Regulation of Coronary Blood Flow During Exercise

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Exercise is the most important physiological stimulus for increased myocardial oxygen demand. The requirement of exercising muscle for increased blood flow necessitates an increase in cardiac output that results in increases in the three main determinants of myocardial oxygen demand: heart rate, myocardial contractility, and ventricular work. The approximately sixfold increase in oxygen demands of the left ventricle during heavy exercise is met principally by augmenting coronary blood flow (~5-fold), as hemoglobin concentration and oxygen extraction (which is already 70–80% at rest) increase only modestly in most species. In contrast, in the right ventricle, oxygen extraction is lower at rest and increases substantially during exercise, similar to skeletal muscle, suggesting fundamental differences in blood flow regulation between these two cardiac chambers. The increase in heart rate also increases the relative time spent in systole, thereby increasing the net extravascular compressive forces acting on the microvasculature within the wall of the left ventricle, in particular in its subendocardial layers. Hence, appropriate adjustment of coronary vascular resistance is critical for the cardiac response to exercise. Coronary resistance vessel tone results from the culmination of myriad vasodilator and vasoconstrictor influences, including neurohormones and endothelial and myocardial factors. Unraveling of the integrative mechanisms controlling coronary vasodilation in response to exercise has been difficult, in part due to the redundancies in coronary vasomotor control and differences between animal species. Exercise training is associated with adaptations in the coronary microvasculature including increased arteriolar densities and/or diameters, which provide a morphometric basis for the observed increase in peak coronary blood flow rates in exercise-trained animals. In larger animals trained by treadmill exercise, the formation of new capillaries maintains capillary density at a level commensurate with the degree of exercise-induced physiological myocardial hypertrophy. Nevertheless, training alters the distribution of coronary vascular resistance so that more capillaries are recruited, resulting in an increase in the permeability-surface area product without a change in capillary numerical density. Maintenance of a- and B-adrenergic tone in the presence of lower circulating catecholamine levels appears to be due to increased receptor responsiveness to adrenergic stimulation. Exercise training also alters local control of coronary resistance vessels. Thus arterioles exhibit increased myogenic tone, likely due to a calcium-dependent protein kinase C signaling-mediated alteration in voltage-gated calcium channel activity in response to stretch. Conversely, training augments endothelium-dependent vasodilation throughout the coronary microcirculation. This enhanced responsiveness appears to result principally from an increased expression of nitric oxide (NO) synthase. Finally, physical conditioning decreases extravascular compressive forces at rest and at comparable levels of exercise,
mainly because of a decrease in heart rate. Impedance to coronary inflow due to an epicardial coronary artery stenosis results in marked redistribution of myocardial blood flow during exercise away from the subendocardium towards the subepicardium. However, in contrast to the traditional view that myocardial ischemia causes maximal microvascular dilation, more recent studies have shown that the coronary microvessels retain some degree of vasodilator reserve during exercise-induced ischemia and remain responsive to vasoconstrictor stimuli. These observations have required reassessment of the principal sites of resistance to blood flow in the microcirculation. A significant fraction of resistance is located in small arteries that are outside the metabolic control of the myocardium but are sensitive to shear and nitrovasodilators. The coronary collateral system embodies a dynamic network of interarterial vessels that can undergo both long- and short-term adjustments that can modulate blood flow to the dependent myocardium. Long-term adjustments including recruitment and growth of collateral vessels in response to arterial occlusion are time dependent and determine the maximum blood flow rates available to the collateral-dependent vascular bed during exercise. Rapid short-term adjustments result from active vasomotor activity of the collateral vessels. Mature coronary collateral vessels are responsive to vasodilators such as nitroglycerin and atrial natriuretic peptide, and to vasoconstrictors such as vasopressin, angiotensin II, and the platelet products serotonin and thromboxane A$_2$. During exercise, β-adrenergic activity and endothelium-derived NO and prostanoids exert vasodilator influences on coronary collateral vessels. Importantly, alterations in collateral vasomotor tone, e.g., by exogenous vasopressin, inhibition of endogenous NO or prostanoid production, or increasing local adenosine production can modify collateral conductance, thereby influencing the blood supply to the dependent myocardium. In addition, vasomotor activity in the resistance vessels of the collateral perfused vascular bed can influence the volume and distribution of blood flow within the collateral zone. Finally, there is evidence that vasomotor control of resistance vessels in the normally perfused regions of collateralized hearts is altered, indicating that the vascular adaptations in hearts with a flow-limiting coronary obstruction occur at a global as well as a regional level. Exercise training does not stimulate growth of coronary collateral vessels in the normal heart. However, if exercise produces ischemia, which would be absent or minimal under resting conditions, there is evidence that collateral growth can be enhanced. In addition to ischemia, the pressure gradient between vascular beds, which is a determinant of the flow rate and therefore the shear stress on the collateral vessel endothelium, may also be important in stimulating growth of collateral vessels.

I. INTRODUCTION

Energy production in the normally functioning heart is primarily dependent on oxidative phosphorylation, with $<5\%$ of ATP production resulting from glycolytic metabolism (436). Because of this dependence on oxidative energy production, increases of cardiac activity are dependent on almost instantaneous parallel increases of oxygen availability. In contrast to skeletal muscle, which is quiescent with very low metabolic requirements during resting conditions, the heart continues to pump at a rate of 60–70 beats/min in humans even at rest. Consequently, at rest, oxygen consumption normalized per gram of myocardium is 20-fold higher than that of skeletal muscle. As an adaptation to the high oxygen demands, the heart maintains a very high level of oxygen extraction so that 70–80% of the arterially delivered oxygen is extracted, compared with 30–40% in skeletal muscle (181, 346). This high level of oxygen extraction is facilitated by a high capillary density of 3,000–4,000/mm$^2$ (353), which is substantially higher than the 500–2,000 capillaries/mm$^2$ found in skeletal muscle (226). Because of the high level of oxygen extraction by the myocardium during resting conditions, increases in oxygen demand produced by exercise (increasing up to 6-fold during maximal exercise) are mediated principally by an increase in coronary blood flow.

John Hunter stated in 1794 that “blood goes where it is needed” (485). How the blood “knows” where it is needed, i.e., the mechanism(s) that enable coronary flow to respond to the oxygen demands of the myocardium, most notably during exercise, has been the subject of cardiovascular research for over a century (485). Significant advances in our understanding of coronary blood flow regulation have been made over the past 40 years and are summarized in several previous reviews (53, 138, 181, 346). The aim of this review is to provide a comprehensive update of the acute and chronic adaptations that regulate coronary blood flow in response to dynamic exercise under physiological conditions in the healthy heart (sect. ii) and in the heart with impaired coronary arterial inflow (sect. iii).

II. CORONARY BLOOD FLOW IN THE NORMAL HEART DURING EXERCISE

A. Myocardial Oxygen Demand

Oxygen consumption by the heart is principally required for contraction, with requirements for maintaining basal metabolism comprising only 10–20% of total oxygen consumption (58, 617). The oxygen required for contraction is related to heart rate (62, 302, 582), ventricular wall tension (217), muscle shortening (78, 217), and contrac-
tility (43, 162, 217, 417). Precise determination of the relative contributions of these individual variables in vivo has been difficult, as pharmacological or electrical modulation of one of these variables often results in alterations of one or more of the other variables. An integrated model of these mechanical determinants of oxygen consumption has been proposed by Suga and Sagawa (544, 545). These authors demonstrated that the oxygen consumption per heart beat is determined by ventricular work (represented by the ventricular pressure-volume area which integrates wall tension and shortening) and contractility ($E_{\text{max}}$, represented by the slope of the end-systolic pressure volume relation) (Fig. 1, top panels).

Exercise is the most important physiological stimulus for increasing myocardial oxygen demands. The requirement of exercising skeletal muscle for increased blood flow is met by vasodilation of resistance vessels in the skeletal muscle, which requires an increase in cardiac output, and is facilitated by an increase in arterial pressure. The hemodynamic adjustments that result in the increased cardiac output and arterial pressure during exercise cause increases in each of the major determinants of myocardial oxygen demands: heart rate, contractility, and ventricular work (Fig. 1, bottom panels, and Fig. 2).

1. Heart rate

Early studies comparing myocardial oxygen consumption during heavy exercise with similar increases in heart rate produced by cardiac pacing suggested that 30–40% of the increase in coronary blood flow during exercise can be attributed to the increase in heart rate (302, 582). However, the contribution of the increase in heart rate to the increase in myocardial oxygen consumption was likely underestimated, as pacing decreases end-diastolic volume and stroke volume, thereby reducing ventricular work (72, 531). Indeed, other studies (214, 242, 258, 396, 588) suggest that the increase in heart rate accounts for 50–70% of the increase in myocardial oxygen consumption during exercise (Fig. 2).

2. Contractility

The exercise-induced increase in contractility is due to $\beta$-adrenergic activation as well as the direct positive inotropic effect of heart rate (treppe) (320). Studies in which the inotropic effect produced by the $\beta$-adrenergic nervous system during exercise was blocked with propranolol while heart rate was maintained constant by atrial pacing were interpreted to suggest that up to 30% of the increase in myocardial oxygen demands during exercise could be attributed to the adrenergically mediated...
augmentation of contractility (43, 162, 303, 417). The effect of increased contractility on myocardial oxygen consumption in these studies was likely overestimated, as β-blockade blunted not only the exercise-induced increase in heart rate, but also left ventricular systolic pressure and stroke volume and consequently left ventricular work per beat (43, 162, 303, 417). Therefore, it is estimated that contractility contributes 15–25% of the increase in oxygen consumption during exercise (Figs. 1 and 2).

3. Ventricular work

Left ventricular work increases during exercise in proportion to the increased systolic arterial pressure and secondary to a modest increase of left ventricular end-diastolic volume (279, 456, 581). Stroke volume, and hence external work, is augmented as the increased contractility during exercise causes the ventricle to eject to a smaller end-systolic volume (279, 456, 581) so that total ventricular work increases, accounting for an estimated 15–25% of the increase in oxygen consumption during exercise (Figs. 1 and 2).

B. Myocardial Oxygen Supply

Increased myocardial oxygen demands during exercise are met principally by augmenting coronary blood flow (Fig. 2). In some species such as the dog (313, 583), horse (167, 448), and sheep (415), oxygen delivery is facilitated by a prominent increase in hemoglobin (by up to 30–50%), but in swine (148, 247, 345) and human (484, 486), hemoglobin concentrations increase much less. Although myocardial oxygen extraction also increases during exercise (377, 391, 402, 426, 587, 588), the high level of basal oxygen extraction (typically 70–80% during resting conditions) limits further increases. In chronically instrumented dogs, von Restorff et al. (587) found that heavy treadmill exercise caused an increase of myocardial oxygen consumption from 0.09 ± 0.01 at rest to 0.57 ± 0.05 ml·min⁻¹·g⁻¹ during exercise that was provided by a 434% increase of coronary blood flow, an increase of arterial oxygen content from 20 ± 1 to 23 ± 1 ml/dl, and an increase of myocardial oxygen extraction from 79 ± 2 to 93 ± 1% (Fig. 3). Thus the principal mechanism for augmenting myocardial oxygen delivery is by increasing coronary blood flow and, as a result, coronary flow is strongly correlated with myocardial oxygen consumption. The increase in myocardial blood flow results from a combination of coronary vasodilation, with a decrease of coronary vascular resistance during heavy exercise to 20–30% of the resting level, and a 20–40% increase in mean arterial pressure (37, 275, 313, 377, 426, 448, 469, 587, 588).

1. Coronary blood flow

Left ventricular myocardial blood flow during resting conditions in chronically instrumented large animals in
the awake state and in normal human subjects is generally reported in the range of 0.5–1.5 ml/min·g myocardium⁻¹ (17, 24–26, 33, 34, 37, 41, 44, 132, 137, 139–141, 144, 146, 147, 174, 212, 214, 236, 289, 316, 327, 356, 379, 420, 427, 440, 444, 448, 473, 499, 500, 524, 539, 540, 547, 567–569, 588, 593, 603, 614, 615, 624). The wide range of resting values of left ventricular blood flow in awake animals appears to be related to the state of alertness. Animals conditioned to rest quietly in the laboratory have the lowest reported values, whereas animals standing on a treadmill ready to run have higher heart rates and higher coronary flow rates. Dynamic exercise increases coronary blood flow in proportion to the heart rate, with peak values during maximal exercise typically three to five times the resting level (378, 448, 498–500, 574, 588, 603). The strong correlation between coronary flow and heart rate occurs because heart rate is a common multiplier for the other determinants of myocardial oxygen demand (contractility, cardiac work), which are computed per beat. Regression analysis of published left ventricular blood flow data against heart rate demonstrates remarkably similar relationships between human, canine, equine, and porcine data during dynamic exercise (Fig. 4) (17, 24–26, 33, 34, 37, 41, 44, 76, 77, 132, 137, 139–141, 144, 146, 147, 162, 174, 212, 214, 236, 250, 258, 275, 289, 302, 303, 316, 327, 345, 356, 378, 379, 420, 426, 427, 430, 431, 440, 444, 448, 469, 473, 499, 500, 524, 539, 540, 547, 567–569, 588, 593, 603, 614, 615, 624). The values reported by Sanders et al. (498) are for total heart flow and are therefore lower than from other studies in which blood flow from the left ventricle was reported. In some laboratories using fluorescent microspheres, absolute blood flow measurements of 7.5–8.5 ml/min·g myocardium⁻¹ have been reported in swine exercising at heart rates of ~260 beats/min (106, 327); these values are much higher than reported by most other groups in which myocardial blood flow was measured with radioactive microspheres (Fig. 4). These studies have not been included in Figure 4.

A) UNIQUE RESPONSES TO EXERCISE IN RODENTS. An inexpensive small animal model that would reproduce the effects of exercise seen in larger animals and in humans would be extremely useful, especially in light of the availability of genetically modified mouse strains that could be used to assess the contribution of a gene product to the acute and chronic coronary blood flow responses to exercise (55). However, the technical difficulty of measuring coronary blood flow in small animals is formidable. Consequently, no studies of coronary or myocardial blood flow responses to exercise in mice are currently available. Flaim et al. (185) studied myocardial blood flow, measured with radioactive microspheres injected into the left ventricle of rats exercised by swimming or running on a treadmill. The increase in oxygen consumption produced by swimming was due solely to an increased oxygen extraction, so that compared with resting conditions swimming caused no increases of heart rate or cardiac output and no increase of myocardial blood flow. Treadmill exercise at 70 ft./min for 5 min or until exhaustion increased heart rates from ~380 to 480 beats/min and increased cardiac output, while arterial blood pressure was unchanged. Left ventricular myocardial blood flow increased far less during exercise than in large animals, being 5.9 ml/min·g⁻¹ at rest and 7.8 ml/min·g⁻¹ during exercise, an ~30% increase. The very high left ventricular myocardial blood flow rates at rest (~5-fold greater than in large animals or humans) appeared to result from the high basal heart rate of the awake rat and the very high basal heart rate of the human subject (Fig. 4). Relations between heart rate (HR) and left ventricular myocardial blood flow (LVMBF) at rest and during treadmill exercise in dogs (24–26, 33, 34, 37, 41, 44, 132, 137, 140, 141, 144, 147, 174, 212, 214, 236, 289, 356, 427, 440, 444, 473, 524, 567–569, 588, 624), swine (76, 77, 139, 146, 147, 236, 345, 430, 449, 506, 539, 540, 547, 603), and horses (17, 378, 379, 448). Data from humans were obtained principally from young healthy male subjects performing upright bicycle exercise (162, 258, 275, 302, 303, 316, 420, 426, 469, 593, 614, 615). Data from rats (185) have been added (solid circles representing rest and exercise data) to illustrate that the high LVMBF values in this species are the result of the high heart rates, so that the rat data fall right on the regression line for the human data.
rates in rats, and the modest relative increase in myocardial blood flow in response to exercise was proportionate to the modest further increase in heart rate (Fig. 4). Thus myocardial blood flow in the rat is much higher than in larger animals during resting conditions, but the increase in blood flow during treadmill exercise is much less than in larger animals. The lack of hemodynamic response to swimming indicates that this stress is not likely to be useful for examining coronary responses to exercise (35, 185). Furthermore, the response to treadmill exercise in rats is so dissimilar to that of larger animals (including humans) that even treadmill exercise is likely to be of limited value in understanding regulation of coronary blood flow responses to exercise in larger animal species or in humans.

2. Oxygen-carrying capacity of arterial blood

A) HEMOGLOBIN. In the dog, horse, and sheep, oxygen delivery to the myocardium is facilitated by prominent increases in hemoglobin concentration during exercise and the resultant increase in oxygen carrying capacity of arterial blood. The hemoglobin concentration increases because exercise elicits splenic contraction that expresses erythrocyte-rich blood into the general circulation. Thus dogs performing near-maximal treadmill exercise have been reported to sustain a 12–21% increase in hematocrit (313, 588). Vatner et al. (583) reported a 23% increase in hematocrit during heavy exercise in free running dogs which was abolished by splenectomy. Manohar (378) reported that in ponies hemoglobin increased from 11.4 g/dl at rest to 16.9 g/dl at maximal exercise, a 48% increase. This resulted principally from splenic contraction, as in splenectomized ponies hemoglobin content increased from 12.3 g/dl at rest to 13.9 g/dl at maximal exercise, an increase of only 13%. Augmentation of the arterial oxygen content is an important response to exercise, since splenectomized ponies required higher myocardial blood flow rates at similar work loads (378). Furthermore, normal ponies had residual coronary vasodilator reserve in response to adenosine infusion even during maximal exercise, whereas in splenectomized animals, vasodilator reserve was exhausted in the subendocardium during heavy exercise (378). In sheep, hemoglobin concentration increased from 9.1 ± 0.4 g/dl at rest to 13.1 ± 0.8 g/dl at maximal exercise (415). Pretreatment with the nonselective α-adrenergic receptor blocker phenoxybenzamine blunted the increase from 9.0 ± 1.1 to 11.3 ± 0.9 g/dl, indicating that contraction of the spleen is mediated by α-adrenergic receptor activation during exercise. In swine, hemoglobin increases by 10–20% (16, 148, 247, 345, 395, 539, 540, 547); this increase was abolished by pretreatment with the mixed α1/α2-adrenergic receptor antagonist phentolamine, supporting a role for α-adrenergic-mediated splenic contraction during exercise (148). The α-adrenergic receptor involved in the exercise-induced splenic contraction is likely of the α1-subtype, as the exercise-induced increase in hemoglobin can be mimicked with the α1-adrenergic receptor agonist phenylephrine (502). Blockade of the increase in hemoglobin in both swine or dogs requires a greater increase in coronary blood flow at each level of myocardial oxygen consumption (148, 502), indicating that the increase in hemoglobin is physiologically important in these species, although less than in horses. The hemoglobin concentration in humans increases by no more than 15% in response to upright exercise (97); this increase is not the result of splenic contraction, but rather is due principally to a decrease in plasma volume resulting from extravasation of fluid from the capillaries (244, 483, 484).

B) ARTERIAL OXYGEN SATURATION OF HEMOGLOBIN. Arterial oxygen tension and saturation are generally unchanged during submaximal and maximal exercise in normal humans (97). However, in endurance athletes with extremely high values of maximum total body oxygen consumption, decreases in arterial oxygen tension have been reported (127, 296, 551). Arterial oxygen tensions were not changed during maximal exercise in chronically instrumented dogs (247, 587), whereas a 12- to 20-mmHg decrease in arterial oxygen tension has been reported in chronically instrumented ponies during heavy exercise (301, 377), and a 5- to 10-mmHg decrease in exercising swine (16, 145, 247, 394), although this is not a uniform finding in either ponies (378, 448) or swine (149, 345). It is important to note that small changes in arterial oxygen tension contribute little to the arterial oxygen content, since the arterial oxygen-hemoglobin dissociation curve operates at its upper plateau even during resting conditions. Consequently, even in the studies that reported a 12- to 20-mmHg decrease in oxygen tension, arterial hemoglobin oxygen saturation was maintained (301, 377).

