, 867) and thus argue against an obligatory role for myocardial tissue PO_2 as the primary stimulus (error signal) responsible for local metabolic coronary vasodilation.

Adenine nucleotides—The adenosine hypothesis has been reimagined in recent years by a humoral alternative. This newly adapted model, termed the adenine-nucleotide hypothesis, is distinct from the adenosine hypothesis in that it proposes a negative-feedback mechanism under which ATP is released from red blood cells as PO_2 and hemoglobin saturation fall with increases in MVO_2 (309–311, 324, 876–878, 945). It is well documented that ATP is released from erythrocytes in low oxygen environments (310). Thus, considering the steep decline in PO_2 found in coronary capillary beds, it is reasonable to assume that the stimulus for ATP release by erythrocytes exists continuously within the heart. This negative-feedback mechanism is proposed to respond to the magnitude of the hypoxic stimulus with a proportional release of ATP, with hemoglobin saturation serving as the sensor. ATP is then hydrolyzed to its breakdown products, ADP and AMP which can in turn cause vasodilation primarily by binding of ADP to endothelial $P2Y_1$ receptors. Endothelial gap junctions are then believed to conduct this response through the endothelial lining allowing for retrograde signal transduction (343, 344, 388). The net effect of this conducted activation is nitric oxide release by the vascular endothelium both at the site of hypoxic stimulus as well as upstream of the initial error signal.

The Feigl group has made significant inroads advancing this hypothesis by demonstrating that exercise-induced increases in MVO_2 significantly augment coronary venous ATP concentration (324, 768). More recently, they documented that combined blockade of nitric oxide synthase, P1, and $P2Y_1$ receptors significantly decreases the balance between coronary blood flow and myocardial metabolism; as assessed by a parallel shift downward in the relationship between coronary venous hemoglobin saturation and MVO_2 (388) (Fig. 16A). However, even though the error signal (coronary venous hemoglobin saturation) was significantly augmented, the fact that the overall magnitude of exercise-mediated coronary vasodilation was unaffected by this triple blockade indicates that these pathways are not required for metabolic control of coronary blood flow (Fig. 16B). Therefore, while the adenine nucleotide hypothesis provides a compelling mechanism linking myocardial metabolism to coronary blood flow, it currently lacks definitive evidence to support the model (177).

Reactive oxygen species (H_2O_2)—Chilian and colleagues recently proposed a novel feed-forward mechanism for metabolic regulation of coronary vascular flow. They proposed that the leak of electrons from myocardial mitochondrial complexes I and III is proportional to the magnitude of myocardial utilization of ATP and results in production of superoxide (820). This superoxide anion is rapidly converted to hydrogen peroxide (H_2O_2) by the actions of abundantly expressed superoxide dismutase (728, 782). Importantly, H_2O_2 is a well-documented vasodilator when administered exogenously (624, 798, 799, 820, 831, 907) but, more significant to the model is that H_2O_2 has been shown to increase (along with

superoxide production) as a result of progressive stimulation of isolated cardiomyocytes (820). When supernatants from paced myocytes are exposed to isolated coronary microvessels *ex vivo*, a significant catalase-sensitive dilator effect was detected, further implicating a role for H_2O_2 (820).

Unfortunately, *in vivo* interrogation of the role of H_2O_2 has been hindered by the lack of specific agents to inhibit production or stimulate degradation of H_2O_2, as catalase is a very large tetrameric protein with each subunit having a similar molecular weight of albumin (~60 kDa). However, studies in open-chest dogs support that myocardial H_2O_2 concentration increases linearly with pacing or norepinephrine-induced increases in MVO_2 and that these concentrations of H_2O_2 directly correlate with an approximately threefold increase in coronary blood flow (820) (Fig. 17). Although a specific inhibitor is not currently available, there is significant evidence to support that H_2O_2 produces potent coronary vasodilation through redox-dependent modification of smooth muscle K^+ channels (798,799,820,831,907). Importantly, recent work has shown that inhibition of voltage-dependent K^+ (Kv) channels significantly impairs the balance between coronary blood flow and myocardial metabolism in mice (725), dogs (246, 798, 799, 820), and swine (94–96) (see Section "Ion Channels as End Effectors"). Although these findings are compelling, more detailed studies are needed before a definitive conclusion regarding the role of H_2O_2 in metabolic coronary vasodilation can be made. The role of H_2O_2 as an endothelial-derived hyperpolarizing factor is discussed at length in Section "Endothelial-Dependent Control".

In summary, despite more than 50 years of research, determination of the mechanisms of local metabolic control of coronary blood flow remains one of the most intriguing questions of coronary physiologists to this day. At present, it must be acknowledged that our knowledge regarding this fundamental physiologic phenomenon is rather limited, as there are currently more hypotheses than accepted pathways (243). However, although it is well accepted that potent vasodilator mechanisms are recruited at critical levels of myocardial oxygenation, Berne's adenosine hypothesis has been largely refuted as a physiologic mechanism of metabolic coronary vasodilation. Currently proposed mechanisms include adenine nucleotides, H_2O_2, and sympathetic activation of vascular β-adrenoceptors (see Section "Neural Control"), which implicate erythrocytes, mitochondria, and the autonomic nervous system as key mediators of local metabolic control in the coronary circulation (918). Clearly, further studies are needed to elucidate the precise sensors, metabolites, and downstream end effector pathways involved in this vital process.

Endothelial-Dependent Control

Endothelial derived relaxing factors

Blood vessels were originally thought to merely be tunnels through tissues such as the heart until the 19th century discovery of the cellular lining of the vasculature by Friedrich Daniel Recklinghausen (118, 449). Although Heidenhahn is credited with describing these cells as an active secretory system in 1891 (184), the endothelium was largely viewed as a "sheet of nucleated cellophane" until the early 1950s (348, 531). Since this time, countless research studies have established the crucial role of the endothelium in many biological processes, including the regulation of vascular smooth muscle tone, vascular growth/remodeling,

production of cytokines essential to regulation of inflammation, regulation of hemostasis, and, by extension, modulation of vascular thrombosis (178, 289, 339, 688). Extensive reviews of these physiological effects of the endothelium have been previously published by Furchgott and Vanhoutte (363), Moncada (688), Cines (184), and Bohlen (107). A discussion of the role of specific endothelial-derived vasoactive factors in the control of coronary blood flow is provided below. A schematic diagram of key endothelial-derived factors and their associated pathways is shown in Figure 18. Overall, many stimulators of endothelial-paracrine signaling in the coronary circulation have been studied. An exhaustive review of those factors is not provided here, but it should be recognized that acetylcholine, serotonin, ADP, CGRP, substance P, thrombin, bradykinin, histamine, vascular endothelial growth factor (VEGF), and others are known to stimulate the coronary endothelium to produce vasodilator actions (347, 942).

Nitric oxide—In 1980, Furchgott and Zawadski made the seminal observation of the obligatory role of the endothelium in the smooth muscle relaxation to acetylcholine (364). This so-called "endothelial-derived relaxing factor" (EDRF) was later identified as the gasotransmitter nitric oxide in independent studies by Ignarro et al. (495, 496) and Palmer et al. (740) in 1987. Thus, the term EDRF has largely evolved to become synonymous with nitric oxide. Since this initial, Nobel-worthy identification, a variety of pathways linked with nitric oxide have been extensively characterized. Acetylcholine, amongst other agonists (e.g., bradykinin, histamine, serotonin, and substance P), are known to bind to their cognate endothelial receptors and initiate a signaling cascade that leads to the activation of a family of enzymes termed nitric oxide synthases which catalyze the conversion of L-arginine to L-citrulline with nitric oxide production occurring as a byproduct of the reaction (107, 124, 178, 289, 620, 688, 930). In addition to agonist-induced nitric oxide release, mechanical forces such as blood flow related increases in friction along the endothelial layer (shear) have been demonstrated to induce the release of nitric oxide (145, 620, 884, 885).

Abluminal release of nitric oxide produces vasodilation through cyclic guanosine monophosphate (cGMP) dependent hyperpolarization of vascular smooth muscle via the opening of select K^+ channels (247, 688, 696). Clinically, nitric oxide containing compounds such as nitroglycerin have been utilized to alleviate symptoms of acute angina for over a century. Work by the Harrison laboratory documented that the enzymatic machinery for converting nitroglycerin to its putative vasodilator metabolites (S-nitrosocysteine, nitric oxide) is largely absent in the coronary microcirculation (847). Later studies by Chilian and colleagues demonstrated that while nitroglycerin induces concentration-dependent dilation of coronary arterioles to their maximal diameter *in vitro*, coronary vasodilation *in vivo* is transient and overwhelmed by intrinsic autoregulatory escape mechanisms (523). Although there is minimal if any effect of nitrates on absolute coronary blood flow (385, 595, 847, 982–984), relief of angina symptoms appears to be related to reductions in MVO_2, secondary to diminished ventricular afterload and preload (432, 833).

The role of nitric oxide in the control of coronary blood flow has been extensively studied over the past few decades. From these studies it is apparent that nitric oxide-dependent responses occur primarily in upstream arteries and large arterioles (~100–300 μmin

diameter) (170,590,592,593), as inhibition of nitric oxide synthase diminishes resting epicardial coronary artery diameter (81,145,180,181,299,317,435,518, 610,718,745,778,959) and abolishes shear-mediated dilation in small coronary arteries (>160 μm in diameter) (884, 885). This effect of nitric oxide synthase blockade is absent in the classically defined "resistance vasculature" (<100 μm in diameter) (170). However, while this evidence is compelling, controversy about the overall physiologic relevance of this effect begins as numerous studies have repeatedly demonstrated little/no effect of nitric oxide synthase inhibition on baseline coronary flow (7, 93, 145, 223, 269, 299, 317, 497, 634,649,718,744,746,854,865,920,959). Logically, if nitric oxide played a significant role in resting coronary vascular tone, then blockade of nitric oxide synthesis should result in a dose-dependent decrease in coronary flow as basal dilator activity is lost. This is simply not the case. However, it should be pointed out that significant reductions in coronary flow are typically observed in isolated buffer-perfused hearts (9, 68, 126, 599, 747, 864, 928). These discrepant findings are likely related to the extremely high flow rates (>5 mL/min/g) present in isolated, crystalloid-perfused heart, which strongly favors shear-mediated increases in nitric oxide production (129, 139, 576, 592, 600, 885, 930). Furthermore, the half-life of nitric oxide is also likely longer in buffer-perfused hearts due to the lack of hemoglobin which rapidly scavenges free nitric oxide in plasma (880).

Although data from Bernstein et al. (93) and Traverse et al. (915) support that exercise-induced increases in MVO_2 are associated with increases in nitric oxide production, numerous studies have demonstrated that inhibition of nitric oxide synthesis under these conditions has little effect on metabolic coronary vasodilation (7, 93, 279, 497, 667, 920) (Fig. 19A). However, blockade of nitric oxide production is associated with a parallel downward shift in the relationship between coronary venous PO_2 and MVO_2 (Fig. 19B), which has classically been interpreted to indicate a tonic vasodilator effect of nitric oxide across a wide range of MVO_2 (7,93,269,497,667,854,920,959). This modest reduction in the balance between myocardial oxygen supply/demand, which has essentially no effect on either coronary blood flow or MVO_2, is consistent with the loss of shear-mediated increases in diameters of upstream coronary arteries (81, 145, 180, 181, 299, 317, 435, 518, 610, 718, 745, 778, 959). Chilian and colleagues proposed that the physiologic benefit of this arrangement of endothelial-dependent control is that it would act to prevent excessive shear stress on small to large coronary arteries, thus preserving vasodilator reserve capacity in coronary resistance arterioles (522).

Cyclooxygenase-derived dilating factors—Another class of endothelial-derived vasodilator factors includes the metabolites of arachidonic acid. Arachidonic acid is found in the plasma membrane of nearly every cell in the body. Once released by the actions of phospholipases, there are three potential fates for free arachidonic acid in the vasculature: (i) functionally washed out of the system; (ii) reincorporated into the plasma membrane; and (iii)metabolized into different substrates down one of three major metabolic pathways involving either the cyclooxygenase, lipoxygenase or cytochrome P-450 pathway (289,307). In particular, specific metabolites of the cyclooxygenase pathway termed prostaglandins, which won Bergstrom, Samuelsson and Vane the Nobel Prize in 1982 (80,82,83,357,735), include a variety of vasoactive compounds, such as the vasodilator prostaglandin I_2 (PGI_2 or

prostacyclin) as well as the vasoconstrictor compounds prostaglandin H$_2$, prostaglandin F2α and thromboxane A$_2$ (which are discussed in Section *Cyclooxygenase Derived Constricting Factors*). The vascular actions of prostacyclin are mediated by adenylyl cyclase/cAMP-dependent activity on K$^+$ channels which has been repeatedly demonstrated to induce vasodilation in multiple vascular beds of both animal models and humans (100, 289, 340).

The seminal study regarding the role of cyclooxygenase in the control of coronary blood flow was performed by Dai and Bache in 1984 (213). They found that blockade of cyclooxygenase with indomethacin significantly diminished arachidonate-mediated increases coronary blood flow. However, indomethacin failed to influence coronary blood flow at rest or during treadmill exercise in chronically instrumented dogs (Fig. 20). Similar findings have also been reported by other laboratories (439,475), including studies by Edlund et al. in humans (295). Interestingly, the relationship between coronary venous PO$_2$ and MVO$_2$ was unaffected by indomethacin in dogs (213), while a significant parallel downward shift was noted by Merkus et al. in swine (667). Thus, there are no data to support that cyclooxygenase-derived products are required for local metabolic control of coronary blood flow. However, prostaglandin release has been shown to be increased following hypoxia (2), anoxia (103), and myocardial ischemia (4), and inhibition of cyclooxygenase decreases the duration of coronary reactive hyperemia, but only in the presence of a nitric oxide synthesis inhibitor (774). These findings support a physiologic interaction between prostaglandins and nitric oxide, which is consistent with a significant vasoconstrictor effect of cyclooxygenase inhibition reported in patients with coronary artery disease (354).

Endothelial-derived hyperpolarizing factors—Identification of another broad family of endothelial-derived vasodilators came about from observations of sustained endothelial-dependent hyperpolarization and vasodilation in the presence of combined blockade of nitric oxide and cyclooxygenase (307, 340, 347, 419, 421, 719). Following their initial characterization in the early 1990's, numerous endothelial-derived hyperpolarizing factors (EDHFs) have been identified. Although the list of potential versus accepted EDHFs continues to evolve, several factors that have been recognized include cytochrome P-450 metabolites of arachidonic acid [epoxyeicosatrienoic acids (EETs)], H$_2$O$_2$, potassium, H$_2$S, anandamide, and nitroxyl (63, 65, 296, 307, 371, 619, 646, 784). Of these factors, there is growing consensus, largely based on the work of the Gutterman laboratory [see (289,307,419,528) for review], that endothelial-derived H$_2$O$_2$ and fatty acid epoxides EETs are important regulators of coronary vascular tone in response to a variety of stimuli, including cyclic stretch, shear stress (flow-induced dilation), and physiological agonists such as bradykinin and acetylcholine (143, 306, 859) (Fig. 21). These EDHFs mediate vasodilation via direct effects on vascular smooth muscle and may facilitate amplification and/or prolongation of endothelial cell hyperpolarization through the opening of K$_{Ca}$ channels (307). The importance of K$_{Ca}$ channels to endothelial-dependent hyperpolarization is highlighted by the studies which have demonstrated that inhibition of small (SK$_{Ca}$), intermediate (IK$_{Ca}$), and/or large-conductance (BK$_{Ca}$) K$_{Ca}$ channels abolishes hyperpolarization of coronary arteries from humans (64, 112, 604, 679, 680, 831), pigs (63, 134, 140, 297, 970), rats (24, 927), guinea pigs (190, 191, 1001), dogs (594, 743), and mice (640, 750). At present this hyperpolarization is hypothesized to spread in a radial manner

through different layers of the vessel media via homocellular gap junctions in smooth muscle (231) and longitudinally via homocellular gap junctions in endothelium (40). Evidence for the contribution of K_{Ca} channels to endothelial-dependent coronary vasodilation has also been demonstrated *in vivo* (594,743). As outlined earlier, these influences are physiologically advantageous as they act to optimize local changes in coronary resistance between upstream feed arteries with downstream arterioles in response to changes in metabolic demand (100, 307, 519, 520, 522). However, as with nitric oxide and prostaglandins, inhibition of specific EDHFs or K_{Ca} channels has rather minimal effects on the regulation of coronary blood flow *in vivo* (109–111, 594, 1020) (see Section "Ion Channels as End Effectors").

It is important to point out that the specific factors that contribute to endothelial-dependent dilation vary widely across experimental conditions, species and disease states (307, 419). In particular, recent data support that the mediators of flow-mediated dilation change with aging and disease, with prostaglandins predominating in pediatric subjects, nitric oxide primarily contributing in adults without evidence of atherosclerotic disease, and H_2O_2 prevailing in subjects with underlying vascular disease (98, 153, 288–290, 527, 680, 760, 830). These distinct changes have recently been linked with alterations in ceramide and telomerase (99, 353). Furthermore, the complexity of endothelial-dependent control of coronary blood flow is further complicated by the complementary as well as inhibitory interactions among these vasodilator mechanisms (nitric oxide, H_2O_2, and EETs), which can vary depending on the stimulus and/or underlying phenotype of the subject (289, 307). Thus, it is quite apparent that endothelial-derived factors play diverse roles in the in control of coronary blood flow. The extent to which these changes influence physiologic responses of the coronary circulation and/or contribute to the progression of coronary vascular disease remains largely unexplored.

Endothelial-derived contracting factors

Endothelins—Shortly after the identification of nitric oxide as an endothelial-derived relaxing factor, the Masaki laboratory identified the gene and peptide encoding endothelin in 1988 (477, 504, 560, 1003). Endothelin-1 is the best characterized of the endothelial-derived contracting factors and represents the most potent and long-acting vasoconstrictor known to man (473, 638). This 21 amino-acid peptide is produced from nonvasoactive precursors pre-pro-endothelin and big endothelin by endothelin converting enzyme (810). Studies which have focused on the coronary effects of endothelin-1 actually demonstrate disparate effects, with the binding of endothelin-1 to endothelial ET_B receptors stimulating production of nitric oxide and prostacyclin (350, 914) and binding to smooth muscle ET_A or ET_B receptors producing powerful vasoconstriction which can last up to 40 to 60 min (386, 810, 1002). The dominance of constrictor (ET_A) phenotype is evident in studies where intracoronary administration of endothelin-1 produces dose-dependent reductions in coronary flow, with the complete cessation of flow typically occurring at concentrations of ~10 μg (386). This pronounced vasoconstrictor effect is significantly diminished by preadministration of an endothelin receptor antagonist (Fig. 22). However, inhibition of endothelin receptors produces modest increases in coronary venous PO_2 (~2 mmHg) under normal resting

conditions, with relatively little/no change in coronary blood flow or MVO_2 (386, 663, 666, 668, 902).

The finding that blockade of endothelin receptors increases coronary venous PO_2 at rest but not during exercise led Merkus and colleagues to hypothesize that the withdrawal of endothelin-1-mediated coronary vasoconstriction could serve as a metabolic vasodilator influence during increases in MVO_2 (663, 666). This hypothesis is also supported by data which suggest that exercise limits the production of endothelin (230). Although this hypothesis offers an intriguing twist to the classic theory of local metabolic vasodilation, examination of the relationship between coronary blood flow and MVO_2 reveals that endothelin receptor blockade has essentially no effect on the overall balance between flow and metabolism (Fig. 22). It is important to recognize that if endothelin were acting to counter metabolic coronary vasodilation, one would predict to observe a significant increase in coronary flow relative to MVO_2 (either a parallel shift or increase in slope), which clearly does not occur. Therefore, although endothelin-1 is capable of producing profound coronary vasoconstriction, the overall effect of this peptide in modulating coronary blood flow under normal physiologic conditions appears to be rather modest. In contrast, there is experimental evidence to support a more pronounced role of endothelin in disease states such as coronary artery disease which should be further explored (868, 898).