3. Myocardial oxygen extraction

A) RELATION TO MYOCARDIAL OXYGEN CONSUMPTION. In many species, the increase in oxygen delivery to the heart during exercise does not fully match the increased oxygen demand, necessitating an increase of myocardial oxygen extraction, with widening of the arteriovenous oxygen difference and a decrease in coronary venous oxygen content (24, 121, 258, 275, 291, 313, 316, 377, 541, 588). In normal male human subjects who performed bicycle exercise to achieve heart rates of 171 beats/min (~85% of predicted maximum heart rate), coronary sinus oxygen content decreased from 8.5 ± 1.6 ml/dl at rest to 6.6 ± 0.7 ml/dl at peak exercise (22% decrease) (316). Similar findings have been reported by other investigators in human subjects during heavy exercise (258, 275), but lesser exercise loads (<70% of maximum heart rate) did not result in increased myocardial oxygen extraction or decreased coronary ve-
nous oxygen content compared with resting conditions (57, 211, 372, 402, 469, 471). It is likely that the relatively light levels of exercise used in the latter studies can account for the lesser increases of oxygen extraction. Von Restorff et al. (588) reported that heavy treadmill exercise in dogs, which increased heart rate to 284 beats/min, increased myocardial oxygen extraction from 75 ± 2% at rest to 93 ± 1% during exercise, with a decrease in coronary venous oxygen saturation from 24 ± 1 to 9 ± 1%. Bache and Dai (27) observed a decrease in coronary sinus oxygen tension from 21 ± 2 to 13 ± 1 mmHg over a similar exercise range. Similarly, Manohar (377) reported that in horses coronary venous oxygen tension decreased from 22 ± 1 mmHg at rest to 15 ± 1 mmHg during heavy exercise. In contrast, in swine, myocardial oxygen extraction and coronary venous oxygen tension remain unaltered during treadmill exercise, even at levels of up to 80–90% of maximum heart rate (145, 147–149, 393, 395, 396).

Interestingly, Heiss et al. (258) observed in young healthy male volunteers that the coronary venous oxygen content decreased by 8% with no change in coronary venous oxygen tension (Fig. 5). Similarly, in young healthy male volunteers, Grubbstrom et al. (224) observed a marked decrease in coronary venous oxygen saturation from 33 ± 2% at rest to 24 ± 2% during heavy exercise at ~90% of maximum heart rate, whereas coronary venous oxygen tension was minimally affected (21 ± 1 mmHg at rest versus 18 ± 2 mmHg during exercise). These observations suggest that a rightward shift of the hemoglobin oxygen dissociation curve acts to facilitate oxygen delivery to the myocardium during heavy exercise in humans. The decrease in blood pH resulting from lactate production by working skeletal muscle has been reported to cause a rightward shift of the hemoglobin oxygen dissociation curve in humans (224, 258) and horses (377). However, in dogs, the coronary venous blood pH did not change even during maximal exercise (247) and therefore cannot contribute to this rightward shift. This may explain why in dogs coronary venous oxygen tension is decreased at relatively low levels (<70% of maximum) of exercise, whereas in horses and humans coronary venous oxygen tensions decrease less despite similar decrements in oxygen saturation (Fig. 5). The observation that coronary venous oxygen saturation levels are maintained in exercising swine is consistent with the unchanged arterial carbon dioxide tension and pH at submaximal levels of exercise (80–90% of maximum) (149). It is possible that during exhaustive exercise lactate production by skeletal muscle (430, 431) and the associated decrease in blood pH (247) also facilitate a decrease in coronary venous oxygen saturation in swine.

### B) Relation to Vasomotor Control in Coronary Resistance Vessels

Adrenergic vasoconstrictor mechanisms restrain the increase in coronary blood flow during exercise, thereby contributing to the increased oxygen extraction. Thus nonselective α-adrenergic blockade with phentolamine or selective α₁-adrenergic blockade with prazosin increased myocardial blood flow during exercise, which was accompanied by decreased myocardial oxygen extraction and increased coronary venous oxygen tension (27, 31, 122, 214, 214, 266). However, α-adrenergic blockade did not completely eliminate the increase in myocardial oxygen extraction that occurred during exercise (27, 31), which could have resulted from incomplete blockade or from other unidentified factors which restrain coronary vasodilation during exercise. Alternatively, a decrease in coronary venous oxygen tension has been proposed to represent a metabolic error signal, needed for negative-feedback metabolic control of myocardial oxygen delivery and hence coronary blood flow. However, the observation that oxygen tension is minimally affected in exercising swine (148), and during submaximal exercise in humans (258, 471), indicates that a decrease in oxygen tension is not obligatory for the exercise-induced increase in coronary blood flow.

### C) Relation to Vasodilator Reserve, Oxidative Metabolism, and Contractile Function

The increased oxygen extraction indicates that the increase of myocardial blood flow during exercise does not fully compensate for the increased oxygen demands. Failure of blood flow to fully meet the increase in myocardial oxygen consumption is not the

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![Fig. 5. Relation between myocardial oxygen consumption (MVO₂) and coronary venous oxygen tension (left panel) and oxygen saturation (right panel) at rest and during treadmill exercise in swine (148), humans (258), horses (377, 448), and dogs (24, 588). Note that exercise does not alter coronary venous oxygen tension in swine, whereas it is already reduced at low levels of exercise in dogs. Humans and horses demonstrate an intermediate oxygen tension response. During exercise, oxygen saturation decreases in horses and humans (similar to dogs), whereas in swine saturation is not affected, suggesting a rightward shift of the hemoglobin-oxygen dissociation curve during exercise in humans and horses. Also note that despite similar resting coronary venous oxygen tensions, horses and humans have higher hemoglobin oxygen saturations compared with swine and dogs, consistent with the higher P₅₀ values reported in the latter species (286, 474). Data are means ± SE. *P < 0.05 vs. corresponding rest. See text for further explanation.](http://physrev.physiology.org/)

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result of exhaustion of coronary vasodilator reserve during exercise, since a further increase in coronary blood flow can be elicited with a pharmacological or ischemic vasodilator stimulus. For example, during maximal treadmill exercise in dogs and swine, a brief total coronary occlusion has been shown to result in reactive hyperemia with a further increase in blood flow (588, 603). Furthermore, intravenous administration of adenosine to swine resulted in a 15–26% increase in myocardial blood flow during maximum exercise, despite a significant drop in arterial pressure (77, 500, 603). When the results were expressed in terms of coronary resistance, adenosine caused a 20 ± 1% further decrease in coronary vascular resistance in swine during maximal exercise (603). Similarly, dipyridamole administered intravenously or into the left atrium of dogs or swine during near-maximal or maximal treadmill exercise caused a 20–46% further increase in myocardial blood flow (41, 342). An even greater adenosine-recruitable flow reserve was reported in ponies during near-maximal exercise (378, 448), causing an increase in myocardial blood flow from 5.34 ± 0.31 to 9.34 ± 0.66 ml·min⁻¹·g⁻¹ (448). Taken together, these studies demonstrate that in the normal heart substantial coronary vasodilator reserve exists even during maximal exercise.

Although the increase in myocardial oxygen extraction indicates that coronary blood flow does not keep pace with the increased myocardial oxygen demands during exercise, there is no evidence to suggest that this disparity results in ischemia in the normal heart even during heavy exercise. Studies examining myocardial lactate metabolism for evidence of anaerobic glycolysis demonstrated continued lactate consumption even during heavy exercise (258, 275, 291, 402). Nevertheless, Gwirtz and co-workers (230, 232) found that pharmacologically induced increases of coronary blood flow during exercise can enhance contractile function, which is known as the Gregg effect (see Refs. 181, 599 for in depth reviews). These investigators observed that intracoronary administration of the selective α₁-adrenergic blocker prazosin during treadmill exercise in dogs caused a 21 ± 3% increase in coronary artery blood flow that was associated with a 21 ± 4% increase in the maximal rate of regional myocardial segment shortening (total systolic shortening was unchanged) and a 26% increase in myocardial oxygen consumption. The increased velocity of shortening was not mediated by enhanced β-adrenergic activation, since a similar response to prazosin was observed after β-adrenergic blockade with propranolol (232). Similarly, intracoronary administration of adenosine during exercise caused a 25–30% increase in coronary blood flow (230, 291), and this was associated with a 27% increase in the rate of systolic segment shortening (230) and a 16% increase of myocardial oxygen consumption (291). The effects on contractile function produced by both intracoronary adenosine and prazosin occurred with no change in heart rate, left ventricular systolic pressure, or myocardial end-diastolic segment length (230, 232). The observed increases in the velocity of segment shortening and myocardial oxygen utilization in response to pharmacological coronary vasodilation during exercise suggest that coronary flow may modulate the increase of myocardial contractility that occurs during exercise.

C. Determinants of Coronary Blood Flow

1. Effective perfusion pressure: extravascular compressive forces

The effective perfusion pressure of the coronary bed is determined by the pressure drop across the coronary vascular bed, with the entrance pressure being aortic pressure. However, because extravascular forces are exerted on the compressible intramural coronary vasculature by the surrounding myocardium, the effective back pressure that acts to impede coronary blood flow cannot simply be equated to right atrial pressure. The interaction between the intravascular distending pressure and the extravascular compressive forces can be described by the “vascular waterfall” and is especially important during systole (134, 262) but also, albeit to a lesser extent, during diastole (52, 571, 585, 592). Thus, during systole, the contracting myocardium generates a high level of intramyocardial pressure that compresses the coronary microvasculature, thereby impeding blood flow (Figs. 6 and 7; Refs. 20, 154, 163, 274). Conversely, during diastole, intraventricular pressures transmitted into the left ventricular wall exert a small compressive force on the intramural vasculature (20, 154, 163, 274), creating waterfalls at the level of the arterioles and the venules, and possibly the epicardial veins (571, 585, 599). For an in depth review of the interaction of the myocardium and coronary vasculature, the reader is referred to a recent article in this journal (599).

Isolating the impeding effects of cardiac contraction on coronary blood flow requires elimination of active vasomotor influences by producing maximal vasodilation of the coronary vascular bed. An early study reported that “minimum” coronary vascular resistance (calculated as aortic pressure/mean coronary blood flow during intravenous administration of adenosine) was lower during treadmill exercise than at rest (448). However, computation of vascular resistance from single measurements of pressure and flow does not fully characterize the effects of changes in extravascular forces. Comprehensive analysis of mechanical effects of cardiac contraction on blood flow is provided by the pressure-flow relationship, obtained from multiple measurements of coronary blood flow over a range of perfusion pressures. During maximum vasodilation, the pressure-flow relationship is determined by the maximum vascular conductance, repre-
sented by the slope of the relationship, and the \( x \)-intercept or pressure at which flow ceases (zero-flow pressure; \( P_{zf} \)); in the maximally dilated circulation, changes in \( P_{zf} \) are determined principally by changes of the extravascular compressive forces (15, 318, 503, 621). Duncker et al. (151) used this technique to study the effect of exercise on coronary blood flow in dogs. Maximum coronary vasodilation was maintained by intra-arterial infusion of adenosine (50 \( \mu \)g/kg/min); this dose was determined to cause maximum vasodilation, since larger doses caused no further increase in blood flow. As heart rate increased from 118 beats/min at rest to 213 beats/min during treadmill exercise, blood flow in the maximally vasodilated coronary circulation decreased from 5.66 \pm 0.41 ml/min/g during resting conditions to 4.62 \pm 0.43 ml/min/g myocardium \(^{-1}\) despite a significant increase in coronary perfusion pressure (aortic pressure). The decrease of coronary blood flow resulted from an increase of \( P_{zf} \) from 13 \pm 1 mmHg at rest to 23 \pm 2 mmHg during exercise, as well as a decrease in the slope of the pressure-flow relationship from 12.3 \pm 0.9 to 10.9 \pm 0.9 (ml/min/g \(^{-1}\))/mmHg during exercise (Fig. 8). Several factors may contribute to this alteration of the coronary pressure-flow relationship during exercise. First, the increase in heart rate decreases maximum coronary blood flow rates by increasing the total time spent in systole (23). Second, the increased contractility increases systolic compression of the intramural coronary vessels (325, 385, 533, 563). However, the increased contractility simultaneously augments myocardial relaxation which increases the diastolic perfusion time (142, 465, 625). Finally, an increase of left ventricular diastolic filling pressure decreases maximum coronary blood flow (20, 154, 163). Analysis of the individual contributions of each of these variables to the exercise-induced changes in the coronary pressure-flow relationship demonstrated that heart rate and left ventricular diastolic pressure contributed to the increases in the \( P_{zf} \) whereas the increase in contractility did not have a significant effect (137, 151), likely because the impeding effect of the increased force of contraction was offset by enhanced relaxation which increased the diastolic perfusion time.

The increase in extravascular compressive forces during exercise is unlikely to be of physiological significance in the normal coronary circulation, because coronary vasodilator reserve capacity persists even during maximal exercise (41, 77, 342, 378, 448, 500, 603). However, when the oxygen-carrying capacity of the blood is reduced by anemia or hypoxia, or when atherosclerotic coronary artery disease reduces vascular caliber (see sect. iii), then the increased extravascular forces produced by exercise could produce a functionally significant limitation of coronary blood flow rates during exercise.

2. Coronary vascular resistance

During exercise, the increase in aortic pressure only slightly exceeds the increase in effective back pressure so
that the effective perfusion pressure increases by no more than 20–30% (151, 377). Consequently, the exercise-induced four- to sixfold increase in coronary blood flow is mediated principally by a decrease in coronary vascular resistance. Indeed, maximal exercise is associated with decreases in calculated coronary vascular resistance to 20–30% of basal resting values in dogs, swine, and horses (77, 378, 448, 587).

Total coronary resistance is the sum of both passive (structural) and active (smooth muscle tone) components (346, 411). In the completely vasodilated bed, flow to the different regions of the heart is determined by the cross-sectional area of the vessels, the length of the vasculature, and the number of parallel vessels that supply a defined perfusion territory. Measurements of intravascular pressure during basal conditions have shown that ~90% of resistance resides in the small arteries and arterioles, hence the term resistance vessels (101, 105). The total length of the vessels supplying the subendocardium is longer than those supplying the subepicardium. In addition, cardiac contraction compresses the intramural vasculature during systole, impeding blood flow especially to the subendocardium (see sect. II D). To facilitate augmented flow during diastole to compensate for systolic underperfusion, the subendocardium has a 10% higher arteriolar and capillary density (53) so that during maximal pharmacological vasodilation under resting conditions, flow to the subendocardium is similar to flow to the subepicardium (140, 470). In addition, there is evidence that the subendocardial resistance vessels are more sen-
Coronary pressure-flow relation in the dog heart under conditions of maximal coronary vasodilation with intracoronary adenosine (50 μg·kg\(^{-1}\)·min\(^{-1}\)). Shown are the relations at rest and during three incremental levels of treadmill exercise. Note the rightward shift of the pressure-flow relation with an increase in the zero-flow pressure intercept. See text for further explanation. Data are means ± SE. *P < 0.05 vs. corresponding rest. [Data from Duncker et al. (151).]

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D. Transmural Distribution of Left Ventricular Myocardial Blood Flow

1. Systolic compression of intramyocardial vessels

Cardiac contraction impedes myocardial blood flow during systole so that during basal conditions arterial inflow occurs predominantly during diastole. Measurements of proximal coronary artery flow in chronically instrumented dogs (313) and swine (500) demonstrate that during resting conditions only 15–20% of left ventricular flow occurs during systole (Figs. 6 and 7). However, the high heart rates associated with exercise result in progressive encroachment of systole on the diastolic interval, while absolute blood flow rates during systole increase. As a result, during heavy exercise 40–50% of total coronary artery blood flow occurs during systole (313, 500). The increase in the fraction of coronary flow during systole has implications for the transmural distribution of left ventricular myocardial blood flow, as the throttling effect of cardiac contraction on the intramural coronary vessels is expressed nonuniformly across the left ventricular wall (Fig. 9). Myocardial compressive force increases from intrathoracic pressure at the epicardial surface to equal or to exceed intraventricular pressure at the endocardial surface (15, 71). Interaction of this gradient of effective tissue pressure with the intravascular distending pressure acts to create an array of vascular waterfalls across the wall of the left ventricle that selectively impedes subendocardial blood flow during systole (134, 140, 262, 305). Furthermore, blood from vessels within the innermost ventricular layers is squeezed retrograde into more superficial subepicardial arterial vessels during each systole so that subendocardial vessels have to be refilled in diastole (analogous to the emptying and filling of a capacitor; Refs. 274, 305, 599). Consequently, systolic flow is directed toward the subepicardium, while antegrade subendocardial blood flow occurs exclusively during diastole. Moreover, with shortening of diastole when the heart rate increases, a relatively greater part of diastole is required to refill the subendocardial vessels, thereby delaying net forward flow in the subendocardial microcirculation. The effects of the increased force of cardiac contraction and increased heart rate during exercise can be studied by maximally vasodilating the coronary circulation with an intracoronary infusion of adenosine (infused regionally to avoid systemic hemodynamic effects), allowing selective study of the impeding effects of cardiac contraction without the confounding influence of metabolic vasoregulation of coronary resistance vessel tone. Using this approach, we observed that exercise caused a redistribution of blood flow away from the subendocardium toward the subepicardium (Fig. 10). The increase in subepicardial blood flow during exercise is consistent with the presence of an intramyocardial pump (274) but was aided, at least in part, by the exercise-induced increase in coronary perfusion pressure (140).

Despite the mechanical effects of cardiac contraction that act to increase impedance to blood flow to the deeper myocardial layers during exercise, in the normal heart with intact coronary tone a modest net transmural gradient of blood flow favoring the subendocardium exists, reflecting the higher systolic tension development and oxygen requirements of this layer (596). Maintenance of this normal pattern of transmural perfusion requires augmentation of subendocardial flow during diastole in proportion to the degree of systolic underperfusion. This diastolic gradient of blood flow favoring the subendocardium is dependent on a transmural gradient of vasomotor tone, with vascular resistance during diastole being lowest in the subendocardium (23).

2. Subendocardial/subepicardial blood flow ratio

The transmural distribution of myocardial blood flow during exercise has been measured with radioactive microspheres. In most cases, the left ventricular wall has been divided into three or four layers, and the transmural distribution of perfusion was expressed as ratio of blood flow to the innermost layer (subendocar-
dium) divided by blood flow to the outermost layer (subepicardium) (ENDO/EPI ratio). In chronically instrumented awake dogs and swine, END/EPI blood flow ratios at rest have been reported between 1.09 and 1.49 (24, 26, 34, 37, 41, 76, 77, 132, 140, 146, 147, 236, 327, 342, 430, 431, 440, 499, 500). END/EPI ratios are somewhat dependent on the size microsphere used. In early studies in which 7- to 10-μm-diameter microspheres were used, END/EPI ratios decreased during exercise, with values near 1.0 during heavy exercise (37, 41, 603). In contrast, when 15-μm-diameter microspheres were used, higher END/EPI ratios have generally been reported with values of 1.10–1.31 during heavy exercise (24, 26, 327, 430, 431, 440, 499, 500). Conversely, Symons and Stebbins (547) reported higher END/EPI values in awake swine at rest (1.68) and during moderate exercise (1.53) than any other laboratories; an explanation for their findings is not readily found. The reason for the disparity in the transmural distribution of microspheres during exercise based on size is uncertain, but could be the result of streaming of the larger microspheres into the penetrating arteries that deliver blood to the subendocardium, or to arteriovenous shunting of a fraction of the 7- to 10-μm-diameter microspheres from the subendocardial microvessels. Size-dependent characteristics of microsphere measurements in the myocardium have been previously reviewed (573). Ponies and standard bred horses appear to have a more prominent decrease in END/EPI ratio during exercise than either dogs or swine (Fig. 11). Using 15-μm-diam-

![Diagram showing intramyocardial microvasculature and extravascular forces during diastole and systole.](http://physrev.physiology.org/)

**Fig. 9.** Graph showing a schematic drawing of the intramyocardial microvasculature (top panel) and the extravascular forces acting on the coronary microvasculature during diastole (bottom left panel) and systole (bottom right panel). $P_{IM}$, intramyocardial pressure; $P_{LUMEN}$, pressure in left ventricular lumen; $P_{PERI}$, pressure in pericardial space. See text for further explanation.
eter microspheres, Manohar and associates (378, 448) reported that ENDO/EPI ratios in ponies decreased from 1.18–1.27 at rest to 0.97–0.99 during heavy treadmill exercise. Similarly, Armstrong et al. (17) reported a decrease in ENDO/EPI ratio from 1.24 at rest to 1.05 during exercise in standard bred horses. This may be in part the result of the marked increase in left ventricular end-diastolic pressure that occurred in horses from 11 ± 2 mmHg at rest to 36 ± 4 mmHg during heavy exercise, which contrasts with increases in left ventricular end-diastolic or left atrial pressure from 2–5 mmHg at rest to only 5–15 mmHg during heavy exercise in dogs (7, 24, 26, 37, 153, 279, 440) and swine (147, 500, 603).