Cyclooxygenase derived constricting factors—Despite synthesis in the same enzymatic pathway as the vasodilator prostacyclin, prostaglandin H_2 and its downstream products prostaglandin F2α and thromboxane A_2 have been shown to produce marked vasoconstriction in the coronary circulation (10,341,529,792). However, evidence supporting a role of any of these mediators in the regulation of coronary vascular tone under normal-healthy conditions has not been demonstrated. In particular, data from Ammar et al. demonstrated essentially no effect of combined prostaglandin H_2 and thromboxane A_2 receptor blockade on coronary blood flow at rest or during dobutamine-induced increases in MVO_2 (10). Although there is no effect of these antagonists on coronary blood flow under normal physiologic conditions, numerous studies have implicated a pathophysiologic role for thromboxane A_2 and another vasoconstrictor, 5-hydroxytryptamine (i.e., serotonin), in response to platelet activation (21, 301, 379–381, 978, 979) as well as endothelial injury and coronary artery disease (502,573,979,980). These factors are also thought to play a role in coronary vasospasm (491, 580, 856, 941).

Endothelial dysfunction and progression of vascular disease

Endothelial "dysfunction" is a commonly used term which can have many biological meanings. With regard to the vascular effects of the endothelium, this term has classically been used to define a state in which diminished vasodilation or paradoxical vasoconstriction is observed in response to the administration of an endothelial-dependent agonist (71, 108, 232, 339, 611). This inappropriate response is typically mediated by a decrease in the production or bioavailability of nitric oxide via specific alterations in the nitric oxide synthase enzyme or the scavenging of nitric oxide by reactive oxygen species respectively. The dysfunction must also be separated from any potential impairment in the response of vascular smooth muscle to nitric oxide (289, 942). Such an imbalance shifts the vascular

milieu toward enhanced vasoconstriction and a procoagulant, proinflammatory, and proproliferative environment (178, 184, 611).

As outlined above, numerous studies of the role of individual endothelial-derived factors have demonstrated quite modest effects of both endothelial-derived relaxing and constricting factors in the regulation of coronary blood flow, under normal physiologic conditions (7, 93, 213, 279, 295, 497, 667, 668, 920). However, it is important to recognize that studies from the Bache laboratory have demonstrated that inhibition of nitric oxide production exacerbates reductions in coronary blood flow produced by exercise in the presence of a coronary artery stenosis (reduced coronary pressure <65 mmHg) (Fig. 23), with no effect of nitric oxide blockade within normal (nonstenotic) territories (269). These data are consistent with the findings of Smith and Canty who noted that inhibition of nitric oxide synthesis significantly shifts the lower set point of coronary pressure-flow autoregulation by ~15 mmHg; that is, the pressure at which physiologic resistance is at its lowest and flow becomes pressure dependent (865). Taken together, it is apparent that reductions in endothelial "function" in an otherwise normal setting are unlikely to substantially impact myocardial perfusion. However, the same decrease in "function" would likely precipitate the onset of overt ischemia at earlier stages of disease. Furthermore, given that a portion of coronary vascular resistance resides in upstream arterioles (~100–300 μmin diameter) that are responsive to shear forces, and generally not responsive to metabolic vasodilator signals, endothelial dysfunction could diminish maximal coronary flow rates by blunting flow-mediated dilation of these vessels (170, 590, 592, 593). As such, coronary endothelial dysfunction is associated with many cardiovascular-related diseases (71, 614, 644, 779, 780) and thus it is not surprising that impaired endothelial function independently predicts acute cardiovascular events in patients with and without atherosclerotic disease (433).

The other aspect of endothelial dysfunction that should be acknowledged is the potential of damaged endothelium to contribute to the initiation and progression of coronary artery disease. This "response to injury" hypothesis was originally proposed by Ross and Glomset in 1973 (806) and has stimulated countless studies in the field of atherosclerotic disease. Although our understanding of atherosclerosis has substantially improved over the past 40+ years, current dogma continues to cite underlying damage of the endothelium and the promotion of a procoagulant, proinflammatory, and proproliferative environment as contributing factors (802, 803, 805, 969, 981). For a detailed description of endothelial dysfunction and development of vascular disease, readers are encouraged to peruse recent reviews by Higashi et al. (472), Barton (58), Vanhoutte et al. (943, 944), Ross (804), and Belin de Chantemele and Stepp (71).

With regard to potential mechanisms of coronary disease, there is a growing body of evidence implicating adipose tissue that normally surrounds the major coronary conduit arteries. This perivascular adipose tissue (PVAT) is a local source of adipocytokines that are capable of influencing coronary endothelial and smooth muscle function (132, 720, 737, 753–755, 786) and may contribute to the initiation and progression of coronary artery disease (154,155,736,756). From these studies, it is apparent that cardiac adiposity expands with obesity (829), that atherosclerotic plaques occur predominantly in arteries encased by PVAT (249, 405, 815, 816, 829), and that coronary PVAT volume is positively associated

with underlying plaque burden (639). Recent data support distinct phenotypic expression patterns and vascular effects of coronary PVAT relative to other adipose tissue depots (e.g., subcutaneous, mesenteric) which are significantly influenced by the species studied (e.g., rodent, swine, and human) and the overall health status of the model studied (normal, obese, metabolic status, atherosclerosis) (46,154,155,161,654,737, 755, 858). However, the extent to which coronary PVAT-derived factors causally contribute to the development of coronary atherogenesis has yet to be established.

Neural Control

Innervation and functional receptor distribution

It has been known for more than a century that the coronary vasculature is richly innervated with both adrenergic and cholinergic neurons (70). Work by H. H. Woollard in 1926 was among the first to describe in detail sympathetic and parasympathetic innervation of the coronary circulation (Fig. 24) (989). Later electron microscopy studies demonstrated that these nerve fibers are located within the coronary vascular wall (478) and that small arteries and arterioles contain more nerve terminals relative to larger coronary arteries (613, 641). Work by the Zipes laboratory demonstrated that major sympathetic trunks appear localized in the epicardium alongside the coronary arteries, with transmural penetration to innervate the rest of the myocardium; that is, superficial application of phenol to adventitial tissue will denervate downstream arteries. Alternatively, major parasympathetic ventricular pathways remain epicardial until crossing the AV groove where vagal fibers penetrate the myocardial to become located predominantly in the ventricular subendocardium (501, 1023). Regional interruption of autonomic innervation occurs after myocardial infarction and may predispose the heart to arrhythmias and/or alterations in coronary flow, depending on the location and the overall extent of injury (1023). In general, sympathetic nerves release norepinephrine, neuropeptide Y, and ATP, while parasympathetic nerves release acetylcholine and vasoactive intestinal polypeptide (237, 351, 413, 422, 478, 817, 818). Studies by Brody and colleagues also provide seminal evidence of a role for central neural pathways in the regulation of coronary blood flow. In a series of studies, they demonstrated that the lateral reticular formation, anterior hypothalamus, and parabrachial nucleus are major central regions involved in sympathetic-mediated coronary vasoconstriction (19, 416–418, 420, 525). This pathway overlaps with the "fight or flight" response and thus activation by mental stress in the presence of an underlying coronary stenosis can lead to devastating coronary constriction, occlusion, and infarction (903, 952).

Adrenergic receptor expression patterns vary throughout the coronary tree, with β_1 adrenoceptors predominantly expressed in larger conduit arteries (8,709,722,773,842,911, 946, 948, 949, 1010), and β_2 adrenoceptors primarily located in arterioles <100 μm in diameter (410, 452, 698, 896). Data from Murphree and Saffitz support the relatively equal distribution of β_1 versus β_2 adrenoceptors in smaller coronary arteries (~100–400 μmin diameter) and a β_1 versus β_2 expression ratio of ~2:1 in larger vessels (698). Marked coronary vasodilation to β-adrenoceptor activation was demonstrated by Klocke et al. in arrested dog hearts in 1965 (566). The functional contribution of both β_1 and β_2 adrenoceptors to this response was shown by Trivella et al. in 1990 (916). The primary site

for α-adrenoceptors appears to be more upstream in the coronary circulation, with numerous studies supporting a non-uniform distribution of α_1 adrenoceptors in larger arteries and α_2 adrenoceptors in smaller arteries and large arterioles (67,163,164,172,248,464,467,682). Interestingly, functional assessment of α- and β-adrenoceptor responses to norepinephrine in isolated, pressurized coronary vessels revealed dose-dependent constriction of vessels >100 μm in diameter and dilation of vessels <100 μm in diameter (163, 164, 172, 334). Isolated coronary arterioles have also been shown to be refractory to α-adrenoceptor agonists (e.g., phenylephrine) (521,777,908). However, *in vivo* studies have clearly established coronary vasoconstriction in response to selective α_1- and/or α_2-adrenoceptor activation, primarily in dogs (157–159,248,464,487,555,987,988) and humans (67), with minimal constriction evident in swine (840). Reductions in coronary blood flow are typically greater in response to α_2 relative to α_1-adrenoceptor activation (67,157–159,487); however, these responses can be substantially altered in the setting of disease (67, 248, 402–404). The discrepant responses to α- adrenoceptor agonists are reportedly related to myocardial release of endothelin, as inhibition of ET_A and ET_B receptors attenuates α-mediated coronary constriction both *in vivo* (236, 386) and *in vitro* (908).

Coronary blood flow responses to muscarinic receptor activation, either via the administration of acetylcholine or vagal stimulation, are highly species and concentration dependent with experiments in most animal models and healthy human vessels demonstrating significant endothelial-dependent vasodilation in vessels ranging between 50 and 400 μm in diameter (199, 329, 337, 579, 601, 785, 933). Interestingly, acetylcholine administration has also been shown to produce vasoconstriction in human atrial arterioles, but dilation of human ventricular arterioles (675). Studies in swine, calves, and humans with atherosclerosis report vasoconstriction, likely because of the lack of muscarinic receptor expression (198,536,538,1008,1009). Muscarinic coronary vasodilation has been attributed to both M1 and M2 receptors, with stimulation of M2 receptors resulting in the redistribution of blood flow toward the subendocardium (409, 757, 758).

Sympathetic control

Determination of the direct effect of sympathetic neural activation on the control of coronary blood flow is significantly complicated by the distinct competing influences this response elicits. First, β-adrenoceptor-mediated increases in contractility, heart rate, and MVO_2 initiate local metabolic mechanisms, likely through feedback control mechanisms which require an error signal (e.g., decrease in tissue PO_2). Second, activation of coronary β-adrenoceptors leads to direct vasodilation and third, stimulation of coronary α-adrenoceptors elicits vasoconstriction. These direct effects occur through open-loop feed-forward control mechanisms, which do not require an error signal (Fig. 25) (270, 335, 768). This feedforward hypothesis of coronary blood flow control was originally proposed by Miyashiro and Feigl in 1993 and is physiologically advantageous as the stimulus responsible for augmenting myocardial contractility, heart rate, and MVO_2 is the same stimulus responsible for increasing myocardial oxygen delivery (683, 684). However, delineation of the contribution of sympathetic activation to the dynamic regulation of coronary vascular resistance is significantly complicated by the simultaneous stimulation of three separate and opposing pathways. In particular, pharmacologic inhibition of β-adrenoceptors will block

not only direct coronary responses but also attenuate metabolic vasodilation secondary to reductions in heart rate and contractility. Furthermore, administration of α and/or β adrenoceptor inhibitors can result in substantial compensatory increases in catecholamine release, which subsequently exaggerate responses of unblocked adrenoceptors (390, 470, 879).

Early evidence for a predominant β-adrenoceptor "feedforward" mechanism of coronary blood flow control during sympathetic activation can be found in the 1943 study by Essex et al. who demonstrated that decreases in circumflex coronary blood flow in response to exercise were greater in totally denervated hearts relative to partially denervated hearts (320). Reductions in coronary blood flow and metabolism to cardiac denervation were also reported in later studies by Barta et al. in 1966 (57) and by Gregg et al. in 1972 (401). Similar findings have also been documented following selective sympathetic denervation (245, 426, 843). More definitive evidence for β-adrenoceptor-mediated dilation comes from later pharmacologic inhibition studies, which have demonstrated significant reductions in the balance between coronary blood flow and myocardial metabolism in response to β- and/or α + β-adrenoceptor blockade in dogs (60, 389, 390, 683, 684), pigs (280, 368), and humans (304, 526); that is, significant downward shift and steepening of the slope of the relationship between coronary venous PO_2 and MVO_2 following α + β-adrenoceptor blockade (Fig. 26). Therefore, there is considerable support for direct β-adrenoceptor-mediated dilation during sympathetic activation. Quantitative analysis of feedforward sympathetic coronary vasodilation by Gorman et al. indicates that up to 25% of exercise coronary hyperemia can be attributed to norepinephrine-induced activation of coronary β-adrenoceptors, with little role for circulating epinephrine (390).

The contention that sympathetic nerves dilate the coronary circulation has been postulated since studies by Morawitz and Zahn in 1912. However, work by Szentiványi and Juhász Nagy in 1959 clearly demonstrated the ability of sympathetic nerve stimulation to produce coronary vasoconstriction (901). This seminal observation was subsequently corroborated by several other laboratories (90,302,393,643,657,716,800) and independently identified to be mediated by α-adrenoceptors in 1967 by the Feigl laboratory (328) and the Gregg laboratory (763). Further investigation of this question has revealed that while the contribution of α-adrenoceptors has little effect on coronary blood flow under resting conditions, there is strong evidence to support a paradoxical increase in α-adrenoceptor mediated coronary constriction during increases in sympathetic activity with exercise (34, 67, 214, 284, 389, 425, 427, 428, 462, 468, 469, 493, 517, 687) and in response to baroreceptor reflex (250, 315, 702, 766) and muscle metaboreflex (14, 15, 197, 723). This point is illustrated in Figure 26 wherein a significant increase in the slope of the relationship between coronary blood flow and MVO_2 is observed following α-adrenoceptor inhibition, which is accompanied by a flattening (decrease) in the slope of the coronary venous PO_2 versus MVO_2 relationship (389). Although both α_1- and α_2-adrenoceptors can produce coronary vasoconstriction, adrenergic constriction appears to primarily involve α_1 adrenoceptors (215, 888). In contrast, minimal changes in coronary blood flow or coronary venous PO_2 are observed following α-adrenoceptor blockade in exercising swine (280, 840). Definitive data regarding the role of α constriction in healthy humans are presently lacking (460, 461). However, seminal studies by Heusch and colleagues have demonstrated that sympathetic activation in

the presence of mild coronary stenosis results in metabolic vasodilation, while activation in the presence of a critical stenosis produces profound α_2-adrenoceptor mediated vasoconstriction (462). This group has also established that intracoronary administration of α blocking agents significantly improves myocardial perfusion in patients undergoing elective percutaneous coronary intervention (PCI) (402, 404) and PCI following acute myocardial infarction (403).

The presence of coronary α-adrenoceptor constriction in health and disease presents a paradox in that this influence acts to augment vascular resistance and thus oppose local metabolic and other vasodilator mechanisms stimulated by increases in sympathetic nerve activity (460). Feigl proposed this constrictor influence is physiologically beneficial in serving to stiffen transmural penetrating (medium-size) arteries which in turn decreases vascular compliance and acts to lessen to and fro coronary flow oscillation during systole and diastole (689). This effect is quite evident in the study by Morita et al. who determined that α-adrenoceptor blockade significantly augmented wasteful coronary flow oscillations in penetrating septal arteries (Fig. 27) (689). Similar increases in coronary flow oscillations have also been observed during exercise in dogs (389). The consequence of such oscillations is the potential for diminished sub-endocardial blood flow, which has been observed in following α-adrenoceptor blockade at very high heart rates (~240 beats/min) and MVO_2 (>500 μLO_2/min/g) in exercising dogs (493). However, other studies have failed to demonstrate alterations in subendocardial flow at lower heart rates and rates of MVO_2 (66,287,424). Thus, it is apparent that α-adrenoceptor constrictor influences limit metabolic coronary vasodilation during increases in sympathetic activity in a transmurally homogenous manner under most physiologic conditions. However, α-adrenoceptor mediated vasoconstriction does appear to augment epicardial resistance and promote subendocardial perfusion in the setting of ischemia; that is, lessens transmural "steal" during coronary hypoperfusion (128,166,365,378,715). Whether α-constriction augments subendocardial flow may depend on the experimental conditions and model studied, as Bache and Laxson demonstrated that inhibition of α_1-mediated vasoconstriction with prazosin produced a uniform increase in coronary flow across the left ventricular wall in exercising dogs with a critical coronary stenosis (35).

Parasympathetic control

Experimentation to determine the coronary effects of the parasympathetic nervous system date back to vagal stimulation studies by Panum in 1858 (329, 331, 332). However, early studies on the parasympathetic control of the coronary circulation were inconclusive because of the confounding influences of vagal mediated reductions in heart rate and MVO_2. Parasympathetic coronary vasodilation was clearly demonstrated by Feigl in 1969 wherein efferent vagal stimulation increased coronary blood flow ~30% and diminished late diastolic coronary resistance ~60% in dogs with heart rates held constant by cardiac pacing (Fig. 28) (329). This vasodilator effect is essentially abolished by muscarinic receptor inhibition with atropine and is normally mediated by acetylcholine-induced production of nitric oxide by coronary endothelium (124, 331, 855). However, as outlined earlier, parasympathetic dilation is species-dependent and contingent on normal endothelial function and the absence of atherosclerotic disease (137, 479, 490, 955, 1015). Although data from Duncker et al.

indicate that the withdrawal of parasympathetic activity may facilitate β-adrenoceptor dilation in swine during exercise (280), the effects of the parasympathetic nervous system on the control of coronary blood flow are quite modest under most physiologic conditions (198, 280, 332, 335). However, there is evidence to support a role for parasympathetic coronary vasodilation in the carotid chemoreceptor reflex (430,442,700,703,950), Bezold-Jarisch reflex (186,330,1027), and during activation of afferent vagal C fibers in the lung (187, 734).

Hormonal factors

Angiotensin II—Angiotensin II is an octapeptide produced by the cleavage of the decapeptide angiotensin I by angiotensin converting enzyme, which is expressed in the heart and coronary endothelium (218, 291). Intravenous administration of angiotensin II produces concentration-dependent increases in coronary blood flow (Fig. 29), which are relatively modest (up to ~15% increase in coronary blood flow at dose of 100 ng/kg) and mediated by peripheral vasoconstriction and increases in systemic blood pressure (i.e. afterload), which augment MVO_2 and subsequently stimulate local metabolic vasodilator mechanisms (258). In contrast, intracoronary administration of angiotensin II, which does not produce these confounding systemic effects, induces pronounced coronary vasoconstriction (~50% reduction in coronary blood flow at dose of 30 ng/kg) that is completely abolished by inhibition of AT_1 receptors with telmisartan (Fig. 29) (1018). These discrepant findings clearly demonstrate that simple examination of coronary blood flow responses, without consideration of respective changes in MVO_2, can lead to completely erroneous conclusions regarding the vasoactive effects of that particular agonist or antagonist (918). Interestingly, studies in isolated coronary vessels have found that angiotensin II produces moderate constriction of both arteries (319, 616, 706, 764) and arterioles (706, 1017, 1018), with concentrations >10 nmol/L producing vasodilation via effects on AT_2 receptors (1017). Although some studies investigating the physiologic role of angiotensin II in the control of coronary blood flow have found that inhibition of AT_1 receptors can increase coronary flow responses to exercise (881, 899, 900), effects on coronary venous PO_2 and the balance between coronary blood flow and MVO_2 are relatively small in swine (~2 mmHg increase in coronary venous PO_2) (665), and are unchanged in dogs (1018) and humans (769). However, coronary effects of AT_1 receptor inhibition or blockade of angiotensin converting enzyme are significantly augmented in disease states such as obesity, hypertension, and coronary artery disease (319, 635–637, 769, 894, 1018). Thus, it is not surprising that therapeutic inhibition of angiotensin II production or receptor signaling is highly effective in diminishing rates of myocardial infarction, stroke, and death in a broad range of high-risk patients (212, 1013).