3. Influence of vasomotor tone on the transmural distribution of myocardial blood flow

Several studies suggest that active coronary vasomotor tone is important for maintaining subendocardial blood flow during exercise. Thus studies in swine and dogs have demonstrated that coronary vasodilation with adenosine or dipyridamole during exercise caused the ENDO/EPI ratio to fall significantly below 1.0 (Fig. 10; Table 1; Refs. 140, 342, 500, 603). These findings could be interpreted to suggest that at high heart rates during exercise, active vasomotion is required to maintain a gradient of vascular resistance favoring perfusion of the deeper myocardial layers during diastole. In contrast to these reports, Barnard et al. (41) reported that the ENDO/EPI ratio during heavy exercise in dogs increased from 1.03 during control conditions to 1.15 after the administration of dipyridamole. Intravenous adenosine had no effect on the ENDO/EPI ratio during maximal exercise in ponies (378, 448). Furthermore, Breisch et al. (77) reported that during heavy exercise in swine, the ENDO/EPI ratio was maintained near unity during vasodilation with adenosine. The reason for this disparity is unclear but does not appear to be due to adenosine-induced alterations in blood pressure (Table 1). Of greatest importance, however, is the finding that absolute subendocardial blood flow rates increased in response to exogenous adenosine or dipyridamole during heavy exercise (41, 77, 140, 342, 378, 448, 500, 603), indicating that vasodilator reserve had not been exhausted (Table 1).

E. Coronary Blood Flow to the Right Ventricle and the Atria

I. Right ventricular blood flow

During quiet resting conditions, right ventricular blood flow in the dog and horse expressed per gram of
TABLE 1. **Coronary vasodilator reserve during severe treadmill exercise**

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Species</th>
<th>Method of Vasodilation</th>
<th>Exercise</th>
<th>HR, beats/min</th>
<th>Exercise + Vasodilation</th>
<th>Mean Arterial Blood Pressure, mmHg</th>
<th>Mean CBF, ml·min⁻¹·g⁻¹</th>
<th>Endo/Epi</th>
<th>Subendocardial Blood Flow, ml·min⁻¹·g⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Restorff et al. (588)</td>
<td>Dog</td>
<td>Reactive hyperemia to &quot;brief&quot; occlusion</td>
<td>?</td>
<td>284 ± 6</td>
<td>260 ± 9</td>
<td>125 ± 5</td>
<td>2.56 ± 0.10</td>
<td>3.84*</td>
<td>?</td>
</tr>
<tr>
<td>Barnard et al. (41)</td>
<td>Dog</td>
<td>Dipyridamole, 0.75 mg/kg ia</td>
<td>?</td>
<td>271 ± 8</td>
<td>240 ± 3</td>
<td>239 ± 3</td>
<td>2.46 ± 0.24</td>
<td>3.14 ± 0.24</td>
<td>1.05 ± 0.07</td>
</tr>
<tr>
<td>Sanders et al. (500)</td>
<td>Swine</td>
<td>Adenosine, 1.5 mg·kg⁻¹·min⁻¹ iv</td>
<td>?</td>
<td>283 ± 5</td>
<td>282 ± 6</td>
<td>138 ± 5</td>
<td>128 ± 6*</td>
<td>3.82 ± 0.24</td>
<td>4.41 ± 0.29*</td>
</tr>
<tr>
<td>White et al. (603)</td>
<td>Swine</td>
<td>Adenosine, 0.8 mg·kg⁻¹·min⁻¹ iv</td>
<td>?</td>
<td>283 ± 5</td>
<td>283 ± 5</td>
<td>138 ± 5</td>
<td>136 ± 5</td>
<td>3.82 ± 0.24</td>
<td>4.99 ± 0.35*</td>
</tr>
<tr>
<td>Breisch et al. (77)</td>
<td>Swine</td>
<td>Adenosine, 0.8 mg·kg⁻¹·min⁻¹ iv</td>
<td>?</td>
<td>281 ± 6</td>
<td>146 ± 7</td>
<td>71 ± 3*</td>
<td>4.05 ± 0.20</td>
<td>5.10 ± 0.30*</td>
<td>1.00 ± 0.04</td>
</tr>
<tr>
<td>Laughlin et al. (342)</td>
<td>Swine</td>
<td>Dipyridamole, 1-2 mg/kg, iv</td>
<td>?</td>
<td>238 ± 15</td>
<td>293 ± 9*</td>
<td>164 ± 10</td>
<td>133 ± 7*</td>
<td>5.26 ± 0.47</td>
<td>6.17 ± 0.71*</td>
</tr>
<tr>
<td>Parks and Manohar (448)</td>
<td>Pony</td>
<td>Adenosine, 4 μmol·kg⁻¹·min⁻¹ iv</td>
<td>?</td>
<td>225 ± 7</td>
<td>227 ± 6</td>
<td>160 ± 4</td>
<td>153 ± 9</td>
<td>5.34 ± 0.31</td>
<td>9.34 ± 0.66</td>
</tr>
<tr>
<td>Manohar (378)</td>
<td>Pony</td>
<td>Adenosine, 3 μmol·kg⁻¹·min⁻¹ iv</td>
<td>?</td>
<td>224 ± 6</td>
<td>224 ± 5</td>
<td>155 ± 8</td>
<td>138 ± 6*</td>
<td>5.30 ± 0.32</td>
<td>9.40 ± 0.71*</td>
</tr>
</tbody>
</table>

Data are means ± SE. HR, heart rate; CBF, coronary blood flow; Endo/Epi, subendocardial-to-subepicardial blood flow ratio; "?", not reported; ia, intra-atrial (infusion into the left atrium). *P < 0.05, effect of vasodilation during vs. before vasodilation.
myocardium is typically 50–60% of left ventricular blood flow, while the transmural distribution of perfusion is uniform or slightly favors the subendocardium (34, 37, 44, 378, 379, 440). In resting swine, right ventricular blood flow per gram of myocardium is ~70–90% of left ventricular blood flow with an ENDO/EPI ratio of 1.50 (147, 342, 499). The lower resting flows in the right ventricle are the result of the lower oxygen consumption compared with left ventricular, systolic pressure. Interestingly, the lower levels of oxygen consumption are associated with significantly lower levels of myocardial oxygen extraction (46 ± 3%) by the right ventricle (245, 620).

During graded treadmill exercise in dogs, swine, and horses, right ventricular blood flow increases as a direct function of heart rate (Fig. 12). Right ventricular blood flow expressed per gram of myocardium is ~75–90% of flow to the left ventricle during the highest levels of exercise (34, 37, 44, 342, 378, 379), while in one study of swine exercising at 85–90% of maximum heart rate, right ventricular blood flow slightly exceeded left ventricular flow (147). The relatively greater exercise-induced increase in right ventricular blood flow during heavy exercise (3- to 6-fold) compared with left ventricular blood flow (2.5- to 4-fold), likely reflects the greater increase in right ventricular myocardial oxygen consumption (245) secondary to the marked increase in pulmonary artery pressure during exercise (147, 627). The relative increase in right ventricular blood flow during heavy exercise appears to be greatest in ponies (8- to 10-fold; Refs. 378, 379) compared with dogs (5- to 6-fold; Refs. 34, 37), and swine (3- to 4-fold; Refs. 147, 342). This is likely the result of the pronounced pulmonary hypertension that occurs during exercise in horses, with mean pulmonary pressure increasing from 19–30 mmHg at rest to 66–89 mmHg during maximal exercise (378, 379).

In the left ventricle, the high resting level of oxygen extraction (70–80%) necessitates an increase in coronary blood flow even at low levels of exercise. Right ventricular oxygen extraction during resting conditions is much lower, so that ~85% of the increment in oxygen consumption produced by mild exercise (60% of maximal heart rate) was accommodated by an increase in oxygen extraction from 46 ± 3% at rest to 68 ± 2%, with extraction further increasing to 82 ± 1% during exercise at 80% of maximal heart rate (Fig. 13) (245). The difference in regulation of oxygen extraction between the right and left ventricles is incompletely understood, but the blunted response of right ventricular blood flow to exercise with

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**FIG. 12.** Relation between heart rate and right ventricular blood flow (top panels) and left and right atrial blood flow (bottom panels) in dogs (34, 44), swine (342), and horses (378, 379) at rest and during treadmill exercise. Exercise produced significant (P < 0.05) increases in flow to all four cardiac chambers at each level of exercise studied. Note that the absolute increases in right ventricular and atrial flows are similar to the increases in left ventricular flow, but that as a result of the lower resting right ventricular and atrial flows, the relative increases are greater in these cardiac chambers compared with the left ventricle. Data are means ± SE. See text for further explanation.

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increased oxygen extraction is not the result of exhaustion of vasodilator reserve. Thus Manohar (378) demonstrated that infusion of adenosine in ponies during maximal treadmill exercise caused right ventricular blood flow to increase from 4.80 ± 0.31 ml·min⁻¹·g⁻¹ during maximal exercise to 7.54 ± 0.30 ml·min⁻¹·g⁻¹. Furthermore, Bauman et al. (45) reported similar vasodilator reserve in right and left ventricles of dogs at rest and during exercise. Zong et al. (626) demonstrated that the large increase in oxygen extraction during exercise could be in part explained by an exaggerated α-adrenergic vasoconstrictor influence on the right ventricular vasculature. Nevertheless, following α-adrenergic blockade, a significant increase in right ventricular oxygen extraction still occurred, indicating that other mechanisms must be involved as well.

The transmural distribution of right ventricular blood flow in dogs and swine does not change from rest to exercise (34, 37, 342, 440, 499). Furthermore, during maximal exercise in ponies, vasodilator reserve existed in all transmural layers of the right ventricular wall; the right ventricular ENDO/EPI ratio during maximal exercise was 1.00 ± 0.02 and actually increased to 1.32 ± 0.10 when adenosine was infused while exercise continued (378). The finding that maximal pharmacological coronary vasodilation did not result in a relative redistribution of blood flow away from the subendocardium in the right ventricle is likely the result of the lower systolic compressive forces acting on the intramyocardial vasculature in the right compared with the left ventricle (53).

2. Atrial blood flow

During quiet resting conditions, right and left atrial blood flows expressed per gram of myocardium are typically 20–40% of left ventricular blood flow in dogs (342), swine (342), and horses (379). During treadmill exercise, atrial flows can increase up to 15-fold reaching 50–60% of left ventricular flow levels during heavy exercise in dogs and swine, and up to 70% of left ventricular flows in ponies (Fig. 12). These increases in blood flow do not require maximal vasodilation of atrial vasculature, as the degree of vasodilator reserve during exercise was reported to be comparable to those in the ventricular chambers (45). Within the atria, blood flow was reported to be lowest in the appendage (0.15–0.30 ml·min⁻¹·g⁻¹) compared with the nonappendage regions (0.33–0.37 ml·min⁻¹·g⁻¹), whereas the exercise-induced increase in flow was greater in the appendages (6- to 11-fold in right and left atria, respectively) compared with the nonappendage regions (4- to 5-fold). These observations suggest that the appendages perform less work than the body of the atria under resting conditions, but become increasingly more active as atrial filling is enhanced during exercise (44).

F. Control of Coronary Vascular Resistance

Regulation of coronary vascular resistance is the result of a balance between a myriad of vasodilator and vasoconstrictor signals exerted by neurohormonal influences, the endothelium, and metabolic signals from the myocardium (Fig. 14). These vasomotor influences allow the myocardium to match the coronary blood supply to the requirement for oxygen and nutrients, while maintaining a consistently high level of oxygen extraction. The ability of coronary resistance vessels to dilate in response to increments in myocardial oxygen demand, as illustrated by the tight correlation between myocardial oxygen consumption and coronary blood flow, is critical for maintaining an adequate supply of oxygen to the myocardium. The matching of coronary vasomotor tone to myocardial metabolism is best studied by examining the relation between coronary venous oxygen tension and myocardial oxygen consumption (27, 143, 266, 267, 565, 566). For example, an increase in coronary resistance vessel tone will limit coronary blood flow and hence the oxygen supply, thereby forcing the myocardium to increase oxygen extraction, with a consequent reduction in coronary venous oxygen levels. Conversely, a decrease in coronary tone will increase blood flow and the oxygen supply to the heart; if oxygen consumption remains constant, oxygen consumption and coronary blood flow, is critical for maintaining an adequate supply of oxygen to the myocardium. The matching of coronary vasomotor tone to myocardial metabolism is best studied by examining the relation between coronary venous oxygen tension and myocardial oxygen consumption (27, 143, 266, 267, 565, 566). For example, an increase in coronary resistance vessel tone will limit coronary blood flow and hence the oxygen supply, thereby forcing the myocardium to increase oxygen extraction, with a consequent reduction in coronary venous oxygen levels. Conversely, a decrease in coronary tone will increase blood flow and the oxygen supply to the heart; if oxygen consumption remains constant, oxygen
extraction will decrease and coronary venous oxygen levels will increase. Thus coronary venous oxygen tension is an index of tissue oxygenation that reflects the balance between the oxygen supply and demand of the heart and is ultimately determined by coronary resistance vessel tone (565).

1. Autonomic nervous system

Autonomic influences have been studied by examining coronary blood flow at rest and during exercise after surgical or chemical denervation of the heart or in the presence of selective autonomic receptor antagonists.

A) CARDIAC NEURAL ABLATION. The coronary vascular bed is richly innervated by both the sympathetic and parasympathetic divisions of the autonomic nervous system (46, 104, 181, 182, 598). To study their contributions to coronary blood flow regulation during exercise, techniques have been devised to produce surgical denervation of the heart confirmed by depletion of myocardial norepinephrine stores and lack of an inotropic response to cardiac sympathetic nerve stimulation (133, 311). It should be noted that the results obtained using these preparations are complicated by supersensitivity to circulating catecholamines which develops after sympathetic neural ablation. This supersensitivity appears to be selective, in that the response of myocardial contractility to norepinephrine is augmented (102, 133), whereas Ç-adrenergic responses of the coronary vasculature do not appear to be enhanced (102, 129, 202).

Cardiac neural ablation does not impair the ability to maintain steady-state levels of exercise, although the initial hemodynamic adjustment to exercise is delayed. For example, Gregg et al. (220) observed that in dogs with surgical cardiac denervation, the onset of heavy treadmill exercise resulted in a 25% decrease in arterial blood pressure that did not return to control levels until 36–90 s

FIG. 14. Schematic drawing of a coronary arteriole and the various influences that determine coronary vasomotor tone and diameter. PO₂, oxygen tension; TXA₂, thromboxane A₂ (receptor); 5HT, serotonin or 5-hydroxytryptamine (receptor); P₂X and P₂Y, purinergic receptor subtypes 2X and 2Y that mediate ATP-induced vasoconstriction and vasodilation, respectively; ACh, acetylcholine; M, muscarinic receptor; H₁ and H₂, histamine receptors type 1 and 2; B₂, bradykinin receptor subtype 2; ANG I and ANG II, angiotensin I and II; AT₁, angiotensin II receptor subtype 1; ET, endothelin; ET₅ and ET₆, endothelin receptor subtypes A and B; A₂, adenosine receptor subtype 2; B₂, B₂-adrenergic receptor; α₁ and α₂, a-adrenergic receptors; NO, nitric oxide; eNOS, endothelial NO synthase; PGI₂, prostacyclin; IP, prostacyclin receptor; COX-1, cyclooxygenase-1; EDHF, endothelium-derived hyperpolarizing factor; CYP₄₅₀, cytochrome P₄₅₀ 2C9; Kᵥ, calcium-sensitive K⁺ channel; Kᵦ, ATP-sensitive K⁺ channel; Kᵦ, voltage-sensitive K⁺ channel; AA, arachidonic acid; L-Arg, L-arginine; O₂⁻, superoxide. Receptors, enzymes, and channels are indicated by an oval or rectangle, respectively. See text for further explanation.
after beginning exercise, while in normal dogs arterial pressure decreased only slightly and recovered within 3–6 s after beginning exercise. Similarly, the increase in coronary blood flow was delayed 10–30 s after the onset of treadmill exercise in animals with cardiac denervation, in contrast to a 3- to 6-s delay observed in normal dogs. Gwirtz et al. (231) observed that cardiac sympathectomy decreased left ventricular peak systolic pressure and dP/dt max during exercise, suggesting that the reduction of oxygen consumption was due, at least in part, to decreased myocardial contractility. Myocardial oxygen consumption and coronary blood flow were substantially decreased in dogs following surgical denervation at rest and during treadmill exercise (220, 231). Oxygen extraction at rest was similar in control and denervated hearts, suggesting that autonomic control of coronary vasomotor tone is minimal under resting conditions. In contrast, the exercise-induced increase in myocardial oxygen extraction and decrease in coronary venous oxygen content were enhanced in denervated compared with innervated hearts (Fig. 15), indicating that intact innervation contributes in a feed-forward manner to exercise hyperemia.

Further evidence for a role of neural control of coronary blood flow during exercise was provided by Schwartz and Stone (516) who reported that the increases of heart rate and contractility during exercise were attenuated by ablation of the right but not the left stellate ganglion in dogs, while the increase in coronary blood flow was slightly increased after left stellate ganglionectomy. DiCarlo et al. (130) also found that coronary flow during submaximal exercise was higher after left stellate ganglion ablation, and that nonselective α-adrenergic blockade with intracoronary phentolamine (1 mg) had no further effect, implying that sympathetic neural ablation abolishes α-adrenergic vasoconstriction during exercise. In contrast, Chilian et al. (102) reported that regional sympathetic denervation of the posterior left ventricular wall by epicardial application of phenol caused no difference in mean myocardial blood flow or the transmural distribution of perfusion either at rest or during treadmill exercise, thus failing to support neurogenic coronary vasocostriction during exercise. After β-adrenergic blockade with propranolol, nonselective α-adrenergic blockade with phentolamine decreased coronary vascular resistance in both the innervated (28%) and sympathectomized (23%) regions (likely in part to compensate for an 18% decrease in mean aortic pressure caused by the systemic α-adrenergic blockade). The authors concluded that α-adrenergic coronary vasoconstriction does occur during exercise, but is principally mediated by circulating catecholamines rather than by direct neural connections. Finally, Furuya et al. (202) reported that coronary flow during exercise was slightly higher in denervated than in normal hearts at comparable levels of myocardial oxygen demand (reflected by the heart rate × mean aortic pressure product), but that α-adrenergic receptor blockade with phentolamine (2 mg/kg iv) caused a slight further increase in coronary flow. The authors interpreted these findings to suggest that adrenergic coronary vasoconstriction during exercise is mediated both by circulating catecholamines and by direct neural influences (202). Interpretation of these studies (102, 130, 202, 516) is complicated because myocardial oxygen consumption and coronary venous oxygen content or tension were not determined.

In conclusion, cardiac autonomic denervation (220), or selective sympathetic denervation (130, 231, 516), limits exercise hyperemia in the heart, indicating that sympathetic activity contributes to exercise hyperemia in a feed-forward manner. Although there is evidence to suggest a role for circulating catecholamines in the control of coronary blood flow during exercise as well (102), the weight of evidence is consistent with the concept that autonomic influences on the coronary circulation are principally neurally mediated.