Vasopressin—On rare occasions, physiological mediators are named in such a fashion that the protein name is sufficient to demonstrate its function. Antidiuretic hormone (ADH) is one such protein in that it functions to retain water in the body (710). Additionally, ADH bears an additional moniker, vasopressin, because of its demonstrated ability to constrict blood vessels. Interestingly, pressor activity of vasopressin is variable throughout the coronary circulation with ~35% of coronary arteries demonstrating endothelial-dependent dilator responses (705). This dichotomous response appears to relate to the diameter of the coronary artery in question in that modest endothelial-dependent dilation of vessels is

constrained to those arteries with diameters greater than 100 μmol/L. By contrast, vasopressin has been demonstrated to constrict arteries less than 90 μm in diameter (602). As the majority of effect on the resistance is vasoconstrictive, vasopressin is capable of dose-dependently decreasing coronary flow *in vivo* by as much as 40% (558, 602, 653, 848). While the ability to constrict the coronary circulation is compelling, it does little to elucidate the role of vasopressin under physiologic and pathophysiologic conditions. However, work by Sellke and Quillen has demonstrated that the coronary microvasculature is sensitized to vasopressin subsequent to ischemia-reperfusion injury in that a canine model of that condition was found to respond approximately fivefold greater to vasopressin than control animals (848). Additionally, while circulating vasopressin levels have been shown to increase proportionately with the magnitude of heart failure, studies to date do not support a direct causal role as inhibition of vasopressin-2 (V2) receptors (e.g., tolvaptan or conivaptan) has largely failed to show improvements in clinical outcomes (581, 603, 685, 826, 844, 895, 926).

Histamine—In addition to "classical" mediators of vascular tone, agents of the inflammatory process are also involved in vasomotor regulation. Histamine, an autocoid which is stored in both mast cells and basophils, is formed by the enzymatic decarboxylation of histidine and plays an essential role in allergic responses, inflammation, and injury. Upon release from immune cells, histamine modulates vascular tone through two cognate receptors (i.e., H1 and H2) resulting in arteriolar vasodilation via H2 receptors, venoconstriction via H1 receptors and enhanced capillary permeability (676,953). The coordinated response of these actions is the notable tissue edema seen in acute allergic responses or localized tissue damage. Histamine receptors have been demonstrated in the coronary circulation with coronary endothelial H1 receptors having been shown to stimulate nitric oxide release to a level sufficient to elicit coronary vasodilation in response to exogenously derived and administered histamine (557, 953). However, a role for endogenous histamine in the regulation of coronary vascular tone has yet to be demonstrated in response to a physiologic stimulus (270).

Ion Channels as End Effectors

Ca^{2+} and K^+ channels in the coronary circulation

As in striated muscle, Ca^{2+} is the key regulator of contraction in coronary vascular smooth muscle, as the activity of myosin light chain kinase is dependent upon association with Ca^{2+}/calmodulin. In coronary vascular smooth muscle cells, the two sources of Ca^{2+} are release from intracellular organelles and influx from the extracellular space. The sarcoplasmic reticulum is the principal organelle for Ca^{2+} release in coronary smooth muscle and contains both ryanodine- and inositol trisphosphate-sensitive Ca^{2+} channels (503,882). The cytosolic volume of sarcoplasmic reticulum is quite low in smooth muscle (2%-5%); therefore, this pool of Ca^{2+}, while concentrated, is limited (244). In the unstimulated state, the free Ca^{2+} ions in the extracellular fluid outnumber those in the cytosol by approximately 20,000:1 (pCa 2.7 vs. 7.0); therefore, a large concentration gradient exists for Ca^{2+} entry by diffusion. For extracellular Ca^{2+} ions to enter the cytosol, Ca^{2+}-permeable channels in the sarcolemma must be open. There are a variety of Ca^{2+}-permeable channels in coronary vascular smooth

muscle and they can be assigned to categories based on whether their activity (opening) is influenced by membrane voltage (i.e., voltage-dependent vs. independent Ca^{2+} entry pathways exist).

The voltage-dependent Ca^{2+} channels identified in coronary vascular smooth muscle include L-type (Ca_V 1.2) channels (647, 814) and T-type (likely a Ca_V 3. X family member) channels (366). Voltage-independent Ca^{2+}-permeable pathways in coronary vascular smooth muscle include: (i) some purinergic P2X receptor subtypes (615,1021); (ii) select transient receptor potential (TRP) family members (471, 1004); and (iii) those composed of STIM and Orai subunits (298). A number of important points must be made clear about the relative roles of the various Ca^{2+} entry pathways in coronary vascular smooth muscle. First, L-type Ca^{2+} channels are expressed in all native coronary vascular smooth muscle types that have been studied [e.g., (358, 366, 647) Fig. 30]. Second, major species-specific differences are noted for the expression of T-type Ca^{2+} channels in coronary vascular smooth muscle. T-type channels are not expressed in the coronary smooth muscle cells of rabbits (647), dogs (130, 571), pigs (95, 358), or humans (776). While not present in the primary myocytes, T-type channels appear during the culture of human coronary smooth muscle cells, which may represent a phenotypic change elicited by an artificial environment (305,776). T-type channels are, however, normally expressed in the coronary smooth muscle of guinea pigs (366) and mice (156). Thus, it appears that T-type channels are more characteristic of the coronary myocytes from small animal models than of larger animals and humans. Third, while a number of voltage-independent Ca^{2+} channels are expressed in coronary vascular smooth muscle, their roles are not entirely clear and may have more to do with, for example, cell proliferation than coronary vascular reactivity (476). In contrast, when it comes to regulating coronary vascular tone, L-type Ca^{2+} channels clearly have the most dominant role, as: (i) diltiazem [a benzothiazepine-type Ca^{2+} channel antagonist) blocks ~90% of myogenic tone in human coronary arterioles (674); (ii) nifedipine (a dihydropyrdine-type Ca^{2+} channel antagonist) blocks 100% of agonist-induced tone in porcine coronary arterioles (50); and (iii) diltiazem completely eliminates coronary autoregulation, a mechanism that requires active coronary vasoconstriction (94) Figure 31]. Accordingly, L-type Ca^{2+} channels and their regulation in coronary vascular smooth muscle cells determine myocardial blood flow, as membrane potential and coronary vascular tone are very closely related by electromechanical coupling (647, 661). This electromechanical coupling mechanism necessarily involves K^+ channels.

K^+ channels dominate the membrane conductance of coronary arterial smooth muscle cells; therefore, they determine membrane potential and the activity of L-type Ca^{2+} channels (247). Membrane potentials in coronary artery smooth muscle cells are generally reported around −40 to −50 mV (503, 564, 661). This negative membrane potential is closer to the Nernst potential for K^+ (E_K; roughly −80 mV because of a highly asymmetric distribution of K^+) than the equilibrium potentials of other ions. The deviation of membrane potential from absolute E_K is due to open channels with selectivity for ions with reversal potentials that are less negative (e.g., Cl^-) or positive (e.g., Na^+). A membrane potential in smooth muscle cells near −40 to −50 mV is in a voltage window where L-type Ca^{2+} channel activity and intracellular Ca^{2+} are tightly controlled (346, 540). Several kinds of K^+ channels are expressed in coronary smooth muscle to control membrane potential and vascular reactivity.

Select types include: (i) large conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels; (ii) ATP-dependent K^+ (K_{ATP}) channels; (iii) inwardly rectifying K^+ (K_{ir}) channels, and (iv) voltage-dependent K^+ (K_V) channels (Fig. 32). There are other important types of K^+ channels in the coronary vasculature, but they are not discussed at length here. From the standpoint of coronary smooth muscle, stimuli that open K^+ channels lead to vasodilation through hyperpolarization and the resultant inhibition of L-type Ca^{2+} channels. For example, the K_{ATP} channel opener pinacidil increases coronary blood flow through this mechanism, although it was not completely understood at the time it was observed (729). With regard to the endothelium, stimuli that open K^+ channels lead to coronary vascular relaxation in two ways. First, hyperpolarization, increases the driving force for Ca^{2+} entry into endothelial cells through voltage-independent pathways, which couples to the production of relaxing factors (851). Second, the hyperpolarization spreads to the underlying coronary vascular smooth muscle through myoendothelial junctions (588). In the converse situations, mechanisms that inhibit K^+ channels of coronary smooth muscle and endothelium lead to vasoconstriction. It is ion channels and this kind of electromechanical coupling that controls coronary vascular tone and determines, for example, the transmural distribution of coronary blood flow (Fig. 33).

Transmural flow distribution and the role of ion channels

Myocardial perfusion is not the same in the left and right ventricle, nor is blood flow across the thickness of the myocardium uniform. Specifically, on a weight-to-weight basis, coronary blood flow is modestly higher in the left versus right ventricle and perfusion is greater in the endocardial versus epicardial layer (see Section "*Transmural flow distribution*"). This heterogeneity of flow is multifactorial, but the activity of ion channels in coronary vascular smooth muscle and their relationship to coronary vascular tone are important contributors. Specifically, voltage-dependent L-type Ca^{2+} channels are particularly important in determining the coronary vascular tone and the transmural distribution of coronary blood flow. FR 7534, a light-stable derivative of nifedipine, increases coronary blood flow more effectively than nitroglycerin (a nitrovasodilator) or dipyridamole (a pleiotropic vasodilator) and reduces the ENDO/EPI perfusion ratio (516). Similar effects can be seen with other dihydropyridine L-type Ca^{2+} channel blockers (960). For example, nisoldipine increases transmural coronary blood flow and alters the distribution of coronary vascular conductance, as it decreases the ENDO/EPI perfusion ratio (272,273). Another example of ion channels in the transmural distribution of blood flow can be found in diltiazem, which corrects endocardial ischemia downstream of a flow-limiting stenosis (38). These data indicate that L-type Ca^{2+} channels and electromechanical coupling control the transmural distribution of coronary blood flow. K^+ channels, which regulate the activity of those L-type Ca^{2+} channels through their effects on membrane potential, also influence the transmural distribution of coronary blood flow. Data to support that point have been revealed using the K_{ATP} channel opener pinacidil. Compared to sodium nitroprusside, a nitrovasodilator, pinacidil more selectively increased coronary blood flow and normalized the ENDO/EPI perfusion ratio (268). Similar effects of pinacidil on coronary blood flow and its transmural distribution have been observed in the hypertrophied heart (pressure-overloaded left ventricle) and downstream of a coronary artery stenosis (31). Thus, L-type Ca^{2+} channels directly control coronary vascular tone and the transmural distribution of

coronary blood flow, whereas K^+ channels indirectly affect the same parameters by regulating membrane potential, and thus L-type Ca^{2+} channels. This type of interplay between L-type Ca^{2+} channels and K^+ channels are important in other aspects of coronary vascular reactivity and myocardial flow regulation, such as the myogenic response and pressure-flow autoregulation.

Ion channels, myogenic responses, and coronary autoregulation

The myogenic response, which may be part of the mechanism whereby coronary blood flow is autoregulated (i.e., flow is maintained relatively constant over a wide range of pressures), is characterized as active force development in response to an increase in luminal pressure (see Section "*Myogenic control of coronary vascular resistance*"). Molecular entities that transduce stretch of the vascular wall into depolarization and constriction are not entirely clear, but may include ion channels themselves. Modeling suggests that channels permeable to Ca^{2+} and/or Na^+ in smooth muscle are activated in proportion to wall stress (149). Elegant experiments have demonstrated that in single coronary artery smooth muscle cells from the porcine coronary artery, graded stretch is associated with the activation of a cation current and concomitant increases in intracellular Ca^{2+} [(226,991) Fig. 34]. Intracellular Ca^{2+} increases because of release from intracellular stores and influx from the extracellular space (226). Stretch-induced Ca^{2+} influx is only partially sensitive to block by nifedipine, suggesting the involvement of both L-type Ca^{2+} channels and stretch-activated cation channels (226). These mechanically activated cation channels have been characterized using patch clamp techniques and stretching of the cells with dual micropipettes (991). Cation current, with a reversal potential of −18 mV, was related to cell length and associated with depolarization and increases in intracellular Ca^{2+} (991). While voltage-independent Ca^{2+}-permeable channels exist in coronary myocytes, it is Ca^{2+} influx through voltage-gated L-type channels that is absolutely required for coronary myogenic responses and coronary pressure-flow autoregulation. Other Ca^{2+}-permeable channels like nonselective cation channels are not sufficient to support myogenic contractions and autoregulation (although Na^+/Ca^{2+} influx and depolarization mediated by these channels contribute importantly). The molecular identity of nonselective cation channels underlying stretch-induced responses of coronary vascular smooth muscle remains to be determined. No study has addressed whether T-type Ca^{2+} currents play a role in coronary myogenic responses or pressure-flow autoregulation. In contrast, L-type Ca^{2+} channels are critical for the basal tone and myogenic constriction of coronary arterioles, as diltiazem completely dilates coronary arterioles from human atrium (674) and diltiazem abolishes pressure-flow autoregulation in the swine heart ((96); Fig. 31).

Manipulating K^+ channel activity also shows the importance of voltage-dependent tone (i.e., electromechanical coupling via L-type Ca^{2+} channels) in coronary vascular smooth muscle, as the K_{ATP} channel opener pinacidil elicits complete relaxation of coronary arterioles from swine hearts (912). Open K^+ channels produce membrane hyperpolarization, inhibition of L-type Ca^{2+} channels, and relaxation of coronary smooth muscle. This inhibition of L-type Ca^{2+} channels secondary to K^+ channel activation is fundamental in controlling coronary microvascular resistance. For example, through the autoregulatory mechanism, reductions in coronary perfusion pressure elicit dilation of coronary arterioles and, as shown by intravital

microscopy in dogs, this microvascular adjustment is antagonized by the K_{ATP} channel inhibitor glibenclamide (578). Glibenclamide also decreases coronary blood flow, linearizes the coronary pressure-flow relationship, and reduces the coronary autoregulation index in dogs (714). However, this is not a consistent finding; other studies in dogs demonstrate that glibenclamide reduces coronary blood flow to a similar degree across a wide range of perfusion pressures and this inhibition of K_{ATP} channels does not impact autoregulatory capability (883). Ion channels in the coronary endothelium also influence pressure-flow autoregulation. Specifically, intermediate conductance Ca^{2+}-activated K^+ (IK_{Ca}) channels, through their influence on NO production, modulate coronary autoregulation in dogs (594). Not all K^+ channels appear to function in coronary myogenic responses or autoregulation. For example, inhibition of K_V channels with 4-aminopyridine, while reducing coronary blood flow at any given pressure, had no effect on autoregulatory gain in swine at coronary perfusion pressures 100 mmHg (96). However, limiting pressure-induced increases in coronary blood flow with 4-aminopyridine at perfusion pressures >120 mmHg suggests that K_V channels can act as negative feedback to oppose myogenic constriction at especially high perfusion pressures (3, 96). Thus, the role of various K^+ channels in the regulation of coronary arteriolar tone is complex. This idea of heterogeneous roles for individual K^+ channel types is supported by studies in rat coronary arterioles showing that K_V and K_{ir} channels are active and contribute to spontaneous myogenic tone, whereas BK_{Ca} and K_{ATP} channels do not exert their effects (990). Moreover, the role of various ion channels in coronary vascular regulation is affected by the degree of physical fitness, hormonal status, and disease (605).

A variety of ion channels and their contributions to coronary vascular tone have been investigated with regard to gender, metabolic and endocrine health, and exercise. There are gender-based differences in coronary artery myogenic responses that involve BK_{Ca} channels. Specifically, compared to coronary arteries from intact female rats or estrogen-treated ovariectomized rats, pressure-induced constriction is approximately double in male or ovariectomized rats (965). Moreover, specific inhibition of BK_{Ca} channels with iberiotoxin causes greater constriction in coronary arteries from intact versus ovariectomized females (965). A mechanistic link between endocrine function and myogenic tone may be that testosterone increases the expression of L-type Ca^{2+} channels in coronary smooth muscle cells through a pathway involving protein kinase C (116, 633). Endurance exercise training increases the myogenic tone of coronary arterioles from swine (694). Mechanisms underlying this coronary vascular adaptation to exercise include alterations in cellular signaling, Ca^{2+} regulation, and ion channel function (113–115,444,445,582). For example, endurance exercise training in swine increases the contribution of BK_{Ca} and K_V channels to coronary arterial tone (115). Another mechanism that might explain greater myogenic tone in coronary arterioles from exercise trained swine is that L-type Ca^{2+} current in coronary myocytes is increased (444). Diabetes mellitus, while it impairs the function of K_{ATP} channels in human coronary arterioles, does not affect their myogenic tone (681). A similar lack of effect of diabetes mellitus on myogenic tone has been noted in coronary arterioles of mice (41). In contrast, coronary myogenic tone is diminished in diabetic rats (575), an observation that correlates with increased coronary blood flow at rest in diabetic patients

(761). Mechanisms underlying these species-specific differences and the roles of various ion channels remain to be determined.

The role of ion channels in local metabolic coronary vasodilation

The identity of the coronary metabolic dilator(s) has not been conclusively determined; however, a number of candidate molecules and/or factors have been examined (see Section Metabolic Control of Coronary Blood Flow"). Some putative mediators of coronary metabolic vasodilation like PO_2 and adenosine have fallen out of favor, while others like H_2O_2 and ATP have garnered interest recently (277, 336, 918). Regardless of the true identity of the precise factors that mediate metabolic coronary vasodilation, what the candidate molecules/factors generally have in common is that they alter the activity of ion channels in coronary vascular smooth muscle.

Oxygen and carbon dioxide—Hypoxia dilates rat coronary arteries, but glibenclamide does not inhibit this vasodilation, suggesting that K_{ATP} channels are not involved (629). A similar lack of effect of K_{ATP} channels in hypoxic vasodilation has been demonstrated in rabbit coronary arteries (511). In direct contrast, however, other studies in the same species show that hypoxia vasodilates the microcirculation of rat and rabbit hearts through the activation of K_{ATP} channels (539, 609, 713). Moreover, the impairment of hypoxia-induced vasodilation associated with diabetes mellitus in coronary arterioles from humans has been attributed to diminished activity of K_{ATP} channels (681). In support of K_{ATP} channels as mediators of hypoxic vasodilation, glibenclamide blocks the flow response in guinea-pig hearts and the relaxation of porcine small coronary arteries (222, 618). The reasons for conflicting views on the role of K_{ATP} channels in hypoxic vasodilation are unclear, but the majority of the evidence supports a role for glibenclamide-sensitive channels. In fact, hypoxia-induced activity of single K_{ATP} channels has been observed in swine coronary myocytes, and this correlates with the hypoxia-induced and glibenclamide-sensitive hyperpolarization of bovine coronary arteries (220,370,537). Other diverse K^+ channel types have been shown to participate hypoxic coronary vasodilation, as roles have been demonstrated for voltage-dependent and independent K^+ channels (448, 748). Inhibitors of BK_{Ca}, K_{ATP}, and K_V channels attenuate hypoxia-induced dilation of porcine coronary arteries, but their inhibitory effects are potentiated by simultaneous addition of K_V7 channel antagonists (448). Hypoxia activates Ba^{2+}-sensitive K_{ir} current in rabbit coronary myocytes and Ba^{2+} blocks hypoxia-induced vasodilation in Langendorff-perfused rabbit hearts (748). While acute hypoxia elicits coronary vasodilation via K^+ channels, chronic hypoxia decreases the expression of K_V channels in rat coronary myocytes (494). Further, ischemia secondary to coronary artery ligation in rats increases IK_{Ca} expression in a number of cell types in the vascular wall (819), but how this might impact coronary vascular reactivity remains to be determined. L-type Ca^{2+} channels in coronary vascular smooth muscle are also targets in hypoxic vasodilation, as low PO_2 inhibits Ca^{2+} channel activity in coronary myocytes from swine and humans (352, 862).