**B) α-ADRENERGIC CONTROL.** Blockade of α-adrenergic receptors can influence coronary blood flow through three separate mechanisms. First, blockade of prejunctional α2-adrenoceptors interrupts the negative-feedback control of norepinephrine release (268, 336). The resultant increase in norepinephrine levels augments cardiac β-adrenergic stimulation and increases coronary blood flow secondary to the increased myocardial oxygen consumption. Second, α-adrenergic blockade can increase coronary flow by interrupting vasoconstriction mediated by postjunctional α1- and α2-adrenoceptors located on the smooth muscle cells of small coronary arteries >100 μm (predominantly α1) and arterioles <100 μm (both α1 and α2) (98, 104, 410). Finally, α2-adrenergic receptors on
coronary vascular endothelium stimulate release of nitric oxide (NO) (109), which can oppose the α-adrenergic vasoconstrictor effect (109, 287).

Under basal resting conditions, cardiac sympathetic activity is minimal so that α-adrenergic blockade has a negligible effect on coronary flow in awake resting dogs (100) and humans (263, 272). In contrast, in dogs and swine, exercise produces a greater increase in coronary blood flow after systemic α-adrenergic blockade than during control conditions (27, 122, 148, 233, 266, 365). Systemic nonselective α-adrenergic antagonists exaggerate the β-adrenoceptor-mediated increases of heart rate, left ventricular systolic pressure, and dP/dt\(_{\text{max}}\) during exercise as the result of blockade of prejunctional α\(_{2}\)-adrenergic receptors which normally inhibit norepinephrine release (148, 268, 336). In this situation, β-adrenergic blockade inhibits the marked increase in hemodynamic determinants of myocardial oxygen consumption produced by systemic nonselective α-adrenergic blockade. When nonselective α-adrenergic antagonists were administered to dogs by the intracoronary route to minimize systemic hemodynamic effects, coronary blood flow during exercise was still 10–30% higher than during control exercise (123, 130, 232, 235, 282). Furthermore, at comparable levels of myocardial oxygen consumption, α-adrenergic blockade increased coronary venous oxygen tension (Fig. 16) and decreased coronary vascular resistance, indicating competition between α-adrenergic vasoconstriction and metabolic coronary vasodilation during exercise (27, 31, 122, 266). However, in swine, nonselective α-adrenergic blockade with phentolamine had no effect on the relation between myocardial oxygen consumption and coronary venous oxygen tension (Fig. 16), indicating negligible α-adrenergic control of coronary resistance vessel tone in this species (148, 514). To date, well-controlled studies of α-adrenergic control of coronary resistance vessel tone during exercise in humans are lacking (263).

Both α\(_1\)- and α\(_2\)-adrenoceptors can mediate coronary vasoconstriction, but adrenergic coronary vasoconstriction during exercise in the normal dog heart appears to involve principally α\(_1\)-adrenoceptors. Thus selective α\(_1\)-adrenergic blockade with intracoronary prazosin resulted in higher levels of coronary blood flow and lower coronary vascular resistance during graded treadmill exercise (123, 542), whereas intracoronary administration of the selective α\(_2\)-adrenergic blockers yohimbine or idazoxan did not alter coronary blood flow or coronary resistance during exercise (123, 542). Since the effect of increased release of norepinephrine produced by α\(_2\)-adrenoceptor blockade might be concealed by the α\(_1\)-adrenergic vasoconstriction, which it can produce, studies were repeated with the addition of α\(_1\)-adrenergic blockade. Combined intracoronary administration of α\(_1\)- and α\(_2\)-adrenergic blockers was not more effective in increasing coronary blood flow or coronary venous oxygen tension during exercise than was α\(_1\)-adrenergic blockade alone (123). Although α\(_2\)-adrenergic receptors on coronary vascular endothelium stimulate release of NO (109, 287), the lack of effect of blockade of α\(_2\)-adrenoceptors was not due to simultaneous reduction in NO release, as blockade of α\(_2\)-adrenoceptors failed to increase coronary flow during exercise in the presence of NO blockade (287). Thus the α-adrenergic vasoconstrictor tone that opposes metabolically mediated coronary vasodilation during exercise is mediated principally by postjunctional α\(_1\)-adrenoceptor activity.

Feigl and co-workers (183, 282) proposed that adrenergic coronary vasoconstriction can augment subendocardial blood flow during exercise. They observed that the ENDO/EPI blood flow ratio during exercise was slightly higher in regions with α-adrenoceptors intact than in regions where α-adrenoceptors were blocked with intracoronary phenoxybenzamine, although total blood flow was higher after adrenergic blockade (282). In contrast, α-adrenoceptor blockade caused a transmurally uniform increase of blood flow in myocardial regions perfused by a stenotic coronary artery (355), as well as in the pressure-overloaded hypertrophied left ventricular wall of dogs (155), indicating transmurally uniform α-adrenergic coronary vasoconstriction during exercise. Heusch and co-workers (46) addressed the issue of the uniformity of humoral and neuronal α-adrenergic vasoconstriction across the left ventricular wall in anesthetized dogs under conditions of intact vasomotor tone and during maximal coronary vasodilation with diprydamole. During humoral adrenergic activation, produced by intravenous atropine/norepinephrine, intracoronary phentolamine increased

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**Fig. 16.** Effect of mixed α\(_1\)/α\(_2\)-adrenergic receptor blockade with phentolamine [2 mg/kg iv (27) or 1 mg/kg iv (148)] or selective α\(_1\)-adrenergic receptor blockade with prazosin (0.1 mg/kg iv) on the relation between myocardial oxygen consumption and coronary venous oxygen tension in the left ventricles of dogs (27; left panel) and swine (148; right panel) during treadmill exercise. Data are means ± SE. *P < 0.05 prazosin and phentolamine vs. control. See text for further explanation.
blood flow uniformly in all myocardial layers, irrespective of whether coronary vasomotor tone was intact or abolished. During cardiac sympathetic nerve stimulation, phentolamine increased flow to all layers when coronary tone was intact, but during maximal coronary vasodilation, phentolamine increased flow to subepicardium with a tendency for subendocardial blood flow and the ENDOP/ EPI ratio to decrease (both \( P = NS \)).

It is possible that the differing results might be explained in part by the higher heart rates in the study of Huang and Feigl (\(~240 \text{ beats/min}\)) compared with heart rates of \(~215 \text{ beats/min} (155, 355)\) and \(<200 \text{ beats/min} (46)\). Thus \(\alpha\)-adrenergic stiffening of the intramural penetrating arteries that traverse the myocardium to the subendocardium, and the consequent reduction of systolic retrograde flow, could be of particular importance at high heart rates (183). To address this question, Morita et al. (412) mimicked exercise by combining intravenous noradrenaline infusion with cardiac pacing at 150, 200, and 250 beats/min in open-chest dogs with intact coronary vasomotor tone. At heart rates of 150 and 200 beats/min, intracoronary phenoxybenzamine produced a transmurally homogeneous increase in myocardial blood flow, whereas at 250 beats/min phenoxybenzamine produced a small decrease in blood flow to all myocardial layers. Interpretation of this transmurally homogeneous flow decrease is difficult because myocardial oxygen consumption was not measured. However, the lack of change in ENDOP/EPI ratio fails to support the concept that the \(\alpha\)-adrenergic vasoconstriction acts to protect the subendocardium from hypoperfusion during high work loads. Furthermore, even during maximal exercise, the coronary bed is not maximally vasodilated and retains residual vasomotor tone (see sect. \(\alpha B3c\)). These conditions favor a transmurally homogeneous \(\alpha\)-adrenergic vasoconstrictor influence in the normal heart during exercise (46, 412). To definitively address the issue of whether \(\alpha\)-adrenergic vasoconstriction serves to maintain subendocardial blood flow during heavy exercise, future studies investigating the effects of intracoronary \(\alpha\)-blockade on transmural myocardial blood flow during exercise at maximal heart rates (\(~300 \text{ beats/min} \text{ in dogs}\)) are needed.

In conclusion, study of \(\alpha\)-adrenergic influences is complicated because pharmacological blockers often cause changes in contractile function that produce myocardial metabolic effects on the coronary circulation which exceed their direct vascular effects. For example, postjunctional \(\alpha\)-adrenergic receptors mediate coronary vasoconstriction, but blockade of prejunctional \(\alpha\)-adreceptors interrupts the normal inhibition of norepinephrine release from sympathetic axons so that nonselective \(\alpha\)-adrenergic blockers increase \(\beta\)-adrenergic stimulation of contractility with a resultant increase of myocardial oxygen requirements and, therefore, coronary vasodilation. Consequently, although the primary vascular effect of \(\alpha\)-adrenergic activation is vasoconstriction, the overall response to nonselective \(\alpha\)-adrenergic blockade is dominated by an increase in myocardial oxygen consumption which causes coronary vasodilation. \(\alpha_2\)-Adrenergic mechanisms act to blunt the increase in coronary flow that occurs during exercise, and this results in a decrease in coronary venous oxygen tension in some species as the dog, and possibly humans, but appears to be absent in swine. The weight of evidence indicates that \(\alpha\)-adrenergic vasoconstriction limits myocardial blood flow in a transmurally homogeneous manner during moderate levels of exercise. Whether \(\alpha\)-adrenergic tone acts to maintain subendocardial blood flow during (near) maximal levels of exercise remains to be established.

C) \(\beta\)-ADRENERGIC CONTROL. The direct influence of \(\beta\)-adrenergic control of coronary vascular resistance via \(\beta\)-adrenoceptors [principally \(\beta_2\)-receptors which are located on coronary arterioles \(<100 \mu m (104, 256, 416)\)], is difficult to separate from metabolic alterations in coronary vaso-motor that result from \(\beta\)-adrenergic inotropic and chronotropic effects on the myocardium. In awake resting dogs (43, 267) and swine (148), nonselective \(\beta\)-adrenergic blockade with propranolol decreased myocardial oxygen consumption, and this resulted in a parallel reduction of coronary blood flow; myocardial oxygen extraction was unchanged, suggesting that \(\beta\)-adrenergic control of the coronary circulation is minimal under resting conditions. However, during graded treadmill exercise, propranolol decreased coronary flow more than expected from the decrease in myocardial oxygen consumption, resulting in an increase in myocardial oxygen extraction and a decrease in coronary venous oxygen tension in both dogs and swine (Fig. 17) (43, 148, 214, 215, 266). Similarly, in normal human subjects or patients with angiographically normal coronary arteries (608), \(\beta\)-adrenergic blockade with propranolol or sotalol decreased myocardial blood flow during bicycle exercise out of proportion to the reduction of myocardial oxygen consumption, necessitating an increase in myocardial oxygen extraction (162, 303). The findings imply that \(\beta\)-adrenergic control of the coronary resistance vessels is minimal under resting conditions, but \(\beta\)-adrenergic activation contributes to coronary vasodilation during exercise in a feed-forward manner (408, 409, 566).

Intracoronary administration of the nonselective \(\beta\)-adrenergic blocker propranolol to exercising dogs caused a slightly greater decrease of coronary blood flow than did the selective \(\beta_1\)-adrenergic blocker atenolol, indicating that \(\beta_2\)-adrenergic mechanisms can contribute to adrenergic coronary vasodilation. In support of this, intracoronary administration of the selective \(\beta_2\)-adrenoceptor blocker ICI 118,551 during exercise caused no change in contractile function but produced an 11–14% decrease in coronary flow during moderate treadmill exercise in dogs (130, 386). These findings indicate that \(\beta_2\)-adreno-
Further explanation.

Cardiac response to exercise, with a consequent reduction of coronary resistance vessels. In swine, \( \beta_1/\beta_2 \)-adrenergic receptor blockade in swine (139) and dogs (214). Data are means \( \pm \) SE. * \( P < 0.05 \) vs. Phento alone or vs. control. See text for further explanation.

Receptor activation during exercise causes a small but significant degree of coronary resistance vessel dilation independent of the myocardial effects of \( \beta_1 \)-adrenergic stimulation.

In conclusion, \( \beta \)-adrenergic blockade blunts the myocardial response to exercise, with a consequent reduction of oxygen consumption. However, \( \beta \)-adrenergic blockade causes a greater reduction of coronary flow than of myocardial oxygen consumption, resulting in increased oxygen extraction by the heart and demonstrating a direct feed-forward \( \beta \)-adrenergic vasodilator effect on the coronary vessels. In swine, \( \beta \)-adrenergic activation exerts a feed-forward effect that is unopposed by \( \alpha \)-adrenergic vasoconstriction so that coronary venous oxygen tension does not fall during exercise.

D) PARASYMPATHETIC CONTROL. The coronary resistance vessels are richly innervated by the parasympathetic division of the autonomic nervous system (181). In dogs, pretreated with propranolol and paced to maintain a constant heart rate, stimulation of the vagosympathetic trunk produces coronary vasodilation independent of the cardiac effects of vagal stimulation (79). The coronary vasodilation produced by vagal stimulation was blocked by atropine and was mimicked by acetylcholine, which involves the release of endothelial NO in the dog (79, 525).

To study the vasodilator influence of vagal activity on coronary blood flow during exercise, Gwirtz and Stone (234) administered the muscarinic receptor antagonist atropine into a coronary artery of dogs during submaximal exercise (heart rates of 190–210 beats/min). Atropine had no effect on heart rate or coronary blood flow, indicating that parasympathetic effects on both the myocardium and coronary bed were negligible at this level of exercise. This is in accord with the finding that vagal tone to the myocardium is progressively withdrawn during increasing levels of exercise (434, 584). Importantly, the high vagal tone in the resting dog exerts a small vasodilator influence on the coronary circulation, the inhibition of which will limit rather than support the exercise-induced coronary vasodilation.

In swine, the acetylcholine-induced NO-mediated vasodilation (which predominates in dogs) is outweighed by a direct vasoconstrictor effect on coronary smooth muscle, resulting in a net vasoconstrictor response to acetylcholine (119, 201, 248) or vagal nerve stimulation (201).

Despite ample evidence that stimulation of the parasympathetic system can influence coronary vasomotor tone, the effects of vagal activity under basal resting conditions are generally considered to be negligible even during basal resting conditions when vagal activity is high (119). However, these studies have been conducted principally in anesthetized animal models that could have blunted vagal tone (580). In addition, coronary flow was not related to myocardial oxygen consumption which, in view of potential myocardial effects of vagal inhibition, makes interpretation of these studies difficult. Duncker et al. (148) investigated the effects of muscarinic receptor blockade with intravenous atropine in chronically instrumented swine at rest and during graded treadmill exercise. Atropine elicited a vasodilator response in the coronary resistance vessels under resting conditions that waned with increasing levels of exercise intensity. Vasodilatation was likely the result of increased \( \beta \)-adrenergic activity, since it was fully blocked when studies were repeated in the presence of propranolol. Thus the vasoconstrictor influence that was exerted by the parasympathetic nervous system was due to inhibition of \( \beta \)-adrenergic vasodilator activity. These observations suggest that withdrawal of vagal tone may contribute to \( \beta \)-adrenergic vasodilation at lower levels of exercise. Due to progressive withdrawal of vagal tone with increasing exercise intensity, parasympathetic influences are unlikely to be
physiologically significant during heavy exercise (139, 140, 234, 584).

In conclusion, parasympathetic activation can exert weak species-dependent effects on the coronary vessels. In animals in which acetylcholine causes vasodilatation, parasympathetic activity causes a weak dilator influence at rest when vagal tone is high, but vagal tone is withdrawn during exercise so that parasympathetic effects are negligible during exercise. In species in which acetylcholine causes coronary vasoconstriction, as in swine, withdrawal of vagal tone may augment the increase in coronary flow during exercise.

E) SUMMARY AND INTEGRATION. Although coronary blood flow is strongly responsive to local myocardial metabolic requirements, the autonomic nervous system provides a modulating influence that can alter the coupling between coronary flow and myocardial metabolism. During resting conditions, cardiac sympathetic activity is minimal so that adrenergic blockade has a negligible effect on coronary flow. During exercise, adrenergic activation exerts paradoxical effects that both oppose (alpha) and reinforce (beta) the increase in coronary flow that occurs in response to the increase in cardiac work. The net effect of sympathetic stimulation is beta-adrenergic feed-forward vasodilation (Fig. 17), which has been proposed to account for as much as 25% of the exercise hyperemia (215). However, cardiac denervation or pharmacological inhibition of autonomic control does not result in myocardial ischemia during exercise, implying that other vasodilator mechanisms act to compensate and mediate exercise hyperemia when autonomic control is blocked. These findings are consistent with the concept that autonomic control serves to optimize the matching of coronary blood flow to myocardial metabolic needs but is not essential for exercise hyperemia.

2. Angiotensin II

Angiotensin II (ANG II) is a vasoactive octapeptide produced by cleavage of the decapeptide angiotensin I by angiotensin converting enzyme. ANG II exerts important cardiovascular effects, including positive inotropism and vasoconstriction, as well as causing norepinephrine and aldosterone release, all of which are mediated via the AT₁ receptor (557). Although the AT₂ receptor can mediate a vasodilator response, the (patho)physiological function of this receptor is less clear, as the vasomotor response to exogenous ANG II is principally vasoconstriction (557). In the coronary circulation, exogenous ANG II produces constriction of epicardial conductance arteries (419), as well as small arteries (298) and arterioles (623). Furthermore, intravenous as well as intracoronary administration of ANG II produces coronary vasoconstriction in a variety of species, including rat (374, 394, 513), dog (435, 624), and swine (330), indicating that the AT₁ receptor is present in the coronary microvasculature and is capable of influencing coronary vasomotor tone. Furthermore, during treadmill exercise, sympathetic activity, and hence activity of the renin-angiotensin system, increases. This suggests that the increased levels of ANG II during exercise could act to increase coronary vasomotor tone.

Studies in awake swine examining the role of endogenous ANG II in the control of coronary resistance vessel tone have yielded ambiguous results, with AT₁ receptor blockade having either no effect at rest (539, 547) or during exercise (106), or causing coronary vasodilatation during exercise (539, 547). None of these studies corrected for alterations in coronary vasomotor tone resulting from changes in myocardial metabolic demands produced by AT₁ receptor blockade, making interpretation of the data difficult. This is particularly important since systemic administration of the AT₁ blocker (106, 539, 547) results in alterations of systemic hemodynamics. However, even when systemic hemodynamic effects are avoided by intracoronary administration of the AT₁ antagonist (457, 475), myocardial oxygen demands can be reduced as a result of a decrease in contractility both directly, through blockade of AT₁ receptors on the cardiomyocytes (125), and indirectly, through blockade of AT₁ receptors on the sympathetic nerve endings with consequent blunting of norepinephrine release (310, 493, 550). Hence, the reported failure of coronary blood flow to increase in response to intracoronary losartan in humans with endothelial dysfunction (457) may have been due to a decrease in myocardial oxygen demands produced by presynaptic and cardiomyocyte AT₁ blockade. To isolate the influence of AT₁ receptors on coronary vasomotor tone, Merkus et al. (394) studied the effect of AT₁ blockade on the relation between coronary blood flow and myocardial oxygen demand (143, 565). They found that AT₁ receptor blockade caused coronary vasodilatation at rest and during exercise of awake swine, indicating that endogenous ANG II exerts a tonic vasoconstrictor influence on the coronary resistance vessels (Fig. 18). AT₁ receptor blockade can decrease norepinephrine levels by blockade of presynaptic AT₁ receptors that act to facilitate norepinephrine release (310, 493, 550). Conversely, the decrease in blood pressure that often accompanies AT₁ receptor blockade will activate the baroreceptor reflex-mediated release of norepinephrine. The baroreceptor-mediated increase in norepinephrine is likely the predominant effect, as circulating norepinephrine levels increased slightly following AT₁ receptor blockade, while the transmyocardial norepinephrine gradient remained unchanged, consistent with reports that ANG II-induced presynaptic modulation of catecholamine release in the heart is minimal (310, 330). In swine, norepinephrine exerts its effects on coronary vasomotor tone primarily...
through activation of β-adrenoceptors, thereby causing vasodilation (148) so that the small increase in norepinephrine following AT₁ receptor blockade may have contributed to the observed coronary vasodilation. Nevertheless, a vasodilator effect of AT₁ receptor blockade remained after β-receptor blockade, indicating that the coronary vasodilation produced by systemic AT₁ receptor blockade was not simply the result of increased coronary β-adrenergic stimulation, but also included a direct effect on the coronary resistance vessels.

In contrast to observations in awake swine, studies in awake dogs have failed to reveal a significant role for ANG II in control of coronary resistance vessel tone either at rest or during exercise. Thus Zhang et al. (624) found that AT₁ receptor blockade with telmisartan had no effect on the relation between myocardial oxygen consumption and coronary venous oxygen tension in the left ventricles of dogs (624; left panel) and swine (394; right panel) during treadmill exercise. Data are means ± SE. *P < 0.05 vs. control. See text for further explanation.

Fig. 18. Effect of AT₁ receptor blockade with telmisartan (0.3 mg/kg iv) or irbesartan (1 mg/kg iv) on the relation between myocardial oxygen consumption and coronary venous oxygen tension in awake dogs (Fig. 18), suggesting that ANG II does not contribute to the regulation of coronary resistance vessel tone in the dog. Similarly, a study in resting humans reported that intracoronary losartan had no effect on coronary blood flow or coronary vascular resistance (457). However, a role of ANG II in the regulation of coronary resistance vessel tone in exercising healthy humans, determining the relation between myocardial oxygen consumption and coronary venous oxygen tension has not been investigated to date.

In summary, in swine, ANG II exerts a weak direct vasoconstrictor influence on the coronary circulation, particularly during exercise. In contrast, a role for ANG II in coronary vasomotor control during exercise in the canine and human heart has not been convincingly demonstrated.

3. Autacoids

Histamine and bradykinin are autacoids involved in inflammatory processes that can exert powerful effects on vasomotor tone. However, their role in the regulation of coronary vasomotor tone under normal conditions is still incompletely understood.

A) Histamine. Histamine, formed from histidine by histidine-decarboxylase and stored in mast cells and basophils, plays an important role in hypersensitivity and allergic reactions and can modulate vasomotor tone via stimulation of H₁ and H₂ receptors in the vascular wall. In the coronary circulation, H₁ receptors located on vascular smooth muscle cells of large and small arteries mediate vasoconstriction, while H₂ receptors located on vascular smooth muscle cells of arterioles mediate vasodilation (312, 403). In addition, H₁ receptors located on the endothelium can stimulate NO release to produce coronary vasodilation (312, 586). To our knowledge, there are no studies demonstrating a role for endogenous histamine in regulation of coronary vasomotor tone in awake healthy animals or humans during physiological conditions either at rest or during exercise.

B) Bradykinin. Bradykinin, produced by conversion of kininogens by tissue and plasma kallikreins, plays an important role in inflammation, nociception, and possibly regulation of blood pressure and fluid balance. Bradykinin synthesized within the vascular wall (85, 438) can exert a potent vasodilator influence on coronary arterial vessels of all sizes via stimulation of B₂ receptors to produce the endothelium-derived relaxing factors NO, prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF) (578, 579). In addition, some vasodilation also occurs via B₁ receptor stimulation, which appears to be NO-mediated (543), although this is substantially less than that produced via B₂ receptors, likely because induction of B₁ receptors principally occurs after tissue damage. Although there is some in vitro evidence for basal bradykinin release, obtained in isolated rat hearts (47), in vivo observations in awake healthy dogs failed to define a role for endogenous bradykinin in the regulation of coronary blood flow (460). Groves et al. (223) reported that infusion of the selective B₂ receptor antagonist HOE 140 into a coronary artery of patients without significant coronary stenoses (<30% luminal narrowing) caused vasoconstriction with a decrease in epicardial coronary luminal area and a decrease of coronary blood flow. These observations indicate that both coronary conductance and resistance vessels were subject to a bradykinin-mediated tonic vasodilator influence. Since this study was performed in patients with recurrent chest pain, it is uncertain whether bradykinin contributes to the regulation of coronary vasomotor tone in the normal human heart.

In summary, there is little evidence for a role of histamine or bradykinin in regulation of coronary blood ...
flow in the normal heart. It is likely that proinflammatory conditions, as are likely to occur in isolated heart preparations or in patients with coronary artery disease, will lead to an increased autacoid-mediated influence on coronary vasomotor.

4. Endothelium-derived vasoactive factors

A) NO. The normal coronary endothelium can cause vasodilation as constitutive NO synthase acts on L-arginine to produce NO, which causes relaxation of vascular smooth muscle via an increase in cGMP and consequent activation of calcium-activated K⁺ channels (K_
Ca
) channels and possibly K⁺ATP channels (461, 578). Endothelial production of NO can be triggered by specific receptors (e.g., muscarinic, bradykinin, and histamine receptors) or by mechanical deformation resulting from shear forces or pulsatile strain caused by blood flow (200, 276). NO-dependent mechanisms cause vasodilation of both epicardial arteries and coronary resistance vessels in response to increased blood flow in vitro (328) and contribute to coronary reactive hyperemia in vivo (7, 445, 618). The contribution of NO to maintenance of coronary blood flow has been studied by administering analogs of L-arginine that act as competitive inhibitors of the NO synthesis.

In vivo studies in dogs have generally shown no change (7, 293, 445, 472, 529, 610, 618) or only a small decrease (56, 568) of coronary flow in response to inhibitors of NO synthesis during basal conditions. In both anesthetized (314) and awake swine (147), inhibition of NO synthesis resulted in a small decrease of coronary blood flow that was accompanied by increased oxygen extraction and a decrease in coronary venous oxygen tension. In the human heart, endogenous NO exerts a modest vasodilator influence on the coronary vessels under resting conditions (160, 360, 464). In contrast, in isolated non-blood-perfused rodent hearts (rats, guinea pigs, rabbits), inhibitors of NO synthesis generally cause marked coronary vasoconstriction (9, 49, 81, 332, 447, 528, 570). The discrepancy between the modest contribution of NO in in vivo blood-perfused hearts compared with isolated buffer-perfused rodent hearts is likely due to differences in experimental conditions. In buffer-perfused hearts, flow rates are very high (∼6 ml·min⁻¹·g⁻¹), favoring shear-mediated release of NO. In addition, the absence of blood (and therefore the NO scavenger hemoglobin) is likely to increase the biological half-life of NO in the isolated perfused hearts (42).

Chilian and co-workers (300) reported that inhibition of NO synthesis with N°-nitro-L-arginine methyl ester (L-NAME; 30 μg·kg⁻¹·min⁻¹, intracoronary) constricted small coronary arteries (>100 μm), but this was counterbalanced by vasodilation of arterioles (<100 μm), indicating that compensatory vasomotor adjustments in different segments of the coronary vasculature occurred to maintain blood flow. These data imply that under resting conditions, the effects of NO synthase inhibition can be blunted by compensatory arteriolar dilation but suggest that this basal dilation of the coronary arterioles might limit further exercise-induced increases in coronary blood flow. There is evidence that during exercise coronary NO production is increased in the dog heart (56, 562), likely due to an increase in endothelial shear secondary to the increased coronary flow rates. Furthermore, NO release from erythrocytes could be stimulated in the canine heart during exercise in response to the decrease in intravascular oxygen tension (527, 536). Together these observations suggest that NO might contribute to the increase of coronary blood flow during exercise. However, blockade of NO production with intracoronary N°-nitro-L-arginine (L-NA) did not impair the ability to increase coronary flow during treadmill exercise in dogs (7, 56, 288, 568). In fact, coronary flow rates during exercise were slightly higher after L-NA, in parallel with a slight increase in myocardial oxygen consumption (7, 56, 288). The relation between myocardial oxygen consumption and coronary venous oxygen tension was not significantly altered by L-NA (Fig. 19), indicating that inhibition of NO production did not interfere with metabolic regulation of coronary vasomotor tone (7, 288). In swine, the small decrease in coronary venous oxygen tension that occurred after NO blockade under resting conditions was maintained during exercise (Fig. 19), indicating that the role of NO was not increased compared with resting conditions, and (similar to observations in the dog) that NO is not mandatory for the exercise-induced increase in coronary blood flow in swine (147, 393). It could be argued that NO released from erythrocytes could have contributed to exercise hyperemia in the presence of NO synthase inhibition. However, this mechanism is unlikely to be of importance in swine, in view of the lack of an exercise-induced decrease in coronary venous oxygen tension and saturation in this species.

B) PROSTANOIDS. The coronary endothelium can metabolize arachidonic acid to produce prostacyclin and other vasodilator prostanooids (121, 331) that act to increase myocardial blood flow via an increase in cAMP resulting in opening K⁺ATP channels in coronary vascular smooth muscle (331). Prostanoids have been proposed to contribute to metabolic dilation of coronary resistance vessels in humans (135, 198), although this is not a consistent finding (159, 439). Inhibition of cyclooxygenase with indomethacin in a dose that caused marked blunting of the vasodilator response to intracoronary arachidonic acid caused no change in coronary blood flow during resting conditions and did not impair the increase in coronary flow in response to treadmill exercise in dogs (121) so that the relation between myocardial oxygen consumption and coronary venous oxygen tension remained unaffected (Fig. 19).
Interestingly, several studies have suggested that an interaction exists between NO and prostanoids in the canine coronary circulation. Inhibition of cyclooxygenase shortened the duration of reactive hyperemia in dogs treated with L-NAME, but not in control dogs (459). These findings indicate an increased contribution of prostanoids when NO synthase activity is blunted, and could explain why two of three clinical studies of patients with (minimal) coronary artery disease reported a role for vasodilator prostanoids (135, 198), whereas the single study in healthy human volunteers failed to observe a role (159).

Merkus et al. (396) investigated the effects of blocking endogenous prostanoids with indomethacin in exercising swine. To study possible interactions between NO and prostanoids, experiments were repeated after NO synthase blockade with L-NAME. Indomethacin decreased coronary venous oxygen tension at rest and during exercise (Fig. 19). However, prostanoids were not mandatory for the exercise-induced vasodilation, because coronary venous oxygen tension was not further altered by exercise in the presence of indomethacin. The contribution of prostanoids to the regulation of coronary vascular tone was not enhanced by inhibition of NO synthesis in swine (396). These findings suggest that in the porcine heart, prostanoids and NO do not act in a compensatory manner when one of these pathways is blocked.

C) EDHF. Endothelium-derived relaxing factors other than prostacyclin and NO have been implicated in the endothelium-dependent vasodilation produced by acetylcholine and bradykinin. These factors have been named EDHFs, in view of their ability to hyperpolarize the vascular smooth muscle, via opening of KCa channels to produce vasodilation (463, 579). Several factors appear to participate in endothelium-derived hyperpolarization, including cytochrome P-450-dependent metabolites of arachidonic acid (463) and hydrogen peroxide (229, 495). The role of EDHF in coronary vasodilation in healthy humans or awake dogs at rest or during treadmill exercise has not been studied to date, although preliminary data in swine suggest that inhibition of cytochrome P-450 2C9 with sulfaphenazole had no effect on coronary vasomotor tone in swine (398).

D) ENDOTHELIN. Endothelins are vasoactive peptides that are produced by coronary vascular endothelium. Three isoforms have been identified, of which endothelin-1 (ET) is the most abundant and biologically active isopeptide in the heart (246). ET is produced in endothelial cells by cleavage of its nonvasoactive precursors preproendothelin and big ET (487) and acts on ET receptors located both on the endothelium and vascular smooth muscle. Binding of ET to ETB receptors on the endothelium leads to production of NO and prostacyclin (190, 560), which induce vasodilation. In contrast, binding of ET to ETA receptors on vascular smooth muscle leads to vasoconstriction (487). Administration of exogenous ET causes ETA-mediated vasodilation at low doses but ETB-mediated constriction at high doses, indicating that the ETB receptor on the endothelium is more sensitive to ET than the receptors on vascular smooth muscle (487). Endogenous levels of ET exert a coronary vasoconstrictor influence in vivo. Thus the mixed ETA/ETB receptor antagonist tezosentan caused an increase in coronary venous oxygen tension and saturation both under resting conditions and during treadmill exercise, indicating a small vasoconstrictor influence (Fig. 20). In swine, the ET-mediated vasoconstrictor influence appears to be principally ETA mediated, as the ETA receptor antagonist EMD 122946 resulted in a similar response (305). In contrast, in the coronary circulation of patients with stable angina pectoris, the nonselective ET receptor antagonist bosentan increased artery diameter, but had no effect on coronary flow, indicating that endogenous ET

![FIG. 19. Top panels show the effect of NO synthase inhibition with N-nitro-l-arginine (L-NA, 20 mg/kg iv) on the relation between myocardial oxygen consumption and coronary venous oxygen tension in the left ventricles of dogs (7; left panel) and swine (147; right panel) during treadmill exercise. Bottom panels show the effect of cyclooxygenase inhibition with indomethacin [Indo; 5 mg/kg iv (121) or 10 mg/kg iv (396)] on the relation between myocardial oxygen consumption and coronary venous oxygen tension in the left ventricles of dogs (121; left panel) and swine (396; right panel) during treadmill exercise. Data are means ± SE. *P < 0.05 vs. control. See text for further explanation.](http://physrev.physiology.org/doi/fig/10.1152/physrev.00077.2007)
does not contribute to regulation of coronary resistance vessel tone in humans (597). However, it should be noted that bosentan was administered intravenously and caused a 10% decrease in aortic blood pressure, which likely caused a decrease in myocardial oxygen demand that may have masked a direct coronary vasodilator effect. Interestingly, measurements of ET levels in blood yield concentrations in the picomolar range, while receptor sensitivities are in the nanomolar range, which is likely explained by abluminal secretion of ET (196). Consequently, plasma levels do not accurately represent actual interstitial levels of ET, although they likely reflect directional changes in interstitial levels. The finding that ET receptor antagonists cause coronary vasodilation in awake animals (212, 392, 395, 548) implies that receptor activation does occur despite the subpharmacological plasma levels.

During exercise, the effect of either ET\textsubscript{A} or mixed ET\textsubscript{A}/ET\textsubscript{B} blockade on coronary vascular tone in swine decreased progressively with incremental levels of exercise (392, 395). A similar trend was observed with tezosentan in exercised dogs (212, 548), suggesting that the vasoconstrictor influence of ET was blunted during exercise (Fig. 20). This seemingly paradoxical finding is in accord with in vitro findings that the ET-vasoconstrictor influence on coronary arterioles is modified by the cardiomyocytes according to their metabolic status so that at higher pacing rates myocytes inhibited the vasoconstrictor influence of ET (392). Merkus et al. (397) investigated possible mechanisms for the blunted ET influence during exercise and observed that following inhibition of either NO synthase or cyclooxygenase, the vasodilator response to tezosentan that was observed under resting conditions was now maintained during exercise. Furthermore, when both NO synthase and cyclooxygenase were blocked, the vasodilator effect of tezosentan actually increased with increasing exercise intensity, implying that these vasodilator systems act in concert to limit the vasoconstrictor influence exerted by endogenous ET (Fig. 21).

**E) SUMMARY AND INTEGRATION.** NO and vasodilator prostanoids contribute to the regulation of coronary blood flow in swine, while in dogs a critical role for these endothelium-derived vasodilator substances is lacking. Importantly, in none of these species do NO or vasodilator prostanoids appear mandatory for the exercise-induced increases in coronary blood flow. Conversely, in swine and in dogs, ET exerts a small coronary vasoconstrictor influence under resting conditions which wanes with increasing exercise intensities so that it is virtually absent during heavy exercise. Both NO and prostanoids act in concert during exercise to blunt the coronary vasoconstrictor influence of ET. Finally, the role of EDHF in coronary blood flow regulation has not been studied in
exercising animals or humans and awaits further clarification. In humans, a role for vasodilator prostanoids and particularly for NO is likely under resting conditions, but interpretation is hampered by the fact that most studies have been performed in patients with “minimal” coronary artery disease and hence are likely to have perturbations in endothelial function. Furthermore, in clinical studies, coronary blood flow measurements generally have not been corrected for alterations in myocardial oxygen demand, making interpretation difficult. Future clinical studies should relate coronary blood flow and coronary venous oxygen tension to myocardial oxygen consumption.

5. Metabolic messengers

The accumulation of metabolic messengers, including carbon dioxide, H⁺, and adenosine, has been proposed to contribute to coronary vasodilation in response to an increase in myocardial metabolic activity.

A) Carbon dioxide and pH. Case and colleagues (95, 96), using constant-flow perfused heart preparations to study the role of carbon dioxide in regulating coronary blood flow, observed that coronary vascular resistance correlated well with coronary venous carbon dioxide concentrations. Broten et al. (80) proposed that up to 40% of the increase in coronary blood flow produced by ventricular pacing could be explained by the synergistic interaction between myocardial oxygen and carbon dioxide tensions. The mechanism by which carbon dioxide dilates coronary arterioles is incompletely understood but could be the result of an acidosis-induced opening of KᵥATP channels (292). Despite its attractiveness as a regulator of coronary resistance vessel tone, carbon dioxide is not a likely mediator of the exercise-induced coronary vasodilation, as coronary venous carbon dioxide tension or pH remain essentially unchanged during exercise (Fig. 22), in either dogs (568, 569) or swine (149, 393).

B) Adenosine. Adenosine predominantly dilates arterioles <100 μm in diameter. Vessels of this size correspond to the site at which coronary metabolic regulation (306) and autoregulation occur (307). Adenosine has characteristics which suggest that it could be a messenger by which the coronary resistance vessels are regulated in response to changing myocardial metabolic needs (54, 168, 180). There are two pathways for adenosine production in the heart. Under normal conditions, adenosine is generated mainly via extracellular pathways: from interstitial AMP, via AMP 5’-ectonucleotidase, and from S-adenosylhomocysteine via S-adenosylhomocysteine hy-
drolase (54, 168). Under physiological conditions, the newly formed adenosine is salvaged by the cardiomyocytes for formation of AMP via adenosine kinase; these extracellular pathways of adenosine metabolism are largely independent of the metabolic state of the cardiomyocyte. However, if an increase in cardiac work causes myocardial metabolic requirements to exceed the rate of oxygen delivery, the intracellular pathway for adenosine production is activated. Thus, when the rate of ATP hydrolysis by the contractile apparatus exceeds the rate of resynthesis of ATP through oxidative phosphorylation, cytosolic free ADP increases. Adenylate kinase can then act on two molecules of ADP to form one molecule each of ATP and AMP. The resultant AMP can be catabolized by AMP 5'-nucleotidase to produce adenosine. When cytosolic adenosine concentrations increase from the normal level of 0.8 to ~2 μM, adenosine is removed from the cell via degradation by adenosine deaminase or transported out of the cell into the interstitium via nucleoside transporters where it can act on the coronary arteriolar smooth muscle to cause vasodilation (54, 168). The pathway for adenosine production and release is responsive to the metabolic state of the cell and could thus serve as a metabolic messenger to cause vasodilation of the coronary arterioles. The mechanism of coronary arteriolar dilation by adenosine is not yet fully elucidated, but may involve stimulation of A1 receptors directly coupled to K_ATP channels and A2 receptor-mediated elevation of cAMP/protein kinase A (PKA) which produces vasodilation in part via opening of K_ATP channels (537).