There is little known about the effect of CO_2 on coronary vascular ion channels; however, from an integrative point of view, metabolic production of CO_2 is associated with acidosis and there are some studies available regarding that stimulus. Acidosis dilates swine coronary

arterioles by opening K_{ATP} channels through a signaling pathway that includes pertussis toxin-sensitive G proteins (499, 500). This same intracellular signaling pathway to K_{ATP} channels is impaired by hypercholesterolemia in rabbit coronary smooth muscle (860). Like K^+ channels, Ca^{2+} channels in the coronary vasculature are also affected by pH, as intracellular acidification reduces the availability of L-type Ca^{2+} channels in porcine coronary myocytes (568).

Potassium—There are several ways in which extracellular K^+ ions might influence coronary vascular reactivity through hyperpolarization, such as stimulating the Na^+/K^+-ATPase (which is electrogenic due to stoichiometry) and "activation" of K_{ir} channels. Extracellular K^+ ions do not literally activate (i.e., increase the open probability of) K_{ir} channels; rather they bind external sites and relieve the strong rectification by reducing the interference of intracellular cations with K^+ permeation. This relief increases the small, but physiologically relevant, outward current through K_{ir} channels. KCNJ2 (K_{ir} 2.1 gene) likely encodes the K_{ir} channel of rat coronary artery smooth muscle (117). These K_{ir} channels in rat coronary arteries mediate extracellular K^+-induced hyperpolarization and dilation (569, 797). The functional expression of K_{ir} channels in smooth muscle of the swine coronary tree is inversely related to artery diameter (775). Moreover, activation of Ba^{2+}-sensitive K_{ir} channels mediates remote dilation of swine coronary arterioles, which is a mechanism postulated to be important in metabolic dilation (793).

Adenosine—Adenosine activates whole-cell K_{ATP} current and single channels in smooth muscle cells from the swine coronary artery (219), effects that should lead to hyperpolarization and dilation (221, 565). Accordingly, in dogs, glibenclamide inhibits adenosine-induced coronary vasodilation (185, 286, 497). In fact, inhibition of coronary K_{ATP} channels with glibenclamide dose-dependently diminishes myocardial perfusion until ischemia is evident (285, 497, 823). Moreover, in swine, endothelium-denuded coronary arterioles dilate in response to adenosine and this response is blocked by glibenclamide (450,451). Additionally, the pathway from adenosine stimulation to K_{ATP} channels in swine coronary arterioles is mediated by A_{2A} receptors, depends on the activation of pertussis toxin-sensitive G proteins, but is independent of cyclic nucleotide signaling (450, 451). In rabbit hearts, glibenclamide reduces the dilator response to adenosine, but not acetylcholine (an endothelium-dependent vasodilator) or papaverine (a vasodilator with multiple actions) (712). There is a transmural difference in coronary arteriolar dilation to adenosine in the swine heart, as glibenclamide-sensitive adenosine-induced vasodilation is greater in endocardial vessels (1016). This difference in epicardial versus endocardial arterioles and the role of K_{ATP} channels has been observed directly in the canine heart using intravital microscopy (995). A K^+ channel that is not K_{ATP} may contribute to adenosine-induced relaxation in human coronary arteries, but glibenclamide is without effect (556, 630). Similarly, glibenclamide has no inhibitory effect on adenosine-induced dilation of rat coronary arteries (629). In contrast, glibenclamide-sensitive K_{ATP} channels are involved in adenosine-induced coronary vasodilation in humans *in vivo* (325).

K_{ATP} channels are not the only type of channels involved in adenosine-induced coronary vasodilation. For example, K_V channels play a role in adenosine-induced dilation of the

canine coronary microcirculation (246). Specifically, inhibition of K_V channels with 4-aminopyridine reduces adenosine-induced hyperemia *in vivo* and adenosine-induced dilation of isolated, pressurized arterioles. Moreover, correolide, a selective K_V1 channel blocker, inhibits the dilation of canine coronary arterioles elicited by adenosine (246). The effect of adenosine to increase coronary blood flow in dogs is mediated by A_{2A} receptors and blocking K_V channels with 4-aminopyridine attenuates this hyperemia (97). In coronary arterioles from swine hearts, 4-aminopyridine-sensitive K_V channels participate in adenosine-induced dilation (78). Iberiotoxin, a selective blocker of BK_{Ca} channels, antagonizes adenosine dilation of canine coronary arteries (141). In metabolically healthy swine, BK_{Ca} channels contribute to adenosine-induced dilation of coronary arterioles; however, the contribution of BK_{Ca} channels is reduced in swine with metabolic syndrome (109). Similarly, neither BK_{Ca} nor apamin-sensitive small conductance Ca^{2+}-activated K^+ (SK_{Ca}) channels contribute to adenosine dilation of coronary arterioles from patients with heart disease, but adenylate cyclase and some unidentified Ca^{2+}-activated K^+ channel (perhaps IK_{Ca}) do (832). Small coronary arterioles are more sensitive to the dilating effect of adenosine and small coronary arteries also express more K_{ir} channels (593,775). Moreover, in rabbit hearts and coronary smooth myocytes, adenosine increases K_{ir} current through A_3 receptors and protein kinase A signaling (866). K_V channels (sensitive to tetraethylammonium and 4-aminopyridine) contribute to adenosine-induced dilation of swine coronary arterioles in a gender-specific manner (443). Adenosine-mediated relaxation is significantly attenuated in coronary arterioles from swine with hypercholesterolemia; this is correlated to the loss of K_V current in isolated myocytes (447). Endurance exercise training in swine does not correct impaired adenosine-induced vasodilation in coronary arterioles or activation of K_V channels in coronary muscle cells (445). K_V and K_{ATP} channels contribute to adenosine-induced coronary arteriolar dilation swine, but it is only the contribution of K_{ATP} channels that is impaired by early-stage metabolic syndrome (78).

Adenine nucleotides—Adenine nucleotides (ATP, ADP, and AMP) have coronary vascular effects (345). In dogs, the coronary venous plasma concentration of ATP increases during dynamic exercise and purinergic receptor blockade decreases the balance between the coronary supply of and the myocardial demand for oxygen (324, 388). ATP has been included in a model of coronary blood flow regulation where it acts as a signal controlling functional hyperemia (768). In that negative feedback scheme, ATP is postulated to act on coronary vascular endothelial cells and transmit a hyperpolarizing signal to the smooth muscle in upstream resistance vessels. Determining what that signal is and how it is transmitted will require additional study, but human coronary endothelial cells possess a Cl^- channel that is inhibited by ATP (617). In human coronary myocytes, ATP activates BK_{Ca} and Cl^- channels by releasing stored Ca^{2+} (892). In rat coronary arteries, UTP, which activates some of the same receptors as ATP (e.g., P2Y), causes constriction by classical electromechanical coupling in smooth muscle (966). Specifically, UTP activates an inward Na^+-permeable current and inhibits K_V current; these effects elicit depolarization and increase intracellular Ca^{2+} by activation of nisoldipine-sensitive L-type Ca^{2+} channels. A similar mechanism is likely responsible for the UTP-induced and diltiazem-sensitive constriction of canine coronary arteries (648). When ATP is considered as a signaling molecule, it is also important to consider signaling due to products of its hydrolysis,

including ADP, AMP, and adenosine (the latter, a nucleoside, described in more detail earlier). ADP-induced activation of $P2Y_1$ receptors in swine leads to coronary arteriolar dilation and increased coronary flow; however, the ionic mechanisms involved have not been determined (77). ADP is further acted upon by endothelial enzymes including CD39 and CD37 to produce adenosine; both ADP and adenosine dilate murine and human coronary arteries via hyperpolarization (726). Thus, endothelial ecto-5′-nucleotidases can be viewed as EDHF synthases.

Reactive oxygen species (H_2O_2)—When reactive oxygen species (ROS) and coronary vascular reactivity are mentioned together, the first images conjured are typically of an injurious nature. For example, there are many variations on a theme where ROS damage the coronary endothelium and interfere with NO signaling (1). ROS can also impair ion channel function in smooth muscle. For example, peroxynitrite inhibits BK_{Ca} channel activity in smooth muscle of human coronary arterioles (621) and superoxide impairs K_V channel function in myocytes from rat coronary arteries (622). Importantly, however, it is likely that the amount and type of ROS are important factors, as ROS are also important signaling molecules for normal coronary vascular function in the healthy heart (133). Specifically, recent interest has focused on H_2O_2 as an activator of K^+ channels in coronary myocytes and thus a mediator of coronary vasodilation, as studies show that H_2O_2 is an endothelium-derived relaxing factor and a candidate coronary metabolic vasodilator (307). There are endothelium-dependent and independent effects of H_2O_2 in the dilation of swine coronary arterioles; the smooth muscle effect involves the activation of BK_{Ca}, but not K_{ATP}, channels (907). In human coronary arterioles, the signaling pathway from H_2O_2 to BK_{Ca}-mediated dilation involves the redox-sensitive dimerization of protein kinase G (1019). Tetraethylammonium-sensitive K^+ channels (BK_{Ca} or K_V) in the coronary microvasculature are redox-sensitive targets in the cardioprotective effect of endogenous H_2O_2 during ischemia-reperfusion injury (997). In the dog heart, erythropoietin enhances the H_2O_2- and BK_{Ca}-mediated dilation of coronary collateral arterioles during ischemia (999). Redox-sensitive K_V (but not BK_{Ca}) channels mediate H_2O_2-induced vasodilation in canine coronary arterioles and in the canine heart *in vivo* (799). Similarly, it has been reported that tetraethylammonium-sensitive K^+ channels (BK_{Ca} or K_V) in the coronary microvasculature of dogs are the targets of endogenous H_2O_2 in pacing-induced metabolic coronary vasodilation (1000). In canine coronary myocytes, H_2O_2-induced activation of BK_{Ca} and K_V channels has been demonstrated using patch clamp techniques (798). In porcine coronary myocytes, products of arachidonic acid metabolism mediate H_2O_2-induced stimulation of BK_{Ca} channels (51, 52). While multiple K^+ channel types are activated by H_2O_2, K_V channels may have the most critical role in H_2O_2-induced coronary metabolic vasodilation for four reasons. First, experiments with the generic K_V channel inhibitor 4-aminopyridine show that endogenous, myocardial-derived H_2O_2 is a feed-forward (open-loop) signal in coronary metabolic vasodilation *in vivo* in dogs (820). Second, 4-aminopyridine-sensitive K_V channels contribute to the regulation of coronary blood flow at rest and during increases in myocardial oxygen consumption caused by treadmill exercise in swine (94). Third, in swine, correolide-sensitive K_V1 channels regulate baseline coronary vascular tone and vasodilation in response to increased myocardial metabolism [(384) Fig. 35A]. Fourth, there is a requisite role for smooth muscle $K_V1.5$ channels in coronary metabolic dilation in

mice [(725) Fig. 35B)]. Specifically, there is a linear relationship between coronary blood flow and cardiac metabolism (estimated as the product of mean arterial pressure and heart rate) in wild-type mice; the relationship between myocardial oxygen supply and demand is markedly depressed in global $K_V1.5$ knockout mice. Smooth muscle-specific restoration of $K_V1.5$ channels rescues the coronary vascular phenotype of the global knockout mice (725). K_V7 channels do not contribute to metabolic or ischemic dilation in the swine heart, but these channels do function in coronary vascular responses mediated by the endothelium (383).

Ion channel function in endothelial regulation of the coronary circulation

Coronary vascular endothelium releases a variety of substances that contract or relax the underlying smooth muscle (see Section "Endothelial-Dependent Control"). This paracrine regulation of coronary vascular tone involves ion channels in both the endothelium and smooth muscle. For example, ion channels in coronary vascular endothelium are important signaling mechanisms activated by humoral stimuli (e.g., substance P) and shear stress. Likewise, ion channels in smooth muscle can be the targets or end-effectors of endothelium-derived vasoactive substances (e.g., endothelin and NO). In endothelial cells, an increase in intracellular Ca^{2+} is often an important step in the production of vasoactive molecules. Accordingly, changes in the coronary endothelial cell Ca^{2+} concentration have been recorded during substance P-induced vasodilation in rabbit coronary arterioles (693). Substance P elicits both intracellular Ca^{2+} release and Ca^{2+} influx in endothelial cells from the porcine coronary artery (227). In coronary endothelial cells from swine, increases in intracellular Ca^{2+} are associated with SK_{Ca}- and IK_{Ca}-mediated hyperpolarization, which maintains the driving force for Ca^{2+} entry through voltage-independent channels (227, 851). Moreover, this Ca^{2+} entry elicited by substance P-induced store depletion in porcine coronary endothelium involves signaling via tyrosine kinases (852). The vasodilation elicited by substance P in porcine coronary arterioles is mediated entirely by NO (590); however, the endothelium-derived factors and the ion channels they act on can vary depending upon the type of receptor activated. For example, IK_{Ca} and SK_{Ca} (but not BK_{Ca}) channels mediate thrombin-induced endothelium-dependent dilation of human coronary arterioles (112), whereas the endothelium-dependent responses to bradykinin in those same vessels rely upon the activation of SK_{Ca} and BK_{Ca} (but not K_{ATP}) channels (679). It is not only G-protein-coupled transmembrane receptors that lead to the production of endothelial-derived relaxing factors, as mechanical stimulation of the coronary endothelium is also an important mechanism regulating vascular tone. In human coronary arterioles, H_2O_2 is the transferrable factor mediating flow-induced dilation and it acts via SK_{Ca}, IK_{Ca}, and BK_{Ca} (but not K_{ATP}) channels (619, 678, 680, 1019). The contribution of NO and other endothelium-derived relaxing factors to coronary vasodilation differs depending on vessel diameter and, for example, BK_{Ca} channels are the end-effectors of NO-independent vasodilation in smaller caliber coronary vessels of dogs (719). K_V channels also contribute to endothelium-dependent responses of the coronary circulation (292), as, for instance, K_V7 channel inhibitors attenuate bradykinin-induced coronary vasodilation in swine (160, 383). The role of ion channels in endothelial regulation of coronary vascular tone is impacted by disease, cardiovascular risk factors, and the degree of physical fitness. For example, SK_{Ca}, IK_{Ca}, and gap junctions contribute to conducted vasodilation in human coronary arterioles, a

response that is impaired by aging (327). Similarly, impairments in SK_{Ca} and IK_{Ca} channels contribute to the endothelial dysfunction of coronary arterioles from diabetic patients (623). In comparison, endurance exercise training enhances the contribution of BK_{Ca} channels to endothelium-dependent relaxation of arteries taken from ischemic areas of the swine heart (234).

Endothelin is a major endothelium-derived contracting factor and ion channels in smooth muscle contribute to endothelin-induced constriction of the coronary circulation (552). Signaling centers around L-type Ca^{2+} channel activity and there are two general mechanisms of regulation: (i) transmembrane signaling that directly activates L-type Ca^{2+} channels and (ii) membrane depolarization caused by activation of nonselective cation and Cl^- channels or inhibition of K^+ channels. Endothelin activates L-type Ca^{2+} currents in coronary myocytes (391), an effect that can also be observed at the single-channel level (861). In the cell-attached single channel experiments, the L-type Ca^{2+} channels under study were physically isolated from the bath (and, thus, application of endothelin) by the patch pipette; therefore, these experiments demonstrate that diffusible intracellular signaling entities were responsible for activation. Nonselective cation channels can depolarize the membrane and also serve as a Ca^{2+} entry pathway, as TRPC channels are activated by endothelin in coronary smooth muscle (572, 821, 822). Similarly, endothelin depolarizes coronary smooth muscle membrane potential by stimulating a Ca^{2+}-activated Cl^- current (567) and inhibiting BK_{Ca}, K_{ATP}, and K_{ir} channels (492, 686, 749).

Neural control and end effector ion channels

Ion channels in the coronary vasculature integrate with neural input to regulate myocardial perfusion. Sympathetic regulation of the coronary circulation, which involves catecholamines released from postganglionic fibers innervating the heart as well as those introduced to the circulation from the adrenal medulla, is complex. This is because the neurohumoral factors have effects on: (i) the myocardium (i.e., impacting metabolism and oxygen demand of the heart muscle, which has a major influence on coronary vascular tone); (ii) coronary endothelium; and (iii) coronary smooth muscle. Effects secondary to stimulation of the myocardium fall under the category of metabolic dilation (389), while effects on endothelial cells are in the realm of paracrine signaling (238). Sympathetic regulation of coronary vascular tone is further complicated by the presence of multiple adrenoceptor types (α and β) and subtypes (e.g., α_1 and α_2) in coronary smooth muscle. While these G protein-coupled transmembrane receptors are closely related, they can link to diverse intracellular signaling machinery for vasoconstriction or vasodilation (see Section "Neural Control").

Coronary vasoconstriction elicited by sympathetic stimulation involves α adrenoceptors for catecholamines as well as signaling by neuropeptide Y (NPY), a cotransmitter (412, 464). By whatever mechanisms sympathetic coronary vasoconstriction occurs, it ultimately depends on electrome-chanical coupling in smooth muscle, as nifedipine abolishes it (463,466). For example, nifedipine prevents coronary vasoconstriction elicited by α_1 and α_2 agonists (464). Sympathetic vasoconstriction mediated by α_2 signaling downstream of a coronary stenosis in dogs is not relieved by vasodilators like adenosine, dipyridamole, or

isosorbide dinitrate, but is ameliorated by the blockade of L-type Ca^{2+} channels (465). As for the cotransmitter, coronary injection of NPY in swine elicits vasoconstriction; *in vitro*, NPY-induced coronary artery contraction is nifedipine-sensitive (812). It is clear that signaling through α adrenoceptors can increase coronary microvascular resistance *in vivo*, but the mechanisms involved remain uncertain. This is because mechanistic *in vitro* work with pressure myography, which revealed so many details of myogenic and paracrine signaling in coronary arterioles, has been of little use in the study of adrenergic vasoconstriction. Specifically, α adrenergic constriction of coronary arterioles cannot be observed *in vitro*, but coronary venules under the same conditions do constrict (521). This has led to the idea that α adrenergic coronary vasoconstriction is mediated indirectly via endothelin released from cardiomyocytes (908). Coronary vasodilation elicited by sympathetic stimulation involves β adrenoceptor signaling to ion channels. There is heterogeneous transmural expression of β adrenoceptors, as swine epicardial arterioles dilate more to β_2 agonists than do endocardial arterioles; but effects are mediated by K_{ATP} channel activation in both vessel types (452). Stimulation of β adrenoceptors on porcine coronary myocytes activates BK_{Ca} channels through a membrane-delimited pathway involving the αs G-protein subunit (845). Cyclic nucleotide signaling is also involved in the activation of BK_{Ca} channels by catecholamine receptor signaling (437, 972). Specifically, when receptor stimulation increases cAMP production, there is a cross-activation cGMP-dependent protein kinase resulting in the activation of BK_{Ca} channels (437, 972). In porcine coronary myocytes, dopamine D1 receptor agonists activate K_{ATP} channels through a protein kinase A signaling pathway (554). Another complexity in sympathetic regulation of the coronary circulation regards the localization of adrenoceptors and the source catecholamines. Specifically, some adrenoceptors are localized to sites of innervation (clustered on the postsynaptic membrane), while others are more widely distributed. Thus catecholamines in the circulation, whether injected experimentally or released from the adrenal medulla, can have effects on the coronary circulation that are quantitatively different from those released from sympathetic nerves (169, 390, 436).