Data obtained in dogs do not support a role for adenosine in regulation of coronary blood flow during basal conditions. Thus, in anesthetized open-chest dogs (207, 241, 326, 494, 515) and in chronically instrumented awake dogs (28), augmenting adenosine degradation by intracoronary administration of adenosine deaminase (28, 241, 326, 494), or nonselective blockade of A1/A2 adenosine receptors with either aminophylline (207, 515) or 8-phenyltheophylline (8-PT) (28), did not cause a decrease in basal coronary blood flow or coronary venous oxygen tension (Fig. 23), although one study reported a small decrease in coronary venous oxygen tension (569). In contrast, data obtained in sedated closed-chest swine (204) and awake resting swine (149, 393) suggest that adenosine does contribute to maintenance of basal tone in this species. Thus intravenous administration of aminophylline (204) or 8-phenyltheophylline (149, 393) resulted in small increases in coronary vascular resistance and oxygen extraction, and a small decrease in coronary venous oxygen tension, indicating a slight mismatch between oxygen delivery and consumption (Fig. 23). One study in humans reported no effect of aminophylline on basal coronary blood flow (479), but other studies reported that intravenous theophylline produced small increases in coronary resistance and oxygen extraction and

**Fig. 23.** Integrated metabolic control of coronary vasomotor tone in dogs (left panels) and swine (right panels) at rest and during treadmill exercise. Shown are the effects of adenosine receptor blockade with 8-phenyltheophylline (8PT, 5 mg/kg iv; top panels), the effects of K_ATP channel blockade with glibenclamide [Glib, 50 μg/kg/min ic (153) or 3 mg/kg iv (303)] and additional adenosine receptor blockade (middle panels), and the effects of NO synthase inhibition with N-nitro-L-arginine [L-NA, 1.5 mg/kg ic (288) or 20 mg/kg iv (393)] and additional adenosine receptor blockade and K_ATP channel blockade (bottom panels) on the relation between myocardial oxygen consumption (MVO₂) and coronary venous oxygen tension (CVO₂) in the left ventricles. [Data in dogs are from Refs. 28, 153, 288. Swine data are from Merkus et al. (393).] Data are means ± SE. *P < 0.05 effect of 8PT; †P < 0.05 effect of glibenclamide; ‡P < 0.05 effect of L-NA. See text for further explanation.
decreases in coronary venous oxygen tension (157–159). In conclusion, although endogenous adenosine causes tonic vasodilation of the coronary arterioles in normal swine and possibly humans, this effect is small and does not represent a principal mechanism for maintaining coronary blood flow during basal conditions. This is also supported by observations that adenosine receptor blockade does not impair myocardial contractile performance or cause metabolic evidence of ischemia (28, 149, 616).

Measurement of plasma and tissue levels of adenosine is difficult. Measurements in blood are hampered by rapid breakdown of adenosine (238, 337), while interstitial measurements with microdialysis techniques require insertion of permeable fibers into the myocardium, thereby causing tissue damage and an acute rise in adenosine levels (577). Notwithstanding these difficulties, several studies have reported that adenosine production by the heart is augmented during increased contractile work associated with exercise (22, 166, 391, 594), which was positively correlated with coronary blood flow. Although these observations appear consistent with an exercise-induced increase in myocardial adenosine production, more recent studies have questioned the validity of the techniques to directly measure pericardial and interstitial adenosine measurements (see Ref. 180 for a critical in depth review), and several more recent studies reported that coronary venous and computed interstitial adenosine concentrations failed to increase significantly during exercise (568, 569).

Demonstration of an essential role for an exercise-associated increase in interstitial adenosine concentration in mediating the exercise-induced coronary vasodilation requires that interruption of the adenosine effect interferes with exercise-induced vasodilation. However, blockade of adenosine receptors with 8-phenyltheophylline or increasing adenosine catabolism with adenosine deaminase did not impair exercise-induced increases in coronary blood flow in dogs (28, 568), swine (149, 393), or humans (157–159) and did not change the relation between myocardial oxygen consumption and coronary venous oxygen tension (Fig. 23). These findings indicate that adenosine is not obligatory for the coronary vasodilation that occurs during exercise and could be interpreted to suggest that adenosine is either not important for control of resistance vessel tone under normal inflow conditions or that other vasodilator systems can compensate when adenosine is blocked. It has been suggested that blockade of adenosine receptors would result in increased myocardial interstitial levels of adenosine which might overcome the effects of the competitive adenosine receptor antagonists (390). However, several investigators have failed to find increased myocardial interstitial levels of adenosine following adenosine receptor blockade (569, 616).

In summary, despite the attractiveness of the adenosine hypothesis, there is no evidence to support a role for adenosine in exercise hyperemia in the normal heart of dogs, swine, or humans.

C) ATP. ATP is a potent coronary vasodilator (147, 181) that is progressively released from red blood cells during decreases in oxygen tension (165) and may thus contribute to the regulation of skeletal muscle blood flow (164). A role for ATP as an oxygen sensor, and hence a possible flow regulator, has also been proposed for the coronary circulation. Thus, during treadmill exercise in dogs, coronary venous oxygen tension decreased from 19 to 13 mmHg, and this was accompanied by an increase in coronary venous plasma ATP level from 13 to 51 nM that was linearly related to the increase of coronary blood flow (174). Intravascular ATP produces vasodilation by acting on endothelial purinergic P2Y-receptors to increase NO production (164, 165, 387). In addition, ATP can produce vasodilation after its conversion to adenosine by stimulation of adenosine A2A receptors on vascular smooth muscle cells (421). Studies examining the effects of ATP receptor antagonists on coronary blood flow regulation during exercise are lacking. However, NO synthase inhibition either alone or in combination with adenosine receptor blockade failed to blunt the exercise-induced vasodilation in dogs (288) and swine (393). These observations do not support a critical role for ATP in exercise-induced coronary vasodilation.

6. End effectors: K⁺ channels

A) K<sub>ATP</sub> CHANNELS. Vascular smooth muscle cells contain potassium channels that are sensitive to the intracellular energy charge (425, 537, 538). Opening of the K<sub>ATP</sub> channels results in an outward flux of potassium that increases the membrane potential of the sarcolemma. This hyperpolarization closes voltage-dependent calcium channels, leading to a decreased influx of calcium, thereby causing vasodilation. Conversely, closing of K<sub>ATP</sub> channels decreases smooth muscle membrane potential, thereby opening voltage-dependent calcium channels; increased calcium influx then results in vasoconstriction. The mechanism of regulation of K<sub>ATP</sub> channel activity in the normal heart is still incompletely understood. Coronary arteriolar smooth muscle K<sub>ATP</sub> channels are tonically active under conditions of normal arterial inflow despite the presence of physiological ATP concentrations (4–5 mmol), whereas in vitro studies K<sub>ATP</sub> channels are inactivated at ATP concentrations well below 1 mmol (461). Other regulators of vascular K<sub>ATP</sub> channel activity are prostacyclin, adenosine, and B<sub>2</sub>-adrenoceptors that increase K<sub>ATP</sub> channel activity via cAMP/PKA and NO that activates K<sub>ATP</sub> channels via cGMP (461). Several of these vasodilator mechanisms are operative during normal arterial inflow and can be further activated during myocardial ischemia. In addition, there is substantial evidence for modulation of K<sub>ATP</sub> channel activity by the metabolic state of the vascular
smooth cell, with an increase in ADP/ATP ratio near the sarcolemma, acidosis, and hypoxia all being potent activators of \( K_{\text{ATP}} \) channels directly (461). Thus, rather than the bulk cytosolic ATP concentration, it is likely that the ADP/ATP ratio in the subsarcolemmal microenvironment and vasodilator signaling pathways act in concert to regulate \( K_{\text{ATP}} \) channel activity and maintain coronary blood flow in the normal heart.

The influence of \( K_{\text{ATP}} \) channels on coronary blood flow has been assessed using selective inhibitors of \( K_{\text{ATP}} \) channel activity such as glibenclamide. Intracoronary glibenclamide in doses of 10–50 \( \mu \text{g/kg min}^{-1} \) caused coronary vasoconstriction with a 20–55% decrease in basal coronary blood flow in open-chest dogs (285, 496) or awake resting dogs (150, 153), resulting in reduced coronary venous oxygen tension at a given level of myocardial oxygen consumption (153) (Fig. 23). Systemic administration of glibenclamide to dogs in a dose of 1 mg/kg also resulted in a decrease in coronary venous oxygen tension (473). Similarly, in awake resting swine, glibenclamide (3 mg/kg iv) produced increases in coronary vascular resistance and decreases in coronary venous oxygen tension (145) (Fig. 23). The decrease in coronary blood flow produced by \( K_{\text{ATP}} \) channel blockade was associated with a decrease in regional systolic wall thickening (150, 153, 285). When coronary blood flow was restored to preglibenclamide levels with intracoronary nitroprusside (which by itself was devoid of any effect on systolic wall thickening), contractile performance recovered (150, 285), indicating that glibenclamide caused a primary decrease in coronary flow with a secondary decrease in contractile function. Furthermore, the decrease in coronary flow produced by intracoronary glibenclamide caused metabolic changes of ischemia, including a decrease in myocardial phosphocreatine and phosphorylation potential with an increase of inorganic phosphate and adenosine release (153, 496). This is an important observation, since it indicates that blockade of the endogenous vasodilator system associated with \( K_{\text{ATP}} \) channel activity can cause coronary vasoconstriction sufficient to result in myocardial ischemia.

In humans, a low intracoronary dose of glibenclamide (40 \( \mu \text{g/min} \)) resulted in a small decrease in resting blood flow (176) and blunted the pacing-induced increase in coronary blood flow by ~30% (175), suggesting that \( K_{\text{ATP}} \) channels contribute to coronary vasodilation during increased myocardial metabolic activity. \( K_{\text{ATP}} \) channel blockade also decreases coronary blood flow and coronary venous oxygen tension in normal dogs (150, 153, 473) and swine (145, 393) during treadmill exercise. However, the exercise-induced increase in coronary flow was unaffected so that the increase in oxygen extraction and the decrease in coronary venous oxygen tension were comparable to the changes under resting conditions (145, 150, 153, 393, 473). These findings could be interpreted to suggest either that \( K_{\text{ATP}} \) channels are unimportant for exercise-induced coronary vasodilation, or that other mechanisms compensate when \( K_{\text{ATP}} \) channels are blocked.

b) \( K_{\text{Ca}} \) Channels. \( K_{\text{Ca}} \) channels are abundantly expressed in coronary vascular smooth muscle cells (74, 210). Upon activation, these channels hyperpolarize the cell membrane, thereby closing voltage-sensitive calcium channels to produce vasodilation. The \( K_{\text{Ca}} \) channel family consists of small-, intermediate-, and large-conductance calcium channels (\( K_{\text{Ca}} \)), all with different structural components and gating properties (229). The \( K_{\text{Ca}} \) channel is the most prominent \( K_{\text{Ca}} \) channel in vascular smooth muscle so that small changes in open probability have a significant effect on the sarcolemmal membrane potential and therefore on vasomotor tone (74, 425, 490, 530). Membrane depolarization and increases in intracellular Ca\(^{2+}\) concentration are thought to be the main activators of \( K_{\text{Ca}} \) channels, thereby providing an important negative-feedback mechanism to moderate vasoconstrictor responses (74, 425). In addition, various protein kinases have been shown to modulate the activity of the \( K_{\text{Ca}} \) channels (381, 511). \( K_{\text{Ca}} \) channels are activated by phosphorylation through cGMP-dependent protein kinase (PKG; Refs. 549, 604) and PKA (406, 517), while protein kinase C (PKC) inhibits \( K_{\text{Ca}} \) channels (405, 407, 458). Many endogenous vasoactive substances exert their actions through these protein kinases, thereby modulating \( K_{\text{Ca}} \) channel activity and hence altering coronary resistance vessel tone. In general, vasodilator substances such as adenosine, EDHF, NO, norepinephrine, and H\(^+\) act through stimulation of PKA and PKG (74, 126, 381, 425), resulting in increased opening of \( K_{\text{Ca}} \) channels, while vasoconstrictor substances, such as endothelin and angiotensin II, decrease the opening of \( K_{\text{Ca}} \) channels in part via PKC activation (281, 358, 405). Hence, it is likely that many vasoactive substances act in concert to mediate the exercise-induced opening of \( K_{\text{Ca}} \) channels.

The role of \( K_{\text{Ca}} \) channels has been investigated in anesthetized dogs. The \( K_{\text{Ca}} \) channel antagonistsiberotoxin (429), charybotoxin (443), or tetraethylammonium (477) had no effect on coronary blood flow under basal conditions, which is in accord with the concept that in dogs \( K_{\text{ATP}} \) channels are the principal K\(^+\) channel involved in metabolic regulation of coronary vasomotor tone. In swine, tetraethylammonium administered intravenously in a dose that did not inhibit vasodilation by the \( K_{\text{ATP}} \) channel opener bimakalim produced a small decrease in coronary venous oxygen tension that was progressively amplified with increasing levels of exercise (Fig. 24), suggesting that \( K_{\text{Ca}} \) channels contribute to exercise-induced coronary vasodilation (399). The upstream vasodilator pathways that activate the \( K_{\text{Ca}} \) channels in swine remain to be determined, but are unlikely to involve adenosine, NO, and prostanoids, as these vasodilator substances ex-
C) $K_v$ CHANNELS. Voltage-dependent $K^+$ channels constitute a diverse family of outwardly rectifying $K^+$ channels present in the vascular smooth muscle sarcolemma (229). These channels are sensitive to membrane potential so that depolarization will induce opening of $K_v$ channels and thereby oppose vasoconstriction. In addition, these channels are sensitive to $\beta$-adrenoceptor stimulation and other cAMP-mediated vasodilator responses (2, 363). Alterations in the oxidative state of the vasculature (termed “redox signaling”) most notably superoxide and $H_2O_2$ can also modulate $K_v$ channel activity (229). Thus Rogers et al. (477) recently reported that $K_v$ channels play a role in redox signaling-mediated regulation of coronary blood flow, as the $K_v$ channel antagonist 4-aminopyridine (4-AP) blocked coronary vasodilation produced by intracoronary $H_2O_2$. Furthermore, 4-AP caused a 54 ± 10% decrease in basal blood flow, suggesting that $K_v$ channels play an important role in maintaining resting coronary blood flow. A possible role for $K_v$ channels in mediating the coronary vasodilation that occurs in response to exercise has not been studied. However, evidence for a role of $H_2O_2$ and $K_v$ channels in metabolic regulation of coronary blood flow was recently reported by Saitoh et al. (495), who showed in open-chest dogs that the decrease in coronary venous oxygen tension produced by intracoronary 4-AP increased progressively at higher levels of myocardial oxygen consumption produced by pacing or norepinephrine.

7. Summary and integration of coronary vasodilator mechanisms

Enhanced delivery of oxygen and metabolic substrate is essential for the cardiac response to an increased work load and involves a number of parallel mechanisms that contribute to coronary vasodilation. In the dog, blockade of any of these vasodilator mechanisms fails to blunt the increase in coronary blood flow in response to exercise, suggesting that adenosine, $K_{ATP}$ channel opening, prostanoids, or NO are not mandatory for exercise-induced coronary vasodilation, or that these redundant vasodilator mechanisms can compensate when one mechanism is blocked.

A compensatory role for adenosine in the regulation of coronary blood flow when $K_{ATP}$ channels are blocked was first demonstrated in dogs (153, 496) (Fig. 23). Following $K_{ATP}$ channel blockade with intracoronary glibenclamide, which produced a 20% decrease in coronary blood flow and a 50% decrease in regional wall thickening (150, 153), adenosine receptor blockade resulted in a significant further decrease in coronary flow and regional wall thickening, in particular during exercise (153). In contrast, Richmond et al. (473) found that administration of an intravenous dose of 1 mg/kg glibenclamide, which had no effect on lactate extraction, did not affect coro-
nary venous adenosine concentrations \( P = 0.11 \), either at rest or during exercise. In that study, the dose of glibenclamide may have been too low to fully block vascular \( K_{\text{ATP}} \) channels, as the authors stated that higher doses resulted in coronary flow oscillations, suggesting that larger doses did produce vasoconstriction, but this resulted in generation of an underdamped error signal that overcompensated for the constriction. The latter was shown by Samaha et al. (496) to be due to cyclic release of adenosine resulting from ATP breakdown, i.e., the presence of myocardial ischemia. In swine, the effect of simultaneous blockade of \( K_{\text{ATP}} \) channels and adenosine receptors on oxygen extraction and coronary venous oxygen tension was equal to the sum of the individual effects of 8-PT and glibenclamide (Fig. 23), indicating that loss of \( K_{\text{ATP}} \) channel activity was not compensated for by an increased adenosine-mediated vasodilator influence (393). These findings suggest that adenosine and \( K_{\text{ATP}} \) channels act in an additive fashion in swine. However, adenosine mediates its vasodilator effect on porcine coronary resistance vessels via both \( K_{\text{ATP}} \) channels (255) and \( K_{\text{Ca}} \) channels (250). It is therefore possible that following \( K_{\text{ATP}} \) channel blockade, adenosine levels increased sufficiently to maintain a vasodilator influence via \( K_{\text{Ca}} \). Alternatively, it is possible that following adenosine receptor blockade, \( K_{\text{ATP}} \) channel activity was maintained via a compensatory increase of alternate mediators such as NO and prostacyclin (294, 512).

In awake dogs, inhibition of NO synthase alone or in combination with adenosine receptor blockade did not affect the relation between oxygen consumption and coronary venous oxygen tension (288) (Fig. 23). However, combined blockade of adenosine receptors, NO synthase, and \( K_{\text{ATP}} \) channels markedly (50%) reduced coronary blood flow at rest and nearly abolished the exercise-induced coronary vasodilation (288). Those findings suggest that metabolic dilation of canine coronary resistance vessels is regulated via a myriad of vasodilator systems that act in concert to match coronary blood flow to myocardial oxygen demand so that when one system fails, back-up systems ensure an adequate oxygen supply to the myocardium. The observation that only \( K_{\text{ATP}} \) channel blockade alone decreased coronary blood flow and caused myocardial ischemia suggests that this represents a principal coronary vasodilator pathway in the dog, with adenosine and NO primarily acting as back-up systems (153, 288). In contrast, Tune et al. (567) reported that while simultaneous blockade of adenosine receptors, \( K_{\text{ATP}} \) channels, and NO synthase caused coronary vasoconstriction in awake resting dogs, the triple blockade failed to blunt the exercise-induced coronary vasodilation. Consequently, these authors concluded that these mediators act in a linear additive fashion rather than a nonlinear redundant manner (565). Interpretation of the data and comparison with previous studies in dogs (150, 153, 288) are difficult, however, due to differences in study design. One such difference is the use of a low dose of glibenclamide (1 mg/kg iv) that was selected to avoid reductions of coronary blood flow that resulted in myocardial ischemia (473, 567). However, this may have inadvertently resulted in incomplete \( K_{\text{ATP}} \) channel blockade, allowing coronary blood flow to increase during exercise.

In swine, a high dose of glibenclamide (3 mg/kg iv), which caused signs of anaerobic myocardial metabolism and impaired left ventricular function (393), failed to enhance the vasoconstrictor response to adenosine receptor blockade and NO-synthase inhibition (Fig. 23), suggesting a vasomotor control design in the porcine heart in which vasodilator pathways act in a linear additive fashion (393). Simultaneous blockade of adenosine, \( K_{\text{ATP}} \) channels, and NO caused intense coronary vasoconstriction (forcing oxygen extraction to increase to over 90%) with signs of anaerobic metabolism and impaired left ventricular function under resting conditions (393). However, in contrast to the observations by Ishibashi et al. (288) in the dog heart, the responses of coronary blood flow and oxygen supply in swine to subsequent exercise were essentially unperturbed (393). Apparently, in swine, other vasodilator mechanisms that are not recruited under resting conditions can be recruited during exercise when NO, adenosine, and \( K_{\text{ATP}} \) channels are blocked. Such candidate mechanisms include \( \beta \)-adrenergic feed-forward vasodilation, prostacyclin, EDHF, and \( H^+ \). \( \beta \)-Adrenergic vasodilation plays an important role in exercise-induced vasodilation in swine (148) and could have acted through opening of \( K_{\text{Ca}} \) channels (399).

G. Coronary Blood Flow in the Exercise-Trained Heart

Chronic endurance exercise leads to myocardial hypertrophy that can produce up to a 30% increase of relative left ventricular mass. Morphometric studies have shown that this hypertrophy includes proportionate increases of cardiac myocytes and coronary vasculature with no change in the proportion of extracellular collagen. Coronary vasodilation in response to endothelium-dependent and -independent vasodilators is normal in the physiologically hypertrophied heart so that vasodilator reserve is maintained or increased.

Physical conditioning leads to adaptations in the myocardium that are aimed at increasing maximal cardiac output and maximal total body oxygen consumption. These adaptations also affect the major determinants of myocardial oxygen demand: heart rate, contractility, and left ventricular work (integrated systolic wall stress and shortening). Dynamic exercise training lowers heart rates at rest and at any given level of submaximal exercise, and this reduction is accompanied by parallel decreases in

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myocardial oxygen consumption (107, 258, 383, 588) and coronary blood flow (40, 258, 588). Myocardial contractility is difficult to assess in vivo but appears minimally affected by physical conditioning (87, 432, 492). Left ventricular systolic pressure is not significantly altered by dynamic exercise training in normal individuals but may decrease slightly in older or hypertensive subjects (509). Left ventricular end-diastolic internal diameter and left ventricular end-diastolic wall thickness increase in parallel so that their ratio is not significantly altered (161, 382, 508, 601). Consequently, left ventricular systolic wall stress is minimally affected by exercise training. Stroke volume increases in parallel with the increased end-diastolic volume so that muscle fiber shortening is maintained. As a result, ventricular work per gram of myocardium is minimally affected by dynamic exercise training. These findings indicate that myocardial oxygen demand is decreased at rest or at a given absolute level of exercise mainly because of the decrease in heart rate.

In addition to reducing myocardial oxygen demands at rest and during submaximal exercise, physical conditioning results in coronary vascular adaptations that can increase the myocardial oxygen supply. Although there is no evidence to suggest that coronary flow rates limit oxidative metabolism in the normal heart even during maximal exercise, an increase in myocardial oxygen supply following exercise training could act to facilitate maximal cardiac performance (see sect. II B3c). The oxygen supply can be increased by raising the arterial oxygen-carrying capacity, by increasing oxygen extraction, or by increasing blood flow. The oxygen-carrying capacity of the blood is generally not significantly altered or may decrease (<10%) following exercise training (97). Myocardial oxygen extraction does increase slightly following exercise training (541, 588), but this is very modest since oxygen extraction is already near maximal even in the untrained state. Therefore, an improvement of oxygen supply must stem primarily from an increase of coronary blood flow.

An enhanced ability to increase coronary blood flow can result from adaptations within the coronary vasculature or from a decrease in the extravascular compressive forces acting on the intramural coronary microvessels (Fig. 25). Coronary vascular adaptations in response to exercise training can be divided into structural (angiogenesis and vascular remodeling) and functional adaptations (alterations in vasomotor control) (338–340). Functional adaptations can include changes in neurohumoral control mechanisms or changes in local vascular control mechanisms, i.e., metabolic, myogenic, and endothelial control of vasomotor tone. The following sections will consider each of these effects of exercise training.

1. Structural adaptations

A) CORONARY ARTERIOLES. The effect of chronic treadmill exercise training on numerical density (i.e., the number of vessels per mm²) of coronary arterioles has been studied in domestic (77) and miniature (600, 601) swine (Table 2). Numerical density of arterioles, which were defined as vessels containing at least three layers of smooth muscle and with diameters between 35 and 75 μm, was 40–60% greater in trained swine than in sedentary control animals (77, 601). White et al. (600) studied in more detail the adaptations of arterioles of varying sizes to exercise training up to 16 wk. The total cross-sectional area (μm² arterioles per mm² of myocardium) of arterioles in the range of 20–120 μm increased significantly by 16 wk of training, with a greater increase in total area in arterioles of 20–40 μm (40–60%) than in arterioles of 40–120 μm (15–30%). Interestingly, the mechanism of the cross-sectional area increase also varied depending on the diameter range of the arterioles. Thus, for 20- to 40-μm arte-

![Fig. 25. Graph summarizing the structural and functional coronary microcirculatory adaptations to chronic exercise training. ACh, acetylcholine; M, muscarinic receptor; NE, norepinephrine; α1, α1-adrenergic receptor; β2, β2-adrenergic receptor. See text for further explanation.](http://physrev.physiology.org/)}
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<td>Wyatt and Mitchell</td>
<td>Dog M, F</td>
<td>A</td>
<td>Run</td>
<td>6.4–12.8 km/h, 10%; 60 min/day, 5 days/ wk, 12 wk</td>
<td>HR_REST,</td>
<td>↓, ↑</td>
<td>EM</td>
<td>LV septum full thickness</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>Laughlin and Tomanek</td>
<td>Dog M, F</td>
<td>A</td>
<td>Run</td>
<td>10–20, 75 min/day, 5 days/ wk, 18 wk</td>
<td>SMVO₂,</td>
<td>↑, ↑</td>
<td>Perfusion fixation EM</td>
<td>LV free wall full thickness</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>Breisch et al. (77)</td>
<td>Swine M, F</td>
<td>Y</td>
<td>Run</td>
<td>70–85% of max HR (+ sprints at 80–100% of max HR), 70 min/day, 5 days/wk, 12 wk</td>
<td>V₂max,</td>
<td>↑, HR_REST</td>
<td>Perfusion fixation EM</td>
<td>LV free wall full thickness</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>White et al. (601)</td>
<td>Swine M, F</td>
<td>Y</td>
<td>Run</td>
<td>70–85% of max HR (+ sprints at 80–100% of max HR), 70 min/day, 5 days/wk, 10 wk</td>
<td>V₂max,</td>
<td>↑, SMVO₂</td>
<td>Perfusion fixation LM/EM</td>
<td>LV free wall full thickness</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Subendocardium Subepicardium</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>White et al. (600)</td>
<td>Swine M</td>
<td>Y</td>
<td>Run</td>
<td>70–80% of max HR, 70 min/day, 5 days/ wk, 16 wk</td>
<td>V₂max,</td>
<td>↑, HR_EX</td>
<td>Perfusion fixation LM/EM</td>
<td>LV free wall</td>
<td>↑</td>
<td>↔</td>
</tr>
</tbody>
</table>

M, male; F, female; Y, young; A, adult; “?” = not reported; HR_REST, resting heart rate; HR_EX, heart rate during exercise; SMVO₂, skeletal muscle oxidative capacity; V₂max, maximum total body oxygen consumption; LVW, left ventricular weight; LVW/BW, left ventricular to body weight ratio; HW, heart weight; HW/BW, heart weight-to-body weight ratio; LM, light microscopy; EM, electron microscopy; ↑ = increase; ↓ = decrease; and ↔ = no change. *An increase was noted after 3 wk of training that had disappeared after 8 and 16 wk.
rioles, the increase was principally the result of an increase in numerical density, whereas for arterioles with a diameter between 40 and 120 μm, this was due to an increase in arteriolar diameter (600).

B) CORONARY CAPILLARIES. Several investigators examined the effects of physical conditioning on the capillary-to-fiber ratio (number of capillaries per myocyte), the capillary numerical density (number of capillaries per mm²), or capillary surface density (total capillary surface area per myocardial tissue volume). Early studies in which open capillaries were identified by erythrocyte staining (452, 453) suggested an increase in capillary numerical density and exercise-induced cardiac hypertrophy in young guinea pigs following treadmill-exercise training. Similar results were obtained with hematoxylin-eosin staining in treadmill-exercise conditioned dogs (555). Capillary numerical density was found to be greater in wild than in domesticated rabbits or rats (589, 590), suggesting that greater physical activity of wild animals is associated with higher capillary density. However, it is not clear to what extent natural selection versus physical conditioning caused the increased capillary densities in the wild animals. In contrast, adult guinea pigs subjected to swimming (193) or young guinea pigs subjected to running (237) had decreased capillary numerical densities compared with sedentary controls, as the capillary-to-fiber ratio failed to increase in the face of cardiac hypertrophy.

Subsequent studies examined genetically similar rats trained by either swimming or treadmill exercise. In the rat, the response of myocardial capillary density is critically dependent on age. In young rats trained by swimming or running, exercise-induced capillary angiogenesis occurs as indicated by an increase in [3H]thymidine labeling of capillary endothelial cells (94, 572) and an increase in the capillary-to-fiber ratio (51, 60, 295, 362, 388, 558). Angiogenesis outweighed myocyte hypertrophy in most of these studies, resulting in increased capillary numerical density (13, 60, 295, 553, 558) or relative capillary surface area (388). In adult rats 3–4 mo of age, and in old rats 6–18 mo of age, exercise training was also associated with enhanced formation of capillaries (60, 295, 361, 371, 558, 572). However, in contrast to the young rats, in adult (60, 295, 558) and old rats (60, 558) angiogenesis usually did not outweigh cardiac hypertrophy, leaving capillary numerical density unchanged. Interestingly, in old rats, swimming increased the capillary-to-fiber ratio, but this occurred due to a loss of myocardial fibers (60).

Evidence that supports a positive effect of exercise training on myocardial capillary density stems mainly from studies of young male rats trained by swimming (51, 60, 94, 295, 362, 388, 558). In contrast, studies of treadmill exercise-trained rats have reported both increases (13, 271, 295, 558) as well as no change in capillary density (11, 446, 552). A methodological concern is that several of the rat studies reported histological data exclusively for the left ventricle (371, 388, 446, 558), while other studies reported data averaged for both ventricles (51, 60, 94, 295, 361, 362, 572). Anversa et al. (13) showed that a moderate treadmill exercise program increased capillary numerical density in the right but not the left ventricle. Following a more strenuous exercise program, capillary numerical density again did not change in the left ventricle (12), but actually decreased in the right ventricle (11, 14). These findings raise concern that combined analysis of tissue from both ventricles might obscure individual differences in capillarization induced by exercise training in either the left or the right ventricle.

Most studies in larger animals such as dogs (341, 612, 613) or swine (77) have also failed to observe an increased capillary-to-fiber ratio (77, 341) or capillary numerical density (77, 341, 612, 613) following treadmill exercise training for at least 10 wk (Table 2). Interestingly, significant DNA labeling via tritium-labeled thymidine incorporation in dividing capillary cells and capillary sprouting were observed at 1, 3, and 8 wk of training but were no longer apparent at 16 wk of training (Fig. 26). In addition, capillary growth outweighed myocyte growth at the 3-wk time point, but capillary densities had returned to levels observed in sedentary swine by 8 wk of training (600). These results suggest that during the training program, capillary growth does occur and may even temporarily outgrow the increase in left ventricular mass that occurs early during the training program. However, with prolonged training, capillary growth is not in excess of, but rather commensurate with, the increase in left ventricular mass.

C) SUMMARY AND INTEGRATION. Exercise training is associated with adaptations in the coronary microvasculature including increased arteriolar densities and/or diameters, which provide a morphometric basis for the observed increase in peak coronary blood flow rates in exercise trained animals (Fig. 25; see also sect. 1G4A). Most evidence that exercise training increases myocardial capillary density stems from studies of young male rats trained by swimming. In larger animals trained by treadmill exercise, the formation of new capillaries maintains capillary density at a level commensurate with the degree of myocardial hypertrophy. This does not imply a lack of effect of exercise on the formation of new capillaries, since in pathological forms of hypertrophy caused by hypertension or aortic stenosis capillary rarefaction often occurs (76, 154).

2. Adaptations of neurohumoral control

Alterations in neurohumoral control of the coronary vasculature can result from altered central autonomic activity, changes in the number or affinity of receptors, or changes in postreceptor events. Several studies reported
decreased circulating levels of catecholamines in exercise-trained humans or animals. These differences are most pronounced between comparable absolute levels of submaximal exercise before and after training, suggesting that sympathetic activity is decreased following training (59, 468, 509). Information concerning adaptations at the adrenergic receptor level is sparse and equivocal. Current evidence is controversial with reports indicating that myocardial β-adrenergic receptor density and sensitivity is unchanged (240, 480, 606), or slightly decreased (38). Similarly, α-adrenergic receptor density has been reported to be either decreased (606) or increased (177) in rat myocardium following exercise training. An explanation for these discrepant findings is not readily found. Physical conditioning increases resting parasympathetic tone to the heart, and this is thought to arise from increased vagal nerve activity rather than changes at the muscarinic receptor level, since myocardial receptor density and sensitivity appear to be slightly decreased (63, 606) or unchanged (38, 177). It should be noted that all of these studies pertain to bulk left ventricular myocardium, containing a mixture of cardiomyocytes, fibroblasts, vascular cells, and nerve endings. Studies of the effects of exercise training on adrenergic and muscarinic receptor density and sensitivity in the coronary vasculature are lacking.

A) α-ADRENERGIC CONTROL OF CORONARY RESISTANCE VESSEL TONE. Stone and co-workers (130, 235, 365) examined alterations in neurohumoral control in dogs subjected to daily treadmill exercise for 4–5 wk. With trained dogs and untrained dogs exercising at submaximal exercise levels, the nonselective α-adrenergic receptor antagonist phentolamine produced an increase in diastolic coronary blood flow. The increase in diastolic flow was significantly less in exercise-trained compared with untrained dogs. (365), suggesting that α-adrenergic vasconstrictor influence was lower in trained animals. In subsequent studies from the same laboratory, phentolamine produced significantly greater (235) or smaller (130) increases in mean coronary blood flow in partially trained dogs during submaximal exercise compared with sedentary animals. An explanation for these divergent results is not readily found, but in the latter study phentolamine produced identical increases in mean coronary flow in trained and sedentary dogs during submaximal exercise in the presence of β2-adrenoceptor blockade (130). In open-chest dogs, α1-adrenoceptor blockade caused a slightly greater increment of mean coronary blood flow in exercise-trained than in sedentary animals (339). Taken together, the studies suggest that exercise training maintains or slightly increases α-adrenergic tone in coronary resistance vessels during submaximal exercise.

The finding of maintained or increased α-adrenergic tone during exercise despite lower circulating levels of catecholamines implies increased α-adrenergic receptor responsiveness. There is evidence in both peripheral (357, 376) and coronary vascular beds (129, 235) that resistance vessels undergo greater constriction in response to α1-adrenergic stimulation after exercise training. Thus the increases in coronary blood flow in awake dogs produced by intracoronary injections of the α1-adrenergic agonist phenylephrine or the nonselective agonist norepinephrine
are enhanced following exercise training (129, 235). When dogs were exercised after left stellate ganglionectomy, the training-induced increase of \( \alpha \)-adrenergic responsiveness was abolished, indicating the importance of intact sympathetic innervation for the coronary vascular adaptations to physical conditioning (129). Maintained or slightly increased \( \alpha \)-adrenergic tone in coronary resistance vessels despite lower circulating catecholamines acts to limit “luxury perfusion” of the myocardium and to optimize capillary diffusion (see sect. II). This is supported by the observation that myocardial oxygen extraction is enhanced following exercise training (541, 588).

B) \( \beta \)-ADRENERGIC CONTROL OF CORONARY RESISTANCE VESSEL TONE. Interpretation of studies examining the effects of exercise training on \( \beta \)-adrenergic tone in coronary resistance vessels is complicated by effects of \( \beta \)-adrenergic blockade on the myocardium, which can mask the direct vascular effect of \( \beta \)-adrenergic agents. Several investigators have observed similar coronary flow reductions in response to nonselective (235, 367), \( \beta_1 \)-selective (235, 367), or \( \beta_2 \)-selective (130) adrenoceptor blockade in exercise-trained dogs during submaximal exercise compared with sedentary dogs. \( \beta_2 \)-Adrenergic receptor responsiveness of coronary resistance vessels has been reported to be enhanced following exercise training (129, 242). Thus it appears that a decrease in sympathetic neuronal input during submaximal exercise is balanced by increased responsiveness of vascular \( \beta \)-adrenergic receptors so that vascular \( \beta_2 \)-adrenergic activity is maintained.

C) PARASYMPATHETIC CONTROL OF CORONARY RESISTANCE VESSEL TONE. Although vagal tone is increased by exercise training (197, 209), there is no evidence for altered parasympathetic control of coronary resistance vessel tone after exercise training. Thus the vasoconstrictor responses of isolated porcine arterioles 110 ± 5 \( \mu \)m in diameter to acetylcholine were similar in sedentary and exercise-trained swine (350). Furthermore, muscarinic receptor blockade had no effect on coronary blood flow in exercising dogs before or after exercise training (235), indicating that exercise training did not induce a parasympathetic influence in coronary resistance vessels during submaximal exercise with heart rates of 190–210 beats/min.

D) SUMMARY AND INTEGRATION. The available data indicate that exercise training maintains or slightly increases \( \alpha \)-adrenergic coronary tone and does not alter \( \beta \)-adrenergic tone in coronary resistance vessels during submaximal exercise. Maintenance of adrenergic tone in the presence of lower circulating catecholamine levels appears to be due to increased receptor responsiveness to adrenergic stimulation. Finally, there is no evidence for altered parasympathetic control of coronary resistance vessel tone after exercise training.

3. Local coronary vascular control of resistance vessels

A) METABOLIC CONTROL. Exercise training has generally been reported to result in slightly decreased coronary blood flow rates per gram of myocardium at rest and during submaximal exercise (258, 588). However, at similar levels of cardiac work, coronary blood flow is not altered by exercise training (235, 258, 365, 541, 588), suggesting minimal effect of exercise training on the coupling between myocardial metabolism and coronary blood flow. Von Restorff et al. (588) and Stone (541) reported a slight increase in myocardial oxygen extraction in exercise-trained dogs that was not sufficient to result in a measurable decrease in coronary blood flow at any submaximal heart rate. The slightly increased myocardial oxygen extraction during treadmill exercise likely reflects improved capillary blood flow distribution (see sect. II), but may be facilitated by increased myogenic tone (see sect. II) and/or \( \alpha \)-adrenergic tone (see sect. II) in the coronary resistance vessels.

The mechanisms involved in metabolic regulation of coronary blood flow likely include metabolic mediators released by the myocardium that act on \( K^+ \) channels in the vascular smooth muscle. Although adenosine does not play an essential role in regulation of coronary blood flow under conditions of normal arterial inflow (28), exercise training was reported to increase resistance vessel sensitivity or maximal response to adenosine in dogs in vivo (129, 339, 353), and miniature swine in vivo (351), but not in swine resistance vessels in vitro (414). The reason for this difference is unclear.

Heaps et al. (252) reported that exercise training had no effect on \( K_0 \) or \( K_{Ca} \) channel function in arterioles from remote normally perfused myocardium in hearts with a chronic coronary artery occlusion. Conversely, \( K_0 \) or \( K_{Ca} \) channel activity is increased in large-conductance arteries of exercise-trained swine and may act to facilitate metabolic vasodilation (69). The effects of exercise training on arteriolar \( K \) channel function in the normal heart remain to be determined.

B) MYOGENIC CONTROL. The myogenic mechanism produces an increase in vasoconstrictor tone in response to increased stretch of the vascular smooth muscle. This response has been implicated in autoregulation and reactive hyperemia. Muller et al. (414) studied the effect of exercise training on the myogenic response of small coronary arteries of swine (75–150 \( \mu \)m in diameter) in vitro. Active changes in vessel diameter measured in response to 10-mmHg increments of distending pressure were similar in small arteries from exercise-trained and sedentary swine for intraluminal pressures below 40 mmHg. However, for pressures above 40 mmHg, the myogenic response was significantly greater in vessels from exercise-trained than sedentary swine. The enhanced myogenic tone was shown to be due to calcium-dependent PKC...
signaling in the vascular smooth muscle cells (324), which enhances voltage-gated calcium currents through L-type calcium channels in large arterioles (68). This increase in basal myogenic tone in arterioles from exercise-trained swine appears to be specific to stretch-mediated contractions. Thus neither the receptor-mediated vasoconstriction by acetylcholine and endothelin, nor the vasoconstriction in response to direct voltage-gated calcium channel activation by K+ and the L-type calcium channel agonist BAY K 8644 were altered by exercise training (350). The molecular basis for the exercise-induced alterations in intracellular calcium control in coronary arterial smooth muscle cells remains to be fully elucidated. On the basis of observations in epicardial arteries from exercise-trained animals, it could be speculated that the adaptation involves increased activity of voltage-gated and calcium-activated sarcolemmal K+ channels or adaptations at the level of the sarcoplasmic reticulum (70, 251, 340). However, in view of nonuniform effects of exercise training on coronary vascular smooth muscle throughout the coronary arterial tree, it is clear that these mechanisms that are involved in epicardial arteries await confirmation by observations in coronary arterioles.