Integrative control of the coronary circulation

Normal cardiac function critically depends on adequate myocardial oxygen delivery; therefore, it is unlikely that any single vasodilator mechanism is totally responsible for the local metabolic control of coronary blood flow. That is, multiple vasodilator mechanisms likely participate and compensation is likely to occur when individual mechanisms of coronary vasodilation are inhibited. This principle is exemplified in the studies of Ishibashi et al. and Tune et al. (497,921). In dogs performing treadmill exercise, a combination of pharmacological inhibitors was used to block K_{ATP} channels (glibenclamide), adenosine receptors (8-phenyltheophylline), and NO production (N_G-nitro-L-arginine). As outlined above, blockade of these individual vasodilator mechanisms has little to no effect on the balance between coronary blood flow and myocardial metabolism. However, Ishibashi et al. demonstrated that combining these antagonists significantly steepened the relationship between coronary venous PO_2 and MVO_2 (497) (Fig. 36). This study, along with others by the Bache laboratory support a compensatory role for adenosine following the inhibition of K_{ATP} channels with concentrations of glibenclamide sufficient to diminish baseline coronary blood flow and depress regional cardiac function (283, 285, 286, 497). Alternatively, similar

triple blockade studies which utilized lower systemically administered doses of glibenclamide noted marked reductions in coronary venous PO_2 versus MVO_2 (Fig. 36). This combined inhibition failed to significantly affect exercise-induced increases in coronary blood flow and MVO_2 under these conditions in either dogs (921) or swine (664). These studies further support that adenosine serves as a compensatory dilator mechanism following the onset of ischemia and have led to the idea that wholly parallel and/or redundant mechanisms of coronary metabolic vasodilation exist and act to preserve the balance between myocardial oxygen delivery and metabolism (664). However, understanding of the interplay between these redundant pathways remains poorly understood and an area of much needed research. Such future studies must acknowledge the potential for species variability, the selectivity of antagonists and/or genetic knockout approaches utilized, and the potential for acute and chronic (patho)pathophysiologic compensation which is highly dependent on the overall level of tissue oxygenation.

Conclusion

The heart is uniquely responsible for supplying its own blood supply through the coronary circulation. The coronary arteries arise from the sinuses of Valsalva in the aorta and course over the surface of the heart like a crown(Latin *coronarius* meaning "of a crown"). The epicardial coronary arteries divide over the surface of the heart in a base to apex direction, sending penetrating branches transmurally through the outer epicardium to the inner endocardium. Blood flow through these vessels is influenced on a beat to beat basis by changes in extravascular compressive forces (myocardial tissue pressure). As such, the left ventricle receives ~80% of its blood supply during diastole whereas the much thinner right ventricle, which is subject to much lower myocardial tissue pressures, is primarily perfused during systole. Given the higher compressive forces and oxygen requirements of the left ventricular endocardium, there is a modest gradient for coronary flow across the wall of the heart. Typically, endocardial to epicardial flow ratios range from ~1.1 to 1.5 and are facilitated by higher densities and lower resistances of the endocardial microcirculation.

The coronary circulation possesses a high degree of pressure-flow autoregulation and thus blood flow is maintained relatively constant over a wide range of perfusion pressures (~60–120 mmHg). However, this autoregulatory capacity is recognized to be lower in left ventricular endocardium and the right coronary circulation. It is well recognized that the primary determinant of coronary blood flow and overall myocardial oxygen delivery is the rate of myocardial oxidative metabolism (MVO_2). Extensive research over the past 50+ years has specifically focused on elucidating mechanisms responsible for the regulation of coronary vascular resistance in response to a variety of (patho)-physiologic stimuli such as perfusion pressure, metabolism, hypoxemia, anemia, and episodes of myocardial ischemia. In particular, studies have focused on a variety of mechanisms that include myogenic, local metabolic, endothelial, neural, hormonal, and endothelial and vascular ion channels. While it is clear that each of these mechanisms can have profound influence over myocardial perfusion, our understanding of the collective mechanisms responsible for the regulation of coronary blood flow remains rather limited. Comprehension of the control of coronary flow is further complicated by the recognition that the determinants of blood flow and factors modulating microvascular resistance operate within specific microdomains of the coronary

vascular tree. Furthermore, there is evidence to support that these pathways act in a parallel and redundant manner such that when specific pathways are inhibited pharmacologically or impaired by disease, compensatory mechanisms are activated to prevent an imbalance between myocardial oxygen delivery and metabolism (i.e., myocardial ischemia) (270, 285, 286, 497, 664, 790, 791, 918, 920, 921). Delineation of the precise mechanisms responsible for the dynamic regulation of coronary blood flow is more important than ever as it is now recognized that impaired coronary microvascular function (in the absence of overt coronary atherosclerosis) is a powerful, independent correlate of cardiac mortality (704). Research into these mechanisms stands to provide much needed insight and more effective diagnostic and therapeutic approaches for the treatment of coronary and cardiovascular disorders.

Acknowledgments

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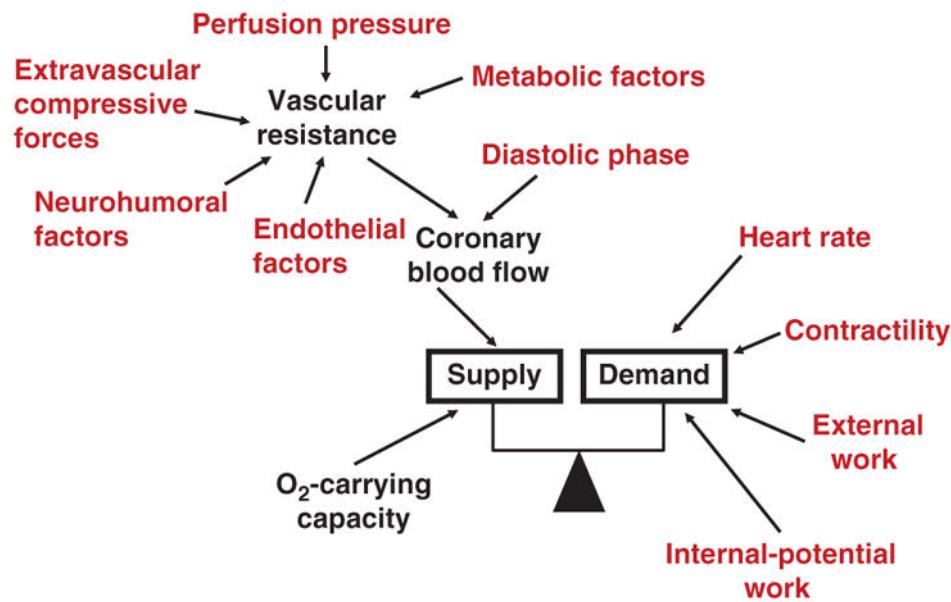
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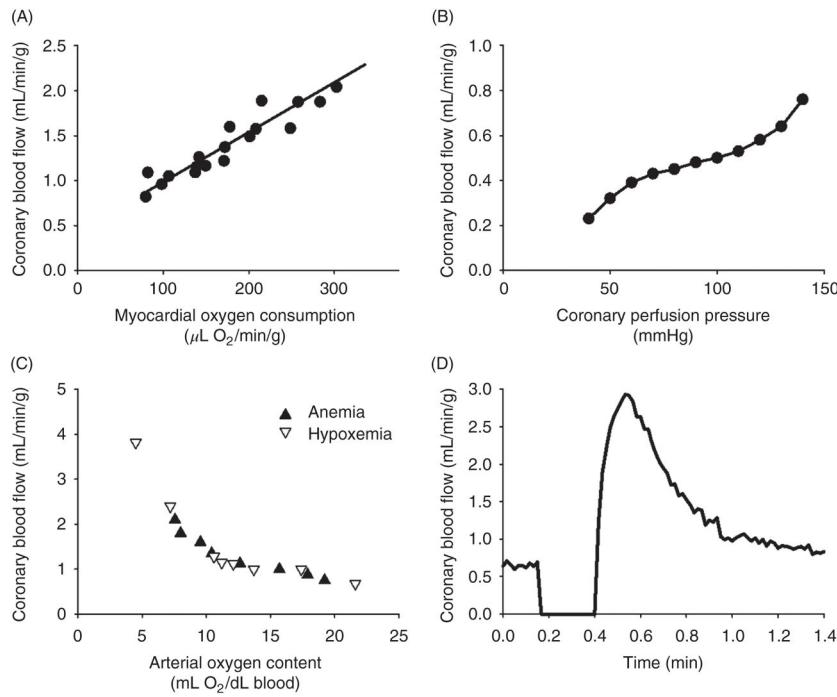
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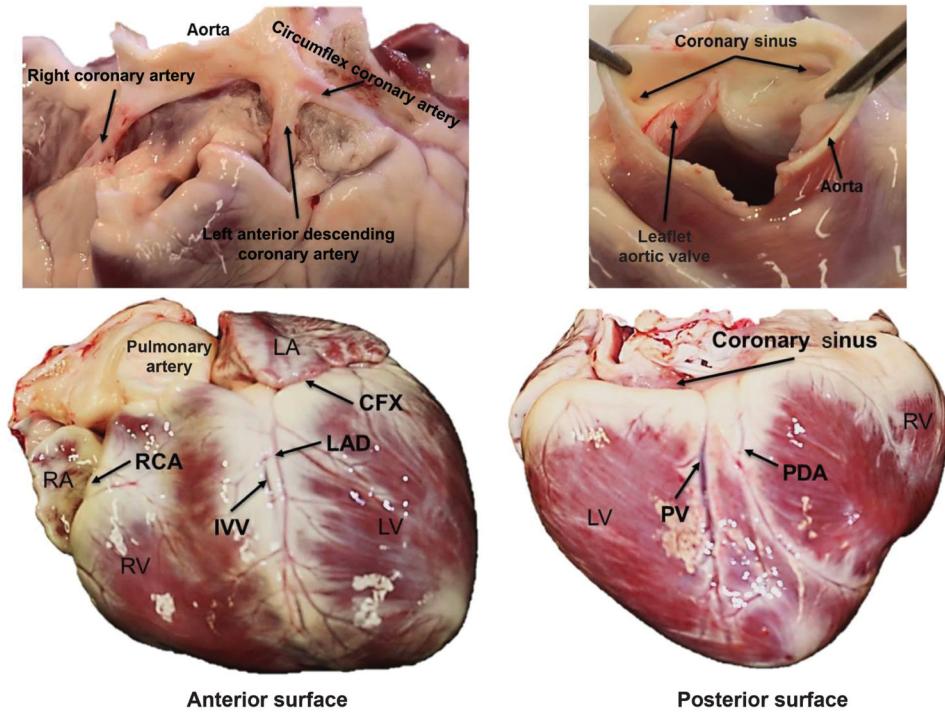
Figure 1.
Schematic diagram of the determinants of myocardial oxygen supply and demand. Adapted, with permission, from Ardehali and Ports (16) and reported by Tune (918).
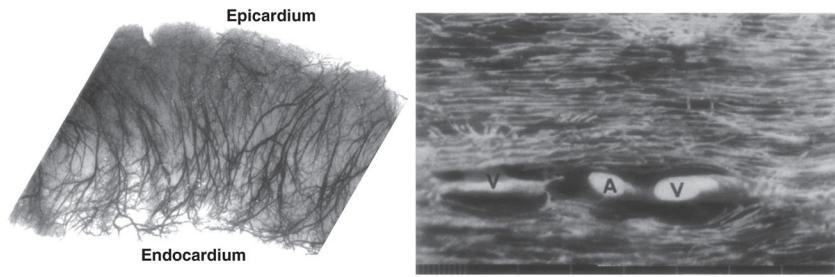
Figure 2.
(A) Relationship between coronary blood flow and myocardial oxygen consumption during exercise in swine [data, with permission, from Berwick et al. (94)]. (B) Relationship between coronary blood flow and coronary perfusion pressure in swine [data, with permission, from Berwick et al. (96)]. (C) Coronary blood flow response to reductions in arterial oxygen content via hemodilution-anemia [data, with permission, from Tarnow et al. (905) and Fan (323)] or hypoxia [data, with permission, from Merrill et al. (670); Walley et al. (958); and Hermann and Feigl (458)]. (D) Coronary response to a transient coronary artery occlusion [data, with permission, from Borbouse et al. (110)].
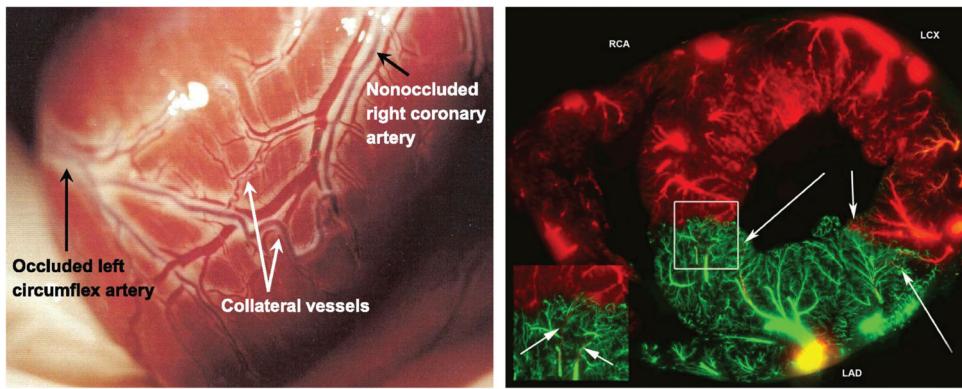
Figure 3.
Representative pictures of the anatomy of the coronary circulation. Right atrium (RA), RCA, right ventricle (RV); interventricular vein (IVV); LAD coronary artery; left atrium (LA); circumflex coronary artery (CFX); left ventricle (LV); posterior vein (PV); PDA [data, with permission, from Tune (918)].
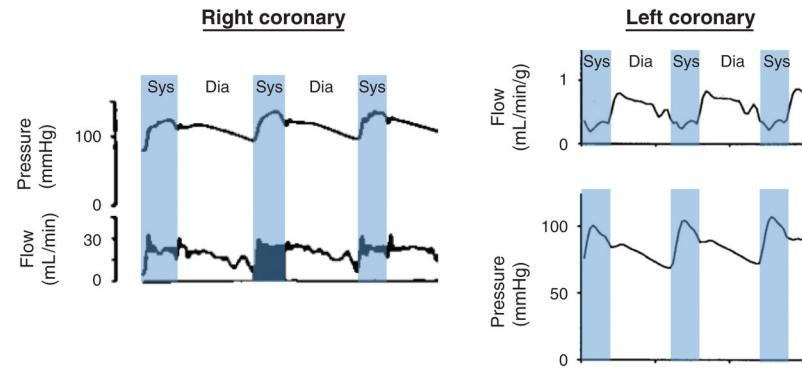
Figure 4.
(A) Radiograph of left ventricular free wall from a 52-year-old man who died of acute arsenic poisoning. He had no occlusive coronary disease and no valvular or myocardial abnormalities. Adapted, with permission, from Estes et al. (321). (B) Microvasculature of the left ventricular myocardium showing an arteriole, A (about 35–40 μm diameter), and two venae comitantes, V. The scale below gives 10- and 100-μm intervals. The venule on the right is about 40×80 μm. This arrangement is the usual one for arterioles from l-mm diameter down to those of 15-μm diameter [data, with permission, from Bassingthwaighte et al. (62)].
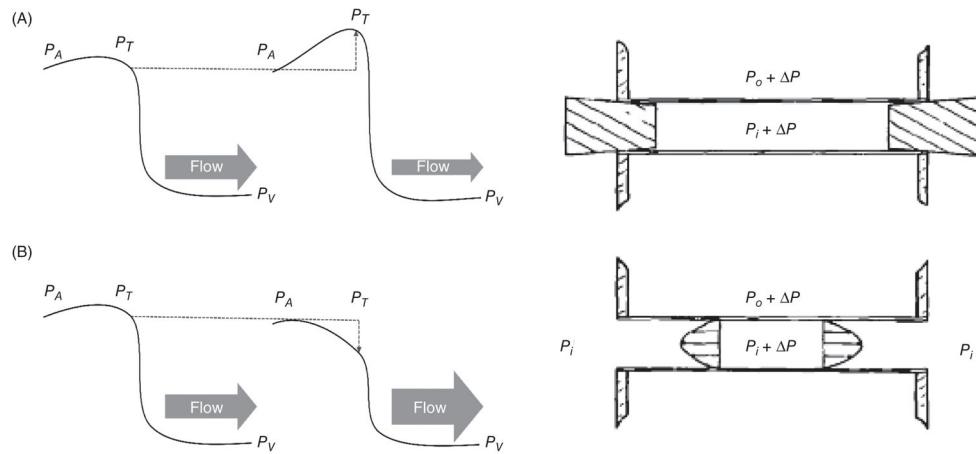
Figure 5.
Left: Representative photograph illustrating the apical view of a canine heart 4 months following placement of an ameroid occluder around the proximal left circumflex coronary artery (entering from the left side of the photograph). Typical canine coronary collateral arteries are clearly visible on the epicardial surface, including both large (~1 mm diameter) and smaller, tortuous arterial connections between a branch of the completely occluded left circumflex coronary artery and a branch of the nonoccluded RCA (446). Right: Green fluorescent replica material was infused in the LAD, and red was infused in the LCX and RCA. Visual inspection reveals at least 2 coronary collaterals between the LAD and LCX as indicated by the two arrows on the *right*. The arrow on the *left* indicates a subendocardial collateral connection between LCA and LCX. The *inset* on the *left* is an enlarged detail of the inner half of the myocardium corresponding to the border between LAD an RCA (see square in the main image), showing mixing of colors along arterioles. Note that the perfusion areas are well defined, yet borders may be frayed between the LAD and LCX or RCA perfusion territories. Some green vessel segments within the red LCX area indicate that a small amount of green contrast may have entered through collateral connections that then has been pushed to smaller vessels upon the arrival of the red dye (932).
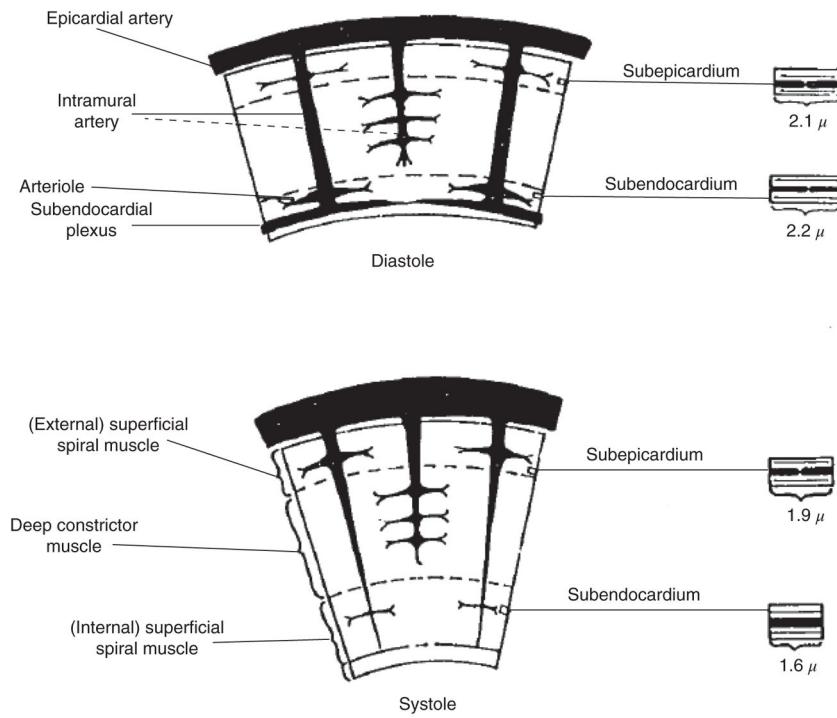
Figure 6.
Phasic tracing of right coronary blood flow [adapted, with permission, from Lowensohn et al. (628)] and left circumflex coronary blood flow [adapted, with permission, from Tune et al. (923)] relative to aortic pressure.
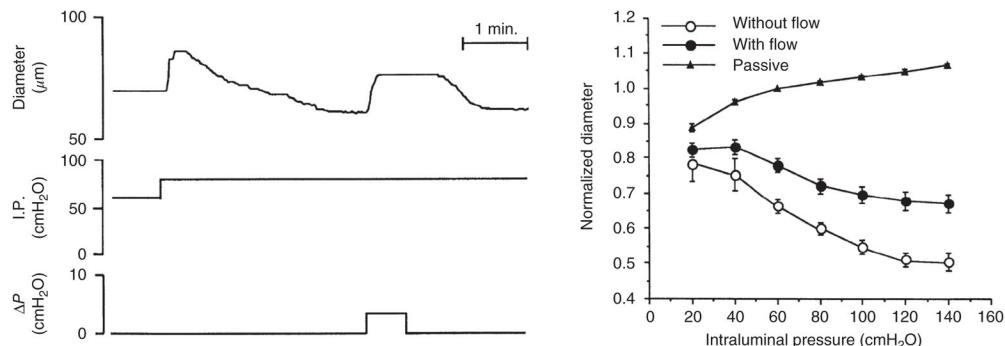
Figure 7.
Left: Schematic representation of a vascular waterfall in which flow is dependent on the elevation between the rim of the falls [tissue pressure (P_T)] and the highest point upstream [arterial pressure (P_A)], irrespective of the overall height of the falls [arterial pressure (P_A) – venous pressure (P_V)]. Right: Principle of the intramyocardial pump. Top: Pressure within a closed elastic tube P_i is in equilibrium with the pressure outside P_o. Enlarging P_o by ΔP leads to an increase in P_i also by ΔP. Bottom: When the flexible tube is open, ΔP also will be transmitted now causing flow which is impeded by viscous forces [data, with permission, from Spaan et al. (871)].
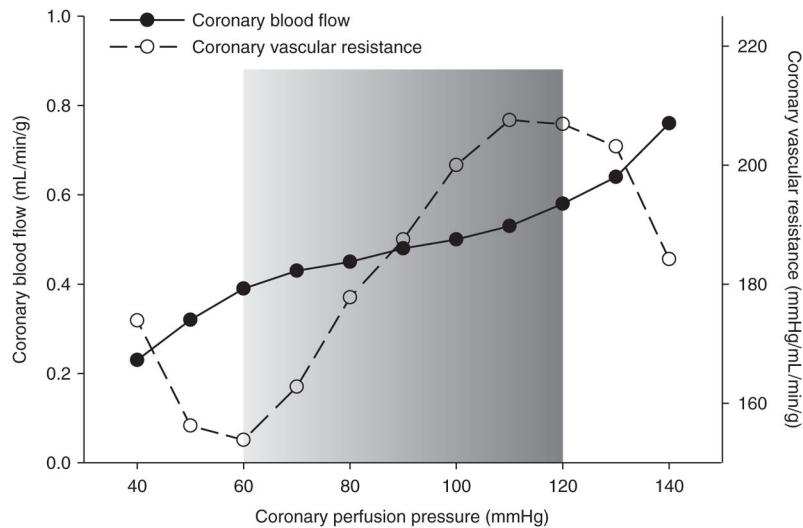
Figure 8.
Schematic cross-section of the myocardial wall at end-diastole and end-systole [data, with permission, from Bell and Fox (72)].
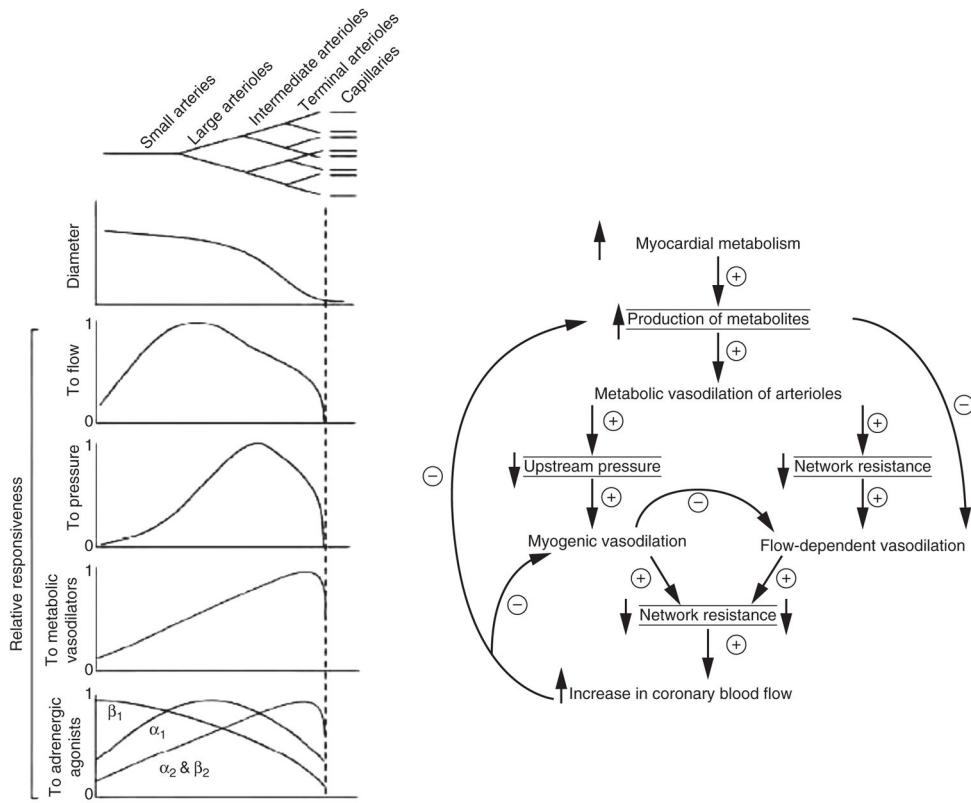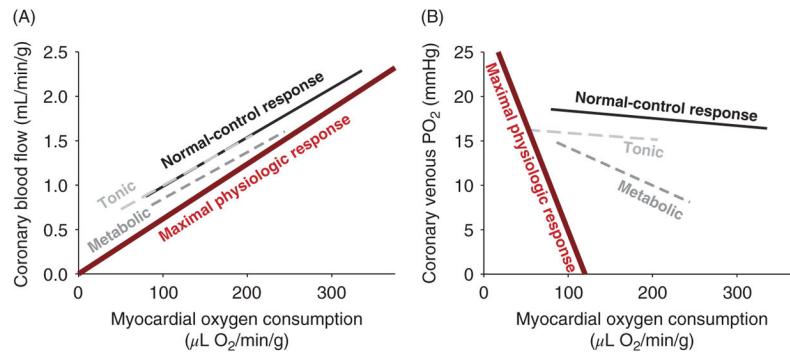
Figure 9.
Left: Example of interaction between pressure-induced myogenic response and flow-dependent dilation in isolated, pressurized subepicardial arteriole. Right: Pressure-diameter relationship of arterioles with and without flow [data, with permission, from Kuo et al. (590)].
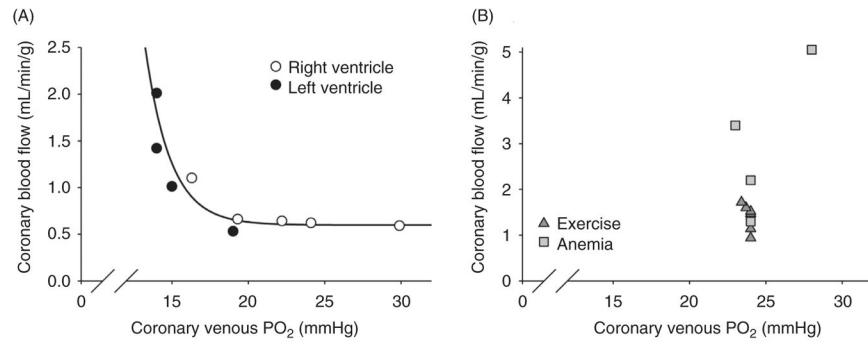
Figure 10.
Relationship between coronary blood flow and coronary vascular resistance relative to coronary perfusion pressure [data, with permission, from Berwick et al. (96)].
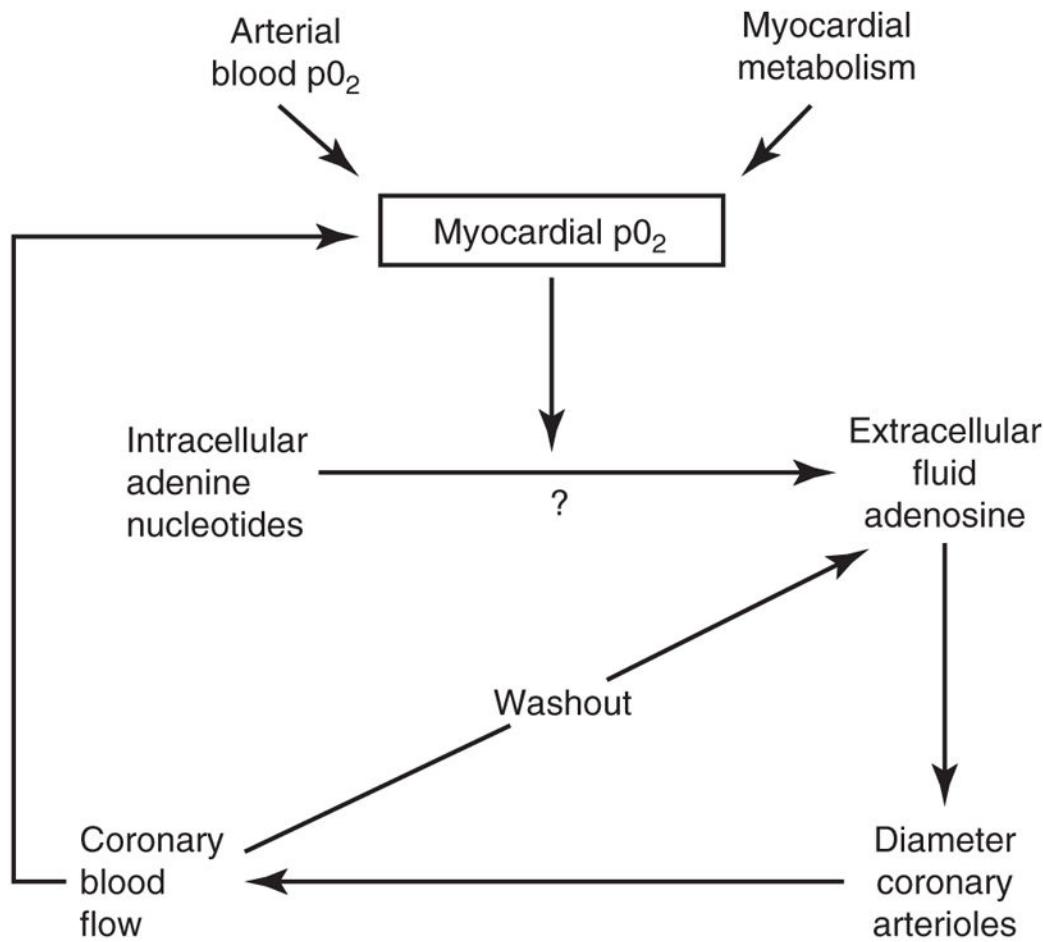
Figure 11.
Left: Schematic diagram for series-coupled segmental responses of coronary vasculature to flow, pressure, metabolic, and adrenergic stimuli [data, with permission, from Davis et al. (225)]. Right: Proposed interaction between metabolic, myogenic, and flow-mediated regulation of coronary microvascular resistance during increases in myocardial metabolism [data, with permission, from Muller et al. (692)].

Figure 12.

Relationship between coronary blood flow (left) and coronary venous PO_2 (right) versus myocardial oxygen consumption in conscious instrumented swine at rest and during exercise under control conditions, following inhibition of pathway that produces similar reductions in coronary flow and myocardial oxygen consumption (tonic), and during a condition that produces progressive limitation in coronary vasodilation with increases in oxygen consumption (metabolic). The physiologic limit of these relationships are depicted by the red line (maximal physiology response) which represents the condition in which all oxygen delivered in extracted and consumed (i.e., 100% oxygen extraction) [data for each plot were derived, with permission, from the same animal (swine) under the same conditions from the study of Berwick et al. (94)].
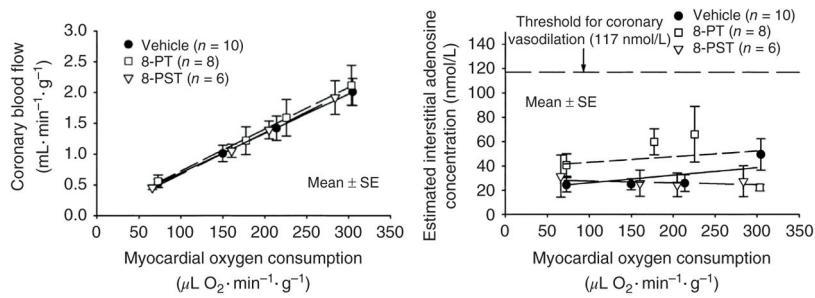
Figure 13.
Left: Relationship between coronary blood flow and coronary venous PO_2 in the right and left ventricle at rest and during exercise in dogs [data, with permission, from Tune et al. (923) and Hart et al. (441)]. Right: Relationship between coronary blood flow and coronary venous PO_2 in response to exercise in swine [data, with permission, from Duncker et al. (281)] and isovolemic hemodilution-induced anemia [data, with permission, from Van Woerkens et al. (935)].
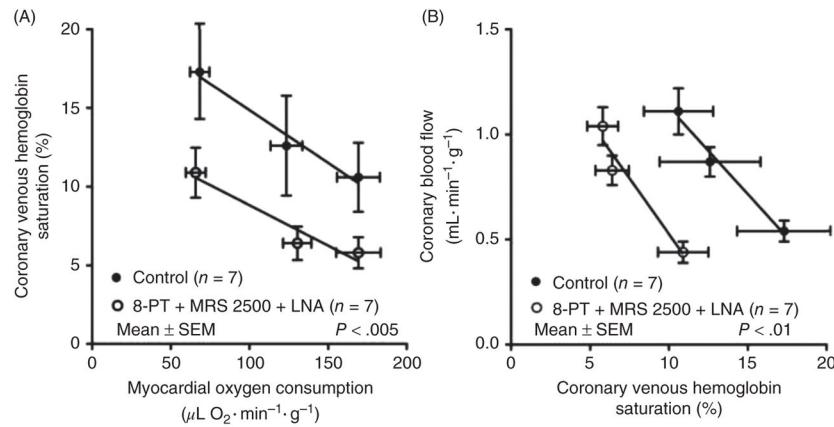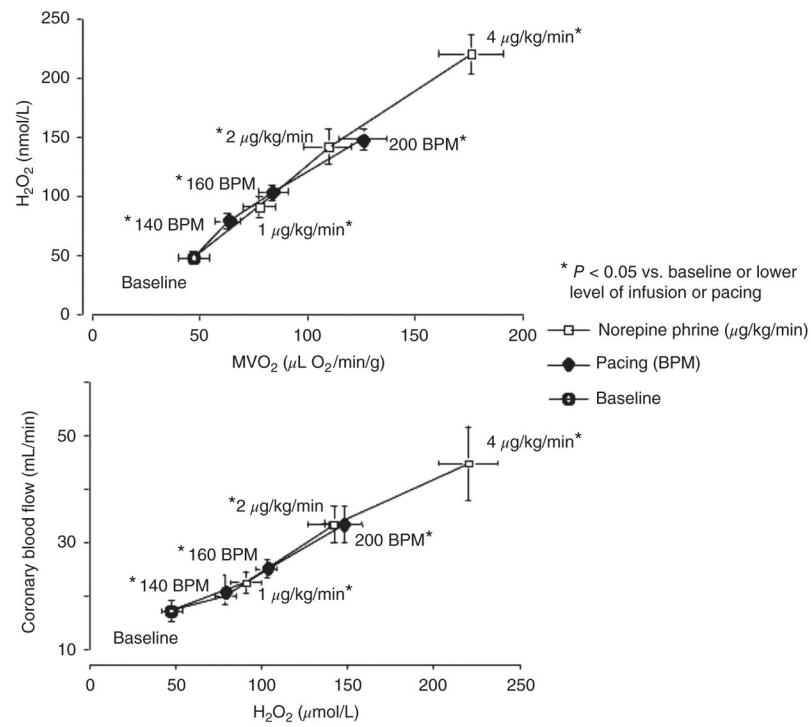
Figure 14.
Berne's adenosine hypothesis of local metabolic control of coronary blood flow as a negative feedback control system [data, with permission, from Berne (85)].
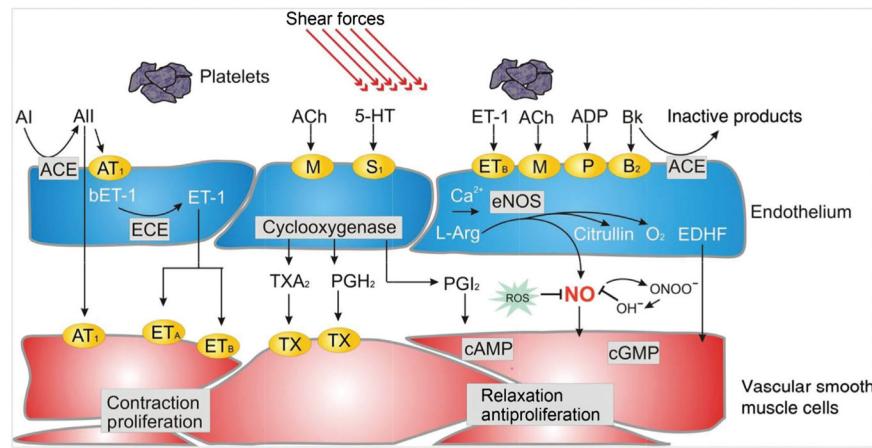
Figure 15.
Left: Relationship between coronary blood flow and myocardial oxygen consumption with and without adenosine receptor blockade [8-phenyltheophylline (8-PT) or 8-sulfophenyltheophylline (8-PST)] in dogs at rest and during graded treadmill exercise. Right: Relationship between estimated interstitial adenosine concentration and myocardial oxygen consumption with and without adenosine receptor blockade in dogs at rest and during graded treadmill exercise [data, with permission, from Tune et al. (923)].
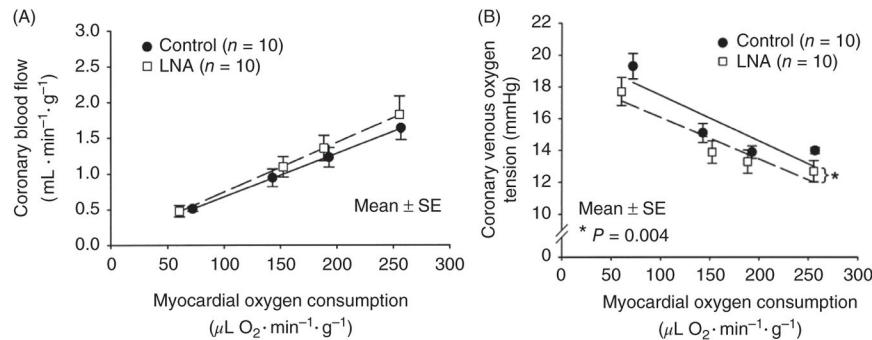
Figure 16.
Relationship between coronary venous hemoglobin saturation versus myocardial oxygen consumption (left) and coronary blood flow versus coronary venous hemoglobin saturation (right) in instrumented dogs at rest and during exericse with and without inhibition of adenosine receptors [8-phenyltheophylline (8-PT), P2Y$_1$ receptors (MRS 2500), and nitric oxide synthase: L-nitro-arginine (LNA)] [data, with permission, from Gorman et al. (388)].
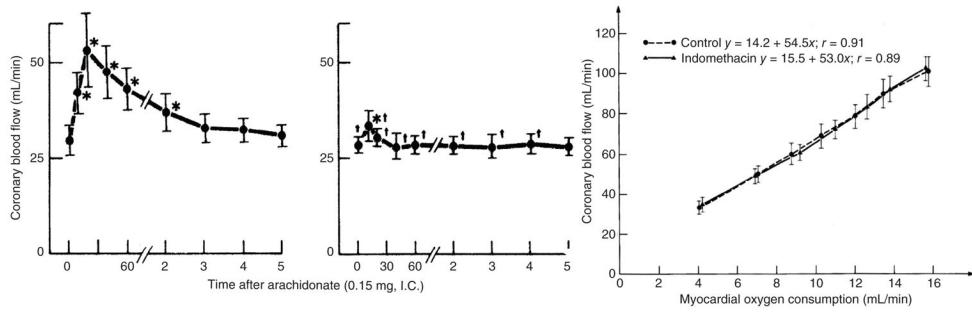
Figure 17.
Relationship between cardiac H_2O_2 concentration and myocardial oxygen consumption (top) and coronary blood flow and H_2O_2 concentration (bottom) in anesthetized, open-chest dogs at baseline, during cardiac pacing, or norepinephrine infusion [data, with permission, from Saitoh et al. (820)].

Figure 18.
Endothelium-derived vasoactive substances. ACE, angiotensin-converting enzyme; Ach, acetylcholine; AI, angiotensin I; AII, angiotensin II; AT1, angiotensin 1 receptor; Bk, bradykinin; COX, cyclooxygenase; ECE, ET-converting enzyme; EDHF, endothelium-derived hyperpolarizing factor; ETA and ETB, endothelin A and B receptors; ET-1, endothelin- 1; l-Arg, l-arginine; M, muscarinic acetylcholine receptor; PGH2, prostaglandin H2; ROS, reactive oxygen species; S1, serotoninergic receptor; TX, thromboxane receptor; TXA2, thromboxane; 5-HT, serotonin [from, with permission, Gutierrez et al. (415)].
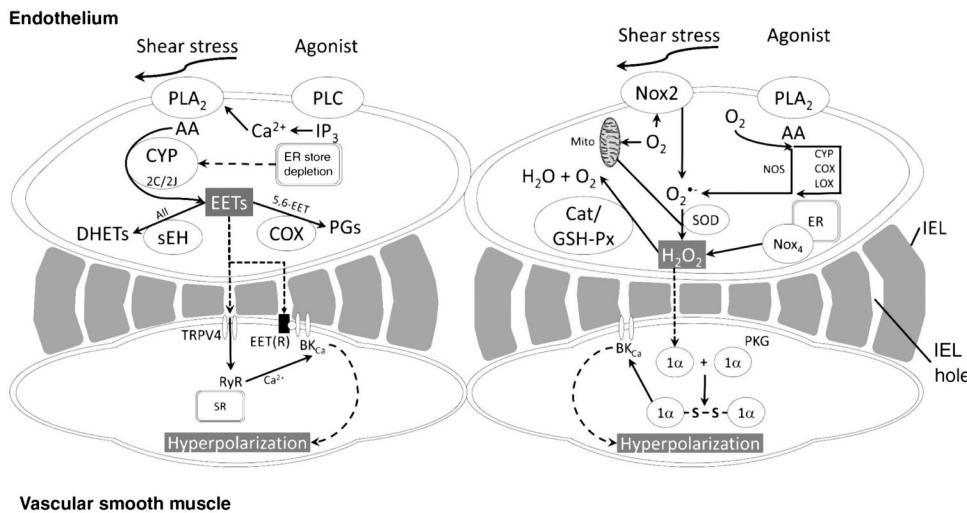
Figure 19.

Relationship between coronary blood flow (left) and coronary venous PO$_2$ (right) versus myocardial oxygen consumption in dogs at rest and during exercise with and without the inhibition of nitric oxide synthase with LNA [data, with permission, from Tune et al. (920)].
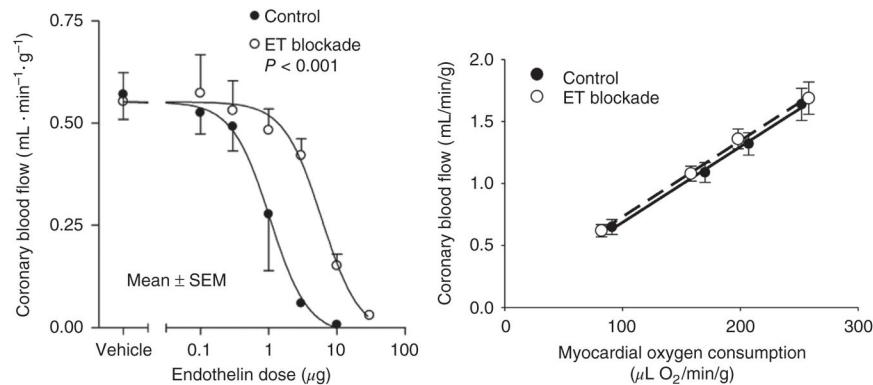
Figure 20.
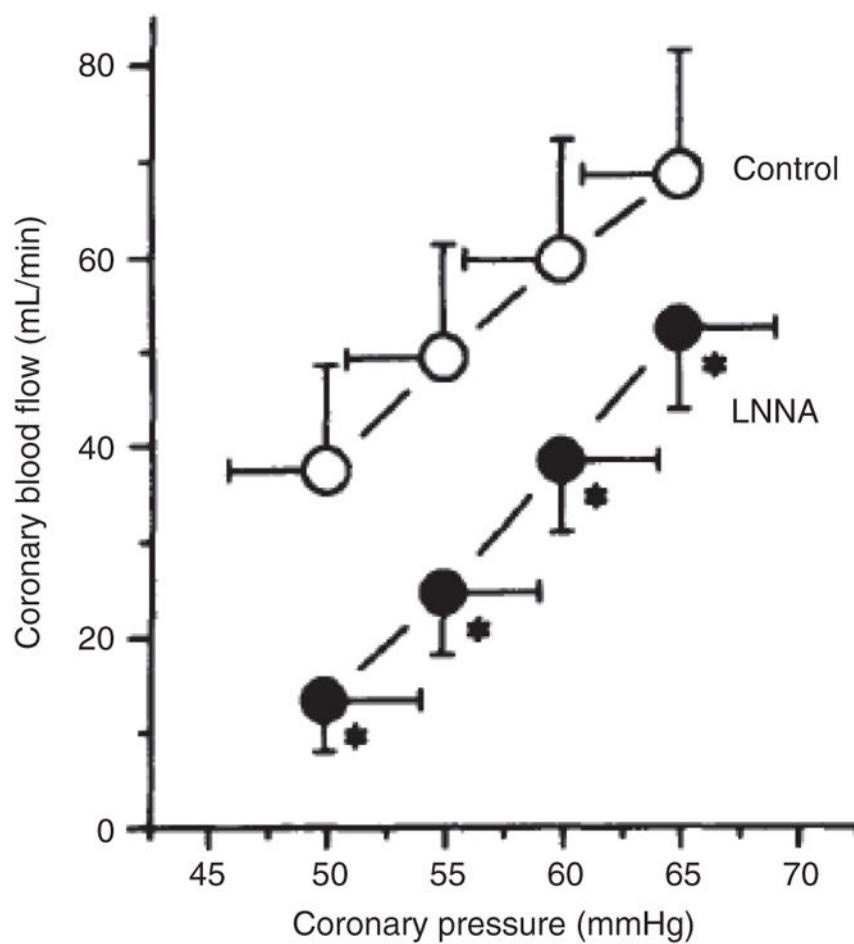
Coronary blood flow response to intracoronary arachidonate before (left) and after inhibition of cyclooxygenase with indomethacin (middle). Right: Relationship between coronary blood flow and myocardial oxygen consumption in dogs at rest and during exercise with and without indomethacin [data, with permission, from Dai and Bache (213)].

Figure 21.
Left: Biosynthesis and bioavailability of EC-derived EETs and H_2O_2. The activation of phospholipase A_2 (PLA_2) following stimulation with shear stress or secondary to IP_3-sensitive ER Ca^{2+} store depletion by agonists leads to synthesis of AA, which is metabolized by CYP 2C or 2J isoenzymes to produce EETs, with (sEH; for all EET regioisomers) and COX (for 5,6-EET only) metabolizing EETs to DHETs and prostaglandins (PGs), respectively, thereby influencing EET bioavailability. Right: Shear stress and agonist stimulation also result in the reduction of molecular O_2 to form the ROS superoxide ($O_2^{\bullet-}$), as a byproduct of metabolism, by a number of sources, including NOS, CYP, COX, lipoxygenase (LOX), and mitochondria (mito). $O_2^{\bullet-}$ is then further reduced by SOD to form H_2O_2, the bioavailability of which is determined by endogenous antioxidant enzymes, which include Cat and glutathione peroxidase (GSH-Px). Nox isoforms (Nox2 and Nox4) synthesize ROS as their sole enzymatic product, with Nox2 producing $O_2^{\bullet-}$ and Nox4 mainly H_2O_2 [adapted, with permission, from Ellinsworth et al. (307)].
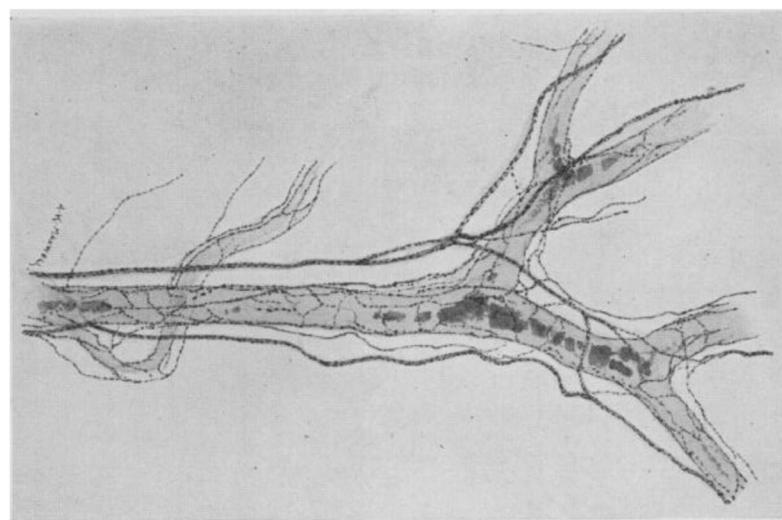
Figure 22.
Left: Effect of intracoronary endothelin administration on coronary blood flow in anesthetized dogs in the absence and presence of endothelin (ET) receptor blockade. Right: Relationship between coronary blood flow and myocardial oxygen consumption in dogs at rest and during exercise in the absence and presence of ET receptor blockade [data, with permission, from Gorman et al. (386)].
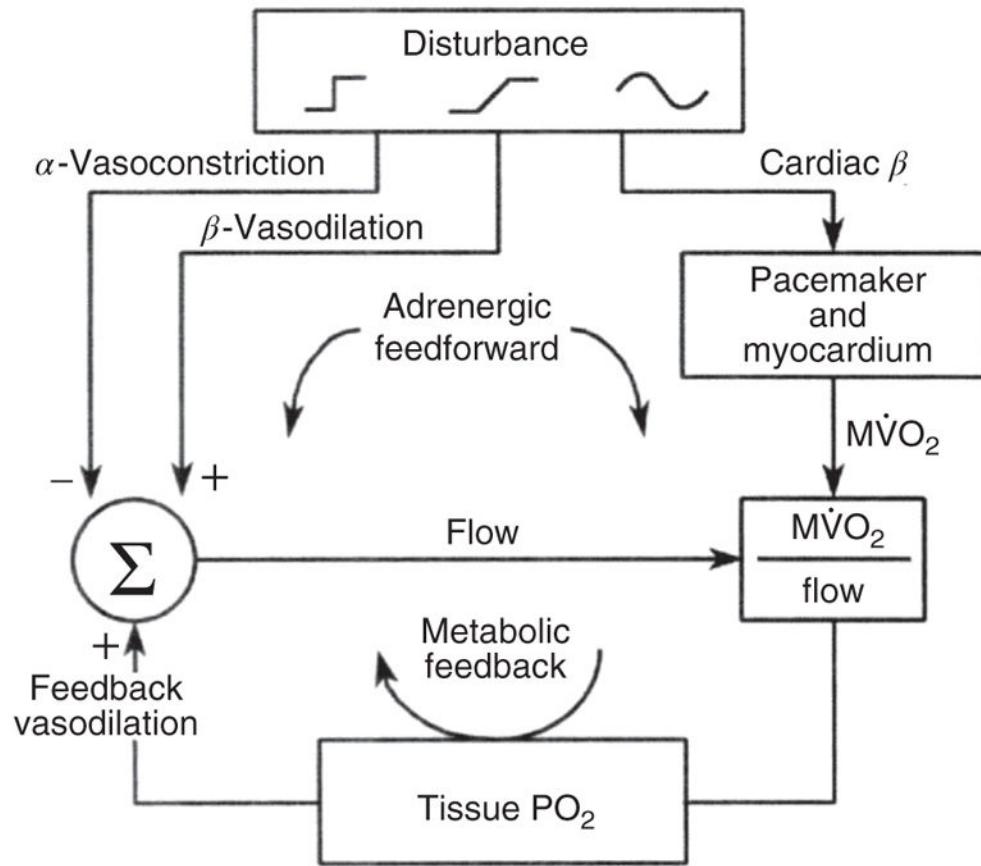
Figure 23.
Graphs showing the descending limb of the coronary pressure-flow relation in the presence of intact vasomotor tone in exercising dogs with and without the nitric oxide synthase inhibitor LNNA [data, with permission, from Duncker and Bache (269)].
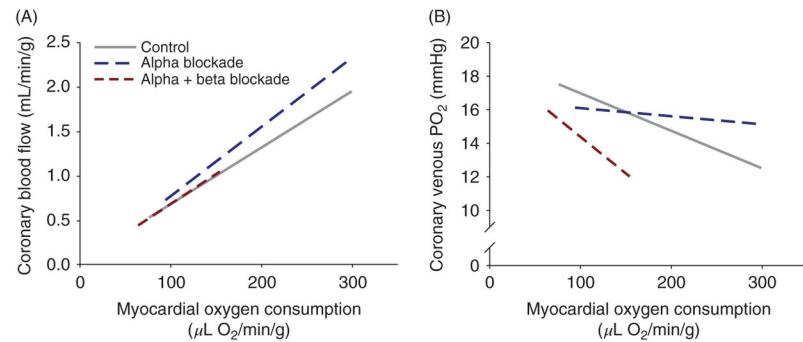
Figure 24.
Representative drawing of innervation of a coronary artery (cat) from Woollard (989).
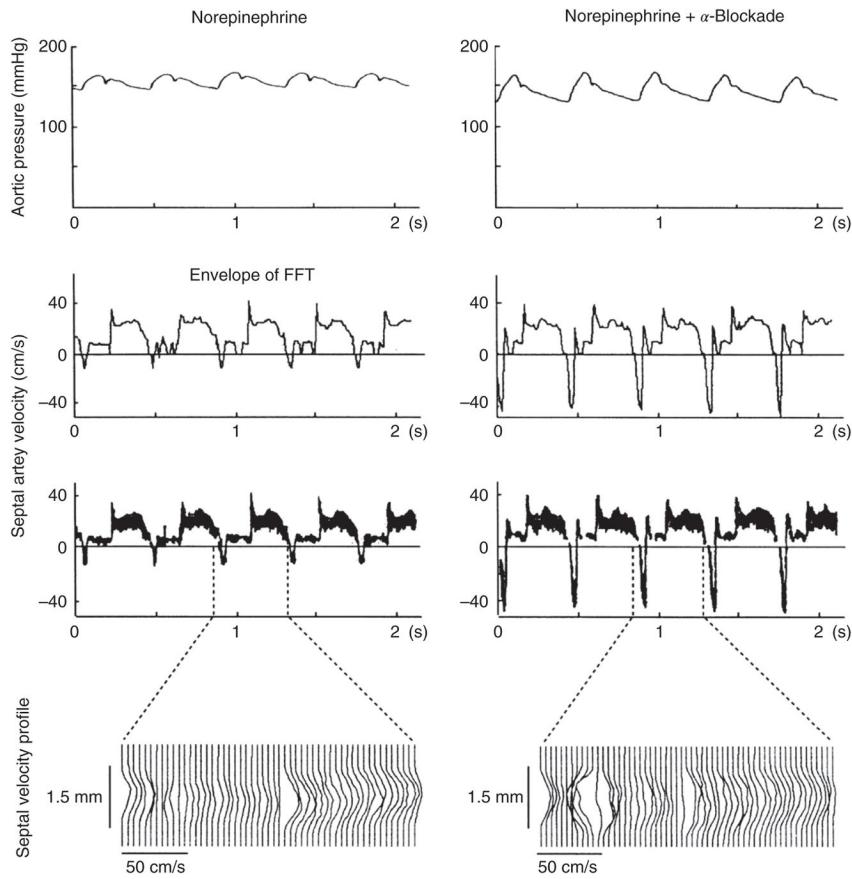
Figure 25.
Schematic diagram of combined adrenergic feedforward (open-loop) and local metabolic feedback (closed-loop) control of coronary blood flow [data, with permission, from Feigl (335)].
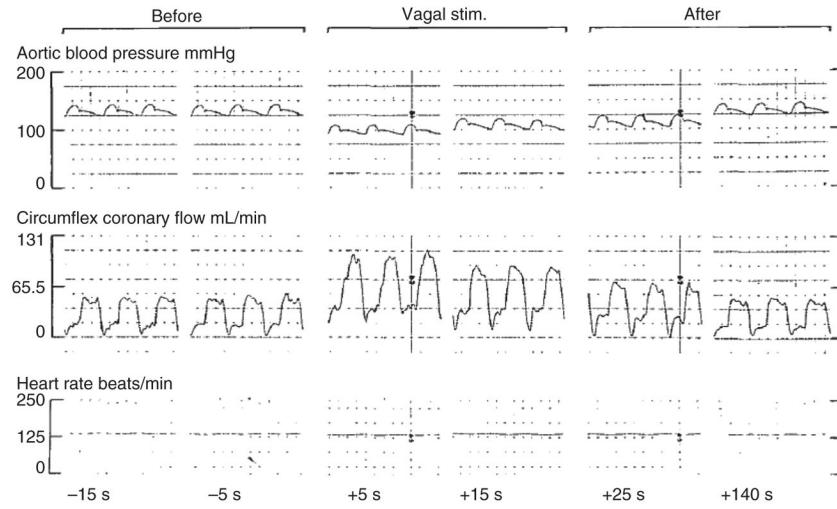
Figure 26.
Relationship between coronary blood flow (left) and coronary venous PO_2 (right) versus myocardial oxygen consumption in dogs at rest and during exercise with and without the inhibition of α-adrenoceptors or α + β-adrenoceptors [data, with permission, from Gorman et al. (389)].
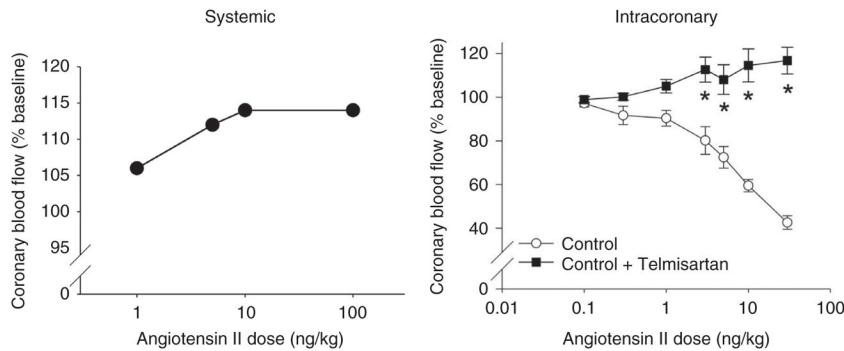
Figure 27.
Recordings from one dog during norepinephrine infusion (0.25 μg · kg^{-1} · min^{-1}) before and after α-adrenoceptor blockade with phenoxybenzamine, with a right atrial paced heart rate of 140 beats/min during low-level vagal stimulation to slow the intrinsic heart rate. FFT of the septal artery flow velocity is shown with the envelope of the FFT calculated at one-half the maximum power. Shown at bottom are septal artery velocity profiles determined every 8 ms during individual cardiac cycles, before and after α-blockade. Forward flow is shown as a curvature of the velocity profile to the right, and retrograde flow is shown by a bowing to the left. Note that negative value retrograde flow velocity was greater after α-receptor blockade than before blockade during norepinephrine infusion [data, with permission, from Morita et al. (689)].
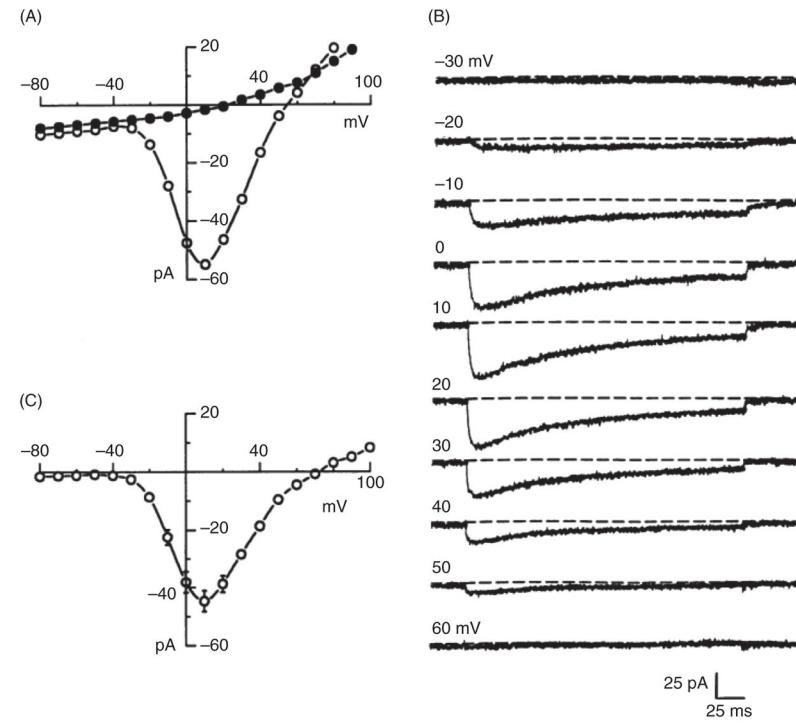
Figure 28.
Effects of a 20-s vagal stimulation (30 Hz, 8 volts, and 2 ms) on blood pressure, left circumflex coronary blood flow, and heart rate in an anesthetized dog [data, with permission, from Feigl (329)].
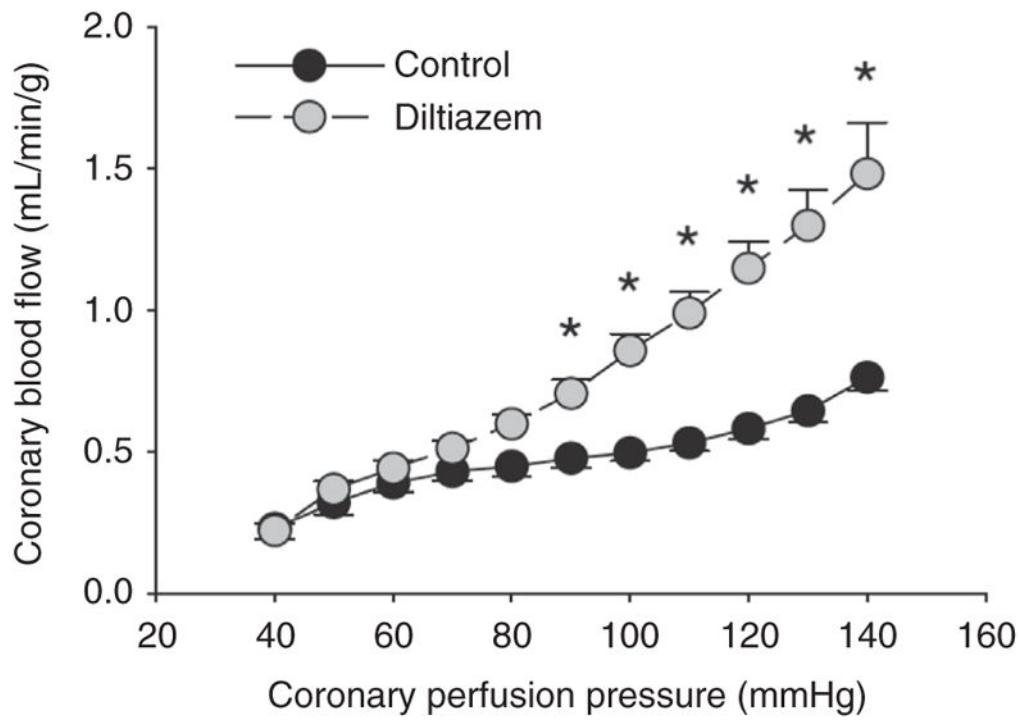
Figure 29.
Left: Coronary blood flow response to systemic (intravenous) administration of angiotensin II [data, with permission, from Doursout et al. (258)]. Right: Coronary blood flow response to intracoronary administration of angiotensin II with coronary perfusion pressure held constant at 100 mmHg by a servo-controlled extracorporeal perfusion system [data, with permission, from Zhang et al. (1018)].
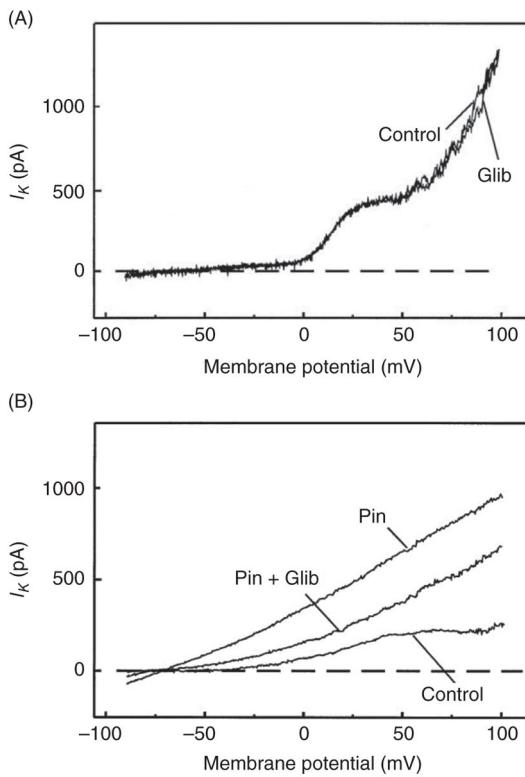
Figure 30.
Patch clamp recordings of voltage-gated Ca^{2+} current in smooth muscle cells from the rabbit coronary artery. Panel A shows a representative I–V relationship in 2.2 mmol/L Ca^{2+} before (open symbols) and after (filled symbols) 500 μmol/L Cd^{2+}. Panel B contains a portion of the family of traces, leak subtracted, used to create the I–V in panel A. Currents were elicited from a holding potential of −80 mV. Panel C is a graph of group data (16 cells) [data, with permission, from Matsuda et al. (647)].
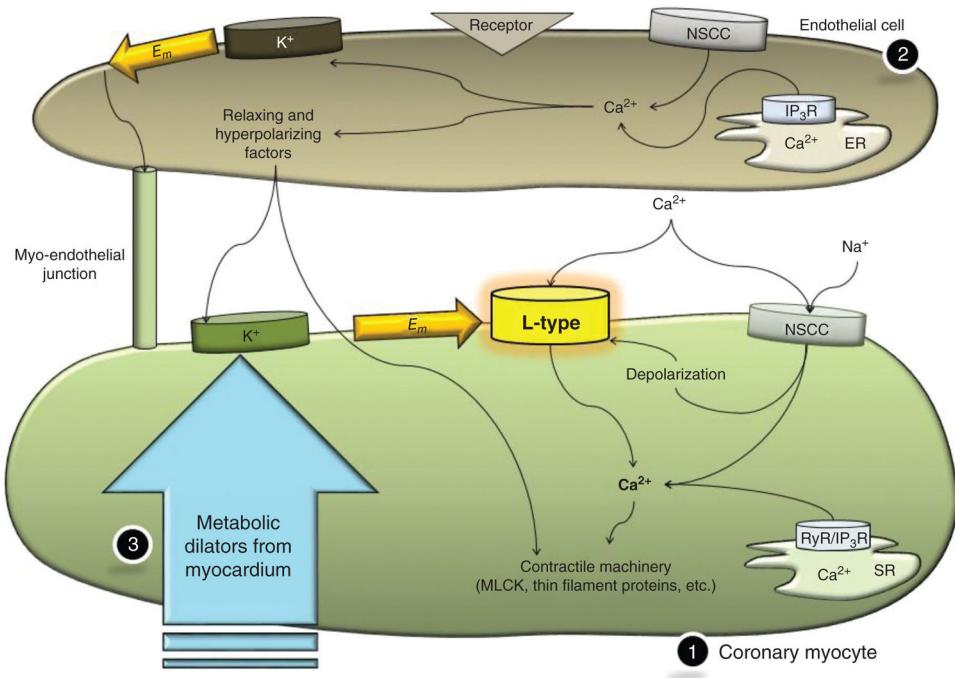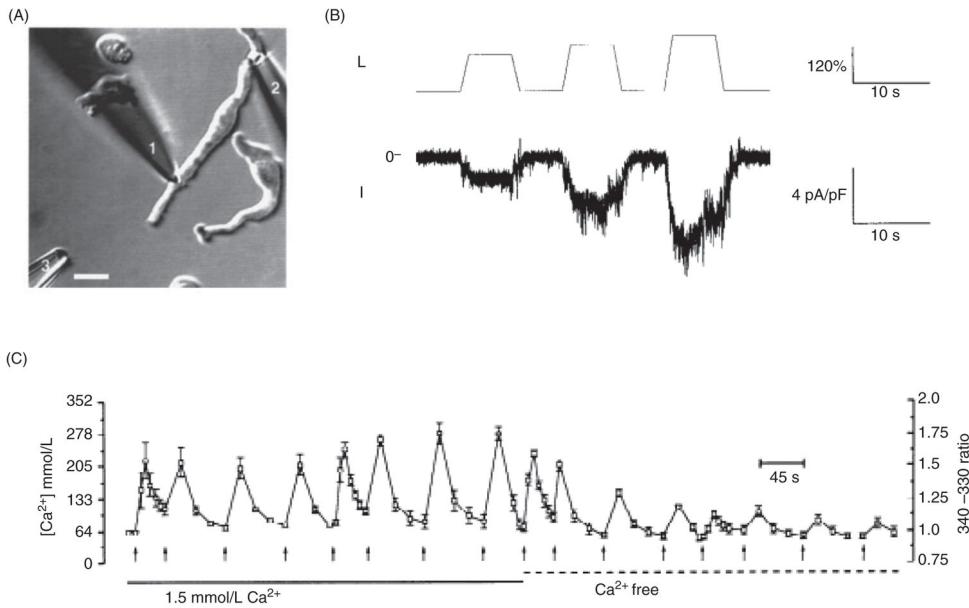
Figure 31.
Dominant role of L-type Ca^{2+} channels in regulating coronary vascular resistance. The coronary pressure-flow relationship in swine was autoregulated under control conditions (filled symbols). Coronary pressure was regulated by a servo-controlled extracorporeal perfusion system while flow was measured. Inhibiting L-type Ca^{2+} channels with intracoronary diltiazem (10 μg/min) abolished pressure-flow autoregulation, indicating a lack of active adjustments to coronary vascular resistance [data, with permission, from Berwick et al. (96)].

(A)

(B)

Figure 32.
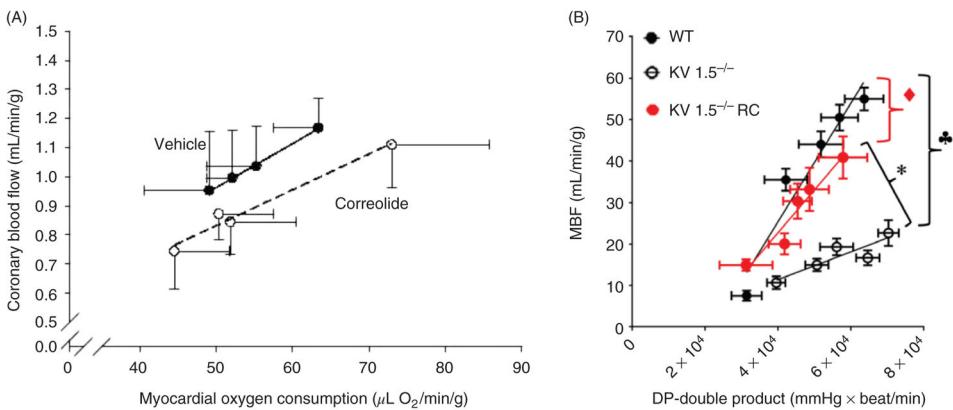
Three components of macroscopic K^+ current in smooth muscle cells from the human coronary artery. Panel A contains representative current tracings before and after the addition of glibenclamide (Glib; 3 μmol/L), an inhibitor of K_{ATP} channels. Only 2 of the 3 major components of K^+ current are active under control conditions: BK_{Ca} and K_V channels (see text for details). Panel B shows that K_{ATP} channels, while not open under control conditions, can be activated by pinacidil (Pin; 1 μmol/L) and blocked by glibenclamide [data, with permission, from Gollasch et al. (382)].

Figure 33.
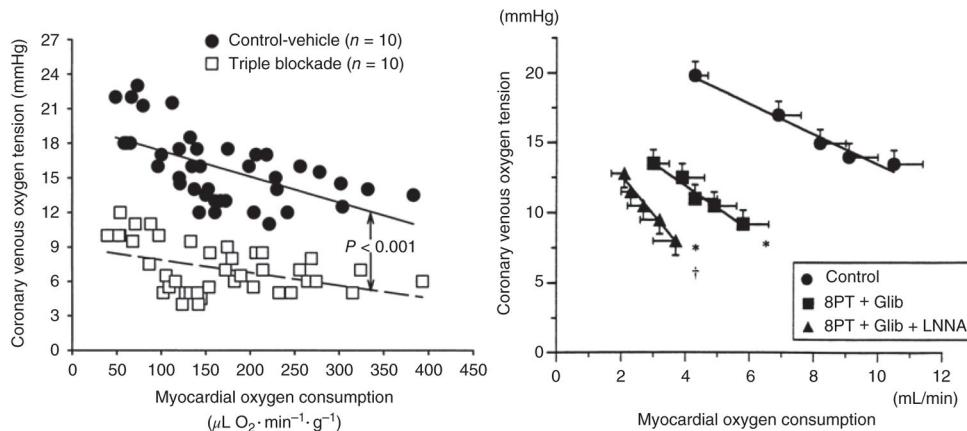
Voltage-dependence of coronary vascular tone: central role of the L-type Ca^{2+} channel in coronary smooth muscle. A cartoon schematic represents a coronary myocyte (1), a coronary endothelial cell (2), and metabolic dilators from the adjacent myocardium (3). The L-type Ca^{2+} channel in coronary vascular smooth muscle is a major target of regulatory mechanisms, as Ca^{2+} influx largely controls the amount of Ca^{2+} available to activate the contractile apparatus. Ca^{2+} release from the sarcoplasmic reticulum (SR; with ryanodine- and IP_3-sensitive Ca^{2+} release channels) and Ca^{2+} influx via nonselective cation channels (NSCC) also contribute. NSCC in smooth muscle also contribute to contraction by depolarizing the membrane potential (E_m) and activating L-type Ca^{2+} channels. Endothelial receptor stimulation (paracrine and mechanical factors) increases Ca^{2+} in endothelial cells, leading to the production of relaxing/hyperpolarizing factors and hyperpolarization of endothelial E_m. Myo-endothelial junctions can spread E_m hyperpolarization to coronary smooth muscle. Relaxing/hyperpolarizing factors diffuse to the smooth muscle, where they activate cell signaling mechanisms to control the contractile apparatus or hyperpolarize E_m via K^+ channels. The most important physiological stimulus regulating coronary vascular resistance on a beat-to-beat basis is metabolic dilators from the myocardium. These factors, which have not been identified conclusively, relax coronary smooth muscle, in large part, by the activation of K^+ (especially K_V) channels and subsequent inhibition of L-type Ca^{2+} channels.

Figure 34.

Stretch-activated nonselective cation current in coronary vascular smooth muscle: effects on the intracellular Ca^{2+} concentration. Panel A contains a photomicrograph of representative porcine coronary smooth muscle cells. A patch clamp pipette is used to hold one end of a cell and record electrical activity (1) while longitudinal stretch is applied with a second pipette and piezoelectric translator; (2) panel B shows that the magnitude of depolarizing inward current (I, lower trace) is related to the degree of longitudinal stretch (L, upper trace) in a porcine coronary smooth muscle cell [data, with permission, from Wu and Davis (991)]. Panel C demonstrates that, in porcine coronary myocytes, stretch-induced increases in intracellular Ca^{2+} ultimately depend upon extracellular Ca^{2+}. Arrows indicate the initiation of longitudinal stretch. In the presence of extracellular Ca^{2+}, stretch-induced increases in intracellular Ca^{2+} were rapid and repeatable. In the absence of extracellular Ca^{2+}, longitudinal stretch still elicited Ca^{2+} transients, but internal stores were quickly depleted [data, with permission, from Davis et al. (226)].

Figure 35.

Role of K_V1 channels in coronary metabolic vasodilation. Panel A contains coronary blood flow data from five pigs treated with correolide, a selective K_V1 channel blocker, and four pigs treated with vehicle only. Myocardial oxygen consumption (MvO_2) was elevated from rest by infusing dobutamine at three increasing doses. K_V1 channels are important for the increase in coronary blood flow elicited by cardiac metabolism, as correolide depressed the relationship between oxygen supply and demand [data, with permission, from Goodwill et al. (384)]. Panel B shows myocardial blood flow versus cardiac double product, an index of cardiac metabolic demand, in wild-type mice (WT), global $K_V1.5$ knockout mice ($K_V1.5^{-/-}$), and mice with smooth muscle-specific restoration of $K_V1.5$ expression ($K_V1.5^{-/-}$ RC). Myocardial blood flow was lower at any given level of myocardial demand in global $K_V1.5$ knockout mice ($P < 0.05$ vs. WT). Smooth muscle-specific restoration of $K_V1.5$ expression normalized the relationship between myocardial blood flow and metabolic demand [not significant from WT; $P < 0.05$ versus global knockout; data, with permission, from Ohanyan et al. (725)].

Figure 36.

Left: Relationship between coronary venous PO_2 and myocardial oxygen consumption at rest and during exercise before and during triple blockade of K_{ATP} channels, nitric oxide synthase and adenosine receptors [data, with permission, from Tune et al. (921)]. Right: Relationship between coronary venous PO_2 and myocardial oxygen consumption at rest and during exercise before and during inhibition of adenosine receptors (8PT), K_{ATP} channels (Glib) and/or nitric oxide synthase (LNNA) [data, with permission, from Ishibashi et al. (497)].