C) ENDOTHELIAL CONTROL. Bove and Dewey (66) observed that 8 wk of exercise training enhanced the increases in myocardial blood flow produced by serotonin in closed-chest anesthetized dogs. Since coronary resistance vessel dilation by serotonin is mediated through endothelial 5-HT receptors, the findings suggest that exercise training augmented endothelium-dependent resistance vessel dilation. Similarly, Muller et al. (414) reported that exercise training augmented vasorelaxation in response to the endothelium-dependent vasodilator bradykinin in isolated coronary arterioles (64–157 μm in diameter) from swine. Indomethacin decreased the vasodilator responses in both groups but did not alter the difference between the two groups. In contrast, Nω-monomethyl-L-arginine (L-NMMA) inhibited the bradykinin-induced vasodilation to a greater extent in the exercise-trained group and eliminated the difference between the two groups, suggesting that exercise training enhances bradykinin-induced vasodilation through increased NO production (414). The observation that cytosolic copper/zinc superoxide dismutase (SOD-1) was upregulated suggests that the increased endothelium-dependent vasodilator responses were, at least in part, the result of decreased quenching of NO by superoxide (491). However, the vasodilator response to sodium nitroprusside was not different between sedentary and exercise-trained swine, suggesting that exercise training also caused an increase in NO production. In support of this, Laughlin et al. (352) demonstrated increases in endothelial NO synthase content in the coronary arterioles of exercise-trained swine.

D) SUMMARY AND INTEGRATION. The available data indicate that exercise training alters local control of coronary resistance vessels (Fig. 25). Arterioles exhibit increased myogenic tone, which appears specific for stretch-induced contractions, as vasoconstrictor responses to various other agonists are not altered. The molecular basis for the increased myogenic tone is likely the result of a calcium-dependent PKC signaling-mediated alteration in voltage-gated calcium channel activity in response to stretch. It is presently unclear whether metabolic control mechanisms, including adenosine and K+ channel activity, are altered in coronary resistance vessels following exercise training. However, exercise training augments endothelium-dependent vasodilation throughout the coronary microcirculation. This enhanced responsiveness appears to be principally the result of an increased expression of NO synthase.

4. Integrated coronary vascular adaptations

To document a beneficial effect of exercise training, it is necessary to show that the structural or functional adaptations of the different vessel segments have the potential to improve myocardial oxygen supply. Increases in maximal blood flow per gram of myocardium or capillary diffusion capacity are the two main determinants of oxygen supply in the normal heart.

A) MAXIMAL CORONARY BLOOD FLOW. There is controversy as to whether maximal coronary blood flow is increased following physical conditioning, with investigators reporting either no change (40, 67, 77, 93, 110, 364, 506, 541, 619) or an increase (48, 86, 129, 345, 366, 451, 535) in blood flow capacity. Several factors may contribute to the differing results, including differences in species, sex, and age of the experimental animals, as well as the type, intensity, and duration of the exercise-training protocol. However, the most important factor appears to be the method used to assess blood flow capacity. Thus studies in which increments in cardiac work load were used to increase blood flow have found no change (40, 67, 541) or increased blood flow capacity (366, 451). Studies in young rat hearts using hypoxia to dilate the coronary vasculature have also yielded divergent results, with increased blood flow in isolated buffer-perfused hearts from exercise-trained animals (48), but similar (619) or increased (535) flow rates in blood-perfused in situ hearts from exercise-trained rats. Laughlin et al. (344) reported an increase in peak reactive hyperemia flow following a 10-s coronary artery occlusion in exercise-trained dogs, whereas Stone (541) found no effect. Vasodilator stimuli like increased cardiac work, hypoxia, or a 10-s occlusion may not elicit maximal coronary vasodilation, nor is it certain that maximal coronary vasodilation was achieved when adenosine was infused intravenously (77, 93, 364). In contrast, when maximal vasodilation was achieved with intracoronary administration of adenosine, maximum coronary blood flow per gram of myocardium was generally increased following exercise training in swine.
of sufficient intensity.

In only two studies in which maximal coronary vasodilation was documented and systemic hemodynamic variables were controlled (110, 506), the size of the perfusion beds was not assessed, and coronary flow was expressed as milliliters per minute so that inter-animal variability might have obscured a difference in flow between the trained and sedentary dogs. Conversely, Di-Carlo (129) reported that maximal coronary flow expressed as milliliters per minute was enhanced by exercise training in dogs. The negative results obtained by Cohen (110) could have been influenced by differences between breeds (trained greyhounds versus sedentary mongrel dogs). In addition, four of the five studies that reported an increase in maximal blood flow rates documented a training effect (86, 129, 339, 351, 353), whereas in neither of the two negative studies was a training effect reported (110, 506) (Table 3). In summary, the weight of evidence suggests that physical conditioning increases maximal coronary blood flow per gram of myocardium when the exercise training program is of sufficient intensity.

B) CAPILLARY DIFFUSION CAPACITY. Capillary exchange capacity is determined by capillary permeability and total capillary surface area. Although exercise training does not increase the capillary numerical density, an increase in the permeability-surface area product (PSA) could still result from optimization of the distribution of blood flow so that all capillaries are perfused close to their exchange capacity. This would then increase the effective capillary surface area without an increase in anatomical surface area. PSA can be determined using indicator dilution techniques that incorporate a diffusible test substance and an intravascular reference substance. Laughlin and associates have shown an increase in PSA in exercise-trained dogs (339, 343, 353) and miniature swine (351). When the PSA and morphometric measurements of capillarization were examined in the same hearts, exercise was found to increase PSA with no change in capillary numerical density (353). This suggests that the increase in PSA resulted from optimization of the distribution of blood flow, thereby increasing the effective surface area. In the maximally vasodilated bed, the PSA is a function of the coronary flow rate, possibly because the latter is associated with recruitment of more capillaries and hence microvascular exchange area (353). Although a higher PSA could be due to the higher maximal flow rates in trained animals when hearts are perfused at comparable coronary artery pressures, this is unlikely because a higher PSA was also observed when exercise-trained and sedentary animals were compared at similar flow rates by lowering coronary pressure in the trained animals (349). In summary, exercise training alters the distribution of coronary vascular resistance so that more capillaries are recruited, resulting in an increase in the PSA without a change in capillary numerical density.

5. Extravascular determinants of coronary blood flow

Alterations of systemic hemodynamic variables resulting from exercise training affect not only myocardial oxygen demands but can also modulate extravascular compressive forces, which can influence coronary flow. For example, exercise training results in a lower heart rate at rest and during submaximal levels of exercise (18, 509). This relative bradycardia not only decreases myocardial oxygen demand (258) but, by reducing the time spent in systole, decreases the net impedance to blood flow produced by systolic compression of the intramural coronary vessels (151). Exercise training slightly improves indices of global left ventricular systolic and diastolic function, mainly because of altered ventricular dimensions and loading conditions (118), as intrinsic myocardial contractility is minimally affected (87, 432). Improvement of systolic and diastolic function has opposing effects on impedance of coronary blood flow and will tend to balance each other (151) with a minimal net effect on impedance to blood flow. Dynamic exercise training also increases left ventricular end-diastolic internal dimensions and wall thickness so that their ratio is not significantly altered (382, 601). Since left ventricular diastolic and systolic pressures are minimally affected by endurance exercise training in normal animals (40, 120, 601), it is likely that left ventricular diastolic and systolic wall stress are not altered by dynamic exercise training.

The available data indicate that physical conditioning decreases extravascular compressive forces at rest and at comparable absolute levels of exercise, mainly because of a decrease in heart rate.

III. CORONARY BLOOD FLOW DISTAL TO A CORONARY ARTERY OBSTRUCTION DURING EXERCISE

A. Regulation of Coronary Blood Flow Distal to a Coronary Artery Stenosis

1. Effects of a coronary stenosis on myocardial blood flow during exercise

Autoregulation is defined as the capacity to maintain constant blood flow in the face of a change in perfusion pressure (with constant metabolic needs). The vasmotor mechanisms that underlie autoregulation appear to include those involved in metabolic regulation but likely also involve the myogenic response. Normally, large epicardial “conductance” coronary arteries contribute little to total coronary resistance. However, autoregulation becomes clinically important when atherosclerosis causes narrowing of a large coronary artery that obliterates over 70% of the luminal cross-sectional area (50% diameter reduction). Such a stenosis results in a significant in-
<table>
<thead>
<tr>
<th>Investigators</th>
<th>Species, Sex</th>
<th>Age Type</th>
<th>Program</th>
<th>Efficacy</th>
<th>Cardiac Hypertrophy</th>
<th>Experimental Conditions</th>
<th>Method of Vasodilation</th>
<th>Maximal Vasodilation</th>
<th>Measured Variable</th>
<th>Maximum Blood Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buttrick et al. (86)</td>
<td>Rat M, F</td>
<td>Y Swim</td>
<td>150 min/day, 5 days/wk, 8–10 wk</td>
<td>?</td>
<td>Male: HW ↔, HW/BW 10% ↑; Female: HW 23% ↑, HW/BW 24% ↑</td>
<td>Isolated buffer-perfused heart</td>
<td>Ado-ic</td>
<td>Yes</td>
<td>CBF/g</td>
<td>↑</td>
</tr>
<tr>
<td>Laughlin et al. (351)</td>
<td>Swine F</td>
<td>A Run</td>
<td>6.4–12.8 km/h, 75 km/min/day, 5 days/wk, 16–22 wk</td>
<td>SMVO₂ ↑, HRetro ↓</td>
<td>HW ↑, HW/BW 35% ↑</td>
<td>Open-chest extracorporeal perfusion</td>
<td>Ado-ic</td>
<td>Yes</td>
<td>CBF/g</td>
<td>↑</td>
</tr>
<tr>
<td>White et al. (600)</td>
<td>Swine M, F</td>
<td>A Run</td>
<td>70–80% of max HR, 70 min/day, 5 days/wk, 16 wk</td>
<td>VO₂max ↑, HRetro ↓</td>
<td>LVW/BW 24% ↑</td>
<td>Open-chest extracorporeal perfusion</td>
<td>Ado-ic</td>
<td>Yes</td>
<td>CBF/g</td>
<td>↑</td>
</tr>
<tr>
<td>Scheel et al. (506)</td>
<td>Dog M</td>
<td>A Run</td>
<td>5.8 km/h, 25% grade; 45 min/day, 7 days/wk, 6 wk</td>
<td>?</td>
<td>LVW ↔, LVW/BW ↔</td>
<td>Isolated blood-perfused heart</td>
<td>Ado-ic</td>
<td>Yes</td>
<td>CBF</td>
<td>↔</td>
</tr>
<tr>
<td>Laughlin (339)</td>
<td>Dog M, F</td>
<td>A Run</td>
<td>9.6 km/h, 10–20%; 75 min/day, 5 days/wk, 12–20 wk</td>
<td>SMVO₂ ↑</td>
<td>HW 18% ↑, HW/BW ↔</td>
<td>Open-chest extracorporeal perfusion</td>
<td>Ado-ic</td>
<td>Yes</td>
<td>CBF/g</td>
<td>↑</td>
</tr>
<tr>
<td>Cohen (110)</td>
<td>Dog M, F</td>
<td>A Run</td>
<td>Greyhound dogs compared with mongrel dogs</td>
<td>?</td>
<td>LVW 100% ↑, LVW/BW 75% ↑</td>
<td>Awake</td>
<td>Ado-ic</td>
<td>Yes</td>
<td>CBF/g</td>
<td>↔</td>
</tr>
<tr>
<td>Laughlin and Tomanek</td>
<td>Dog M, F</td>
<td>A Run</td>
<td>9.6 km/h, 10–20%; 75 min/day, 5 days/wk, 12–20 wk</td>
<td>SMVO₂ ↑</td>
<td>HW ↔, HW/BW ↔</td>
<td>Open-chest extracorporeal perfusion</td>
<td>Ado-ic</td>
<td>Yes</td>
<td>CBF/g</td>
<td>↑</td>
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<tr>
<td>DiCarlo et al. (129)</td>
<td>Dog M, F</td>
<td>A Run</td>
<td>6.4–9.6 km/h, 20%; 5 days/wk, 4–5 wk</td>
<td>?</td>
<td>No*</td>
<td>Awake</td>
<td>Ado-ic</td>
<td>Yes</td>
<td>CBF</td>
<td>↑</td>
</tr>
</tbody>
</table>

HR, heart rate; Ado, adenosine; ic, intracoronary; CBF/g, mean coronary blood flow normalized per gram of myocardium; ?, not reported.*Not reported in that study but based on previous observations from the same laboratory (Stone, 1980; Liang et al., 1984).
crease in proximal resistance and causes a decrease in distal coronary perfusion pressure. In this situation, autoregulation can preserve basal coronary blood flow, but maximum coronary blood flow (as commonly measured using intracoronary administration of adenosine) is reduced (Fig. 27). Consequently, coronary flow reserve (the ratio of maximum to basal coronary flow) is attenuated. When a stenosis becomes sufficiently severe to reduce the poststenotic pressure below 40 mmHg during resting conditions, endogenous vasodilator reserve becomes exhausted and basal flow decreases, resulting in myocardial hypoperfusion (29, 92, 138).

Autoregulatory reserve is not homogeneously distributed across the left ventricular wall. Thus Ball and Bache (36) showed that when dogs were exercised on a treadmill, progressive obstruction of a coronary artery with a hydraulic occluder resulted in a decrease in flow first in the subendocardial myocardium while flow to the subepicardial layers was reduced only when more severe levels of stenosis were applied (Fig. 28). This preferential decrease in subendocardial flow is the result of higher extravascular compressive forces in the subendocardium (274, 599), causing the lower limb of the autoregulation curve to be shifted to the right compared with that in the subepicardial layers (Fig. 27). This also explains the observation that intracoronary infusions of adenosine or dipyridamole (which have no effect on systemic hemodynamics), in the presence of a critical stenosis that has exhausted subendocardial flow reserve can result in “coronary epicardial steal” (29, 138). In this situation, adenosine will increase blood flow in subepicardium, but the resulting increase in coronary arterial inflow will increase the pressure gradient across the stenosis, thereby decreasing poststenotic perfusion pressure and hence subendocardial blood flow (point c to c’ in Fig. 27, top). When myocardial oxygen consumption increases during exercise, the autoregulatory plateau will be shifted upward, transposing the break point to the right (Fig. 27, bottom). During exercise, the increase in heart rate, which results in an increase in average myocardial tissue pressure (as relatively more time is spent in systole) shifts the pressure-flow relation to the right, particularly in the subendocardial layers. This explains why a subcritical coronary stenosis (that has no effect on resting coronary blood flow) can result in selective subendocardial hypoperfusion during exercise (point b to b* in bottom panel of Fig. 27).

2. Coronary vasomotor tone regulation distal to a stenosis: importance of functional anatomy of the coronary microcirculation

Ischemia has generally been assumed to cause maximal vasodilatation of the coronary microvasculature and to render these vessels unresponsive to vasoconstrictor

![Fig. 27. Coronary pressure-flow relation in the subepicardial (Epi) and subendocardial (Endo) layers during autoregulation (auto) or during maximal coronary vasodilation with adenosine (max), at rest (top panel) and during exercise (bottom panel). Top panel shows myocardial blood flow under conditions of normal arterial inflow (a and a’), modest stenosis (b and b’), and severe stenosis (c and c’). Note that with increasing stenosis severity coronary perfusion distal to the stenosis decreases, thereby reducing the maximal achievable myocardial blood flow. In the case of the severe stenosis, infusion of adenosine will result in an increase in subepicardial flow that increases the pressure drop across the stenosis, thereby further decreasing poststenotic coronary pressure, thereby causing a decrease in subendocardial blood flow. Bottom panel shows myocardial blood flow under conditions of normal arterial inflow (a and a’) and modest stenosis (b and b’). Note that exercise causes an upward shift of the autoregulatory plateau. During exercise in the presence of a stenosis, the rightward shift of particularly the subendocardial pressure-maximal flow relation causes subendocardial flow to decrease while subepicardial blood flow shows a normal increase. See text for further explanation.](http://physrev.physiology.org/)
stimuli. However, even during ischemia, the coronary resistance vessels retain some degree of vasomotor tone and can respond to vasoconstrictor stimuli. This finding has required reassessment of the location and function of the principal sites for resistance to blood flow in the coronary circulation. The coronary arterial vasculature has traditionally been divided into two discrete segments: arteries that offer little resistance to blood flow and do not participate in regulation of perfusion, and microvessels, which represent the major locus of resistance to flow. The resistance vessels have generally been treated as a homogeneous array of vessels, which act principally in response to local myocardial needs, but can also respond weakly to systemic vasomotor influences. The development of methods to directly visualize the coronary microvessels has demonstrated that this concept of a functionally homogeneous coronary microvascular circulation is an oversimplification (Figs. 29 and 30). Direct measurements of microvascular pressures in beating hearts have demonstrated that during basal conditions, up to 40% of total coronary resistance resides in small arteries between 100 and 400 μm in diameter, and that during vasodilation these vessels contribute an even greater fraction of total coronary resistance (105, 380, 556). The importance of this finding is that although these small arteries contribute a substantial fraction of total coronary resistance and are capable of active vasomotion, they do not appear to be under local metabolic control. The finding that a substantial fraction of resistance resides at the level of the small arteries may in part explain the finding that myocardial ischemia does not predictably cause maximal vasodilation of the coronary resistance vessels. Persistence of vasomotor tone in the coronary resistance vessels during myocardial ischemia can be ascribed (at least in part) to vasoconstrictor tone in these small arteries, which are not under metabolic control. In addition, there is evidence that even in coronary arterioles which are under metabolic control (<100 micron in diameter), vasoconstrictor influences can compete with metabolic vasodilator activity (103, 380, 556).

A) LARGE EPICARDIAL ARTERIES. In the normal heart, the large arteries (>400 μm in diameter) are truly conduit vessels that contribute <5% of total coronary resistance (101, 105). When atherosclerosis or vasospasm decreases coronary artery cross-sectional area by >70%, a substantial fraction of total resistance can reside in these large vessels, resulting in a pressure drop across the stenotic segment. In this situation, studies of the regulation of vasomotor tone of the coronary bed distal to a stenosis must take into account alterations in stenosis severity and changes in the pressure drop across the stenosis that result from changes in flow. For example, pharmacological agents that dilate large arteries can decrease the severity of a compliant stenosis, thereby improving blood flow. To eliminate effects of changes in stenosis severity, some investigators have employed experimental models in which a stenosis maintains a constant limited rate of arterial inflow. With a constant flow model, vasodilation of the resistance vessels causes a decrease in coronary perfusion pressure as the stenosis prevents flow from increasing in response to distal vasodilation. Since arterial inflow is constant, coronary pressure distal to the stenosis should reflect changes in vasomotor tone of the resistance vessels. A problem with the constant flow model is that at the low perfusion pressures distal to a coronary stenosis, blood flow is influenced not only by active vasomotion of the resistance vessels, but also by interaction between the intravascular distending pressure and the extravascular forces which act to collapse the thin-walled microvessels. If distal coronary pressure falls as the result of microvascular vasodilation while extravascular forces remain constant, then the extravascular forces will exert an increasing influence on blood flow. The influence of extravascular forces becomes progressively more important as distal coronary pressure decreases and is greater in diseased hearts in which left ventricular diastolic pressure is elevated or the rate of relaxation slowed. Because extravascular forces are highest in the subendocardium, a decrease in coronary pressure distal to a stenosis can cause passive redistribution of blood flow away from the subendocardium. The term passive redistribution is used since the redistribution of flow away from the subendocardium with decreasing perfusion pressure can occur independently of active vaso-
motion. To avoid passive alterations in flow secondary to changes in the interaction between extravascular forces and intravascular perfusion pressure (especially at the low coronary pressures distal to a flow-limiting stenosis), experimental models have been used in which a stenosis maintains a constant distal coronary pressure so that only changes in vasomotor tone of the microvasculature result in changes in blood flow (25, 33, 92, 137, 140, 141, 144, 287, 289, 354–356, 529).

B) CORONARY COLLATERAL VESSELS. Collateral vessels that are sufficiently developed to provide an alternate parallel blood supply can complicate interpretation of measurements of blood flow in a myocardial region perfused by a stenotic coronary artery. Thus vasomotion of coronary collaterals can alter both the inflow of arterial blood and the poststenotic perfusion pressure in the terminal vascular bed (192, 317). However, if distal coronary pressure is maintained constant, changes in myocardial tissue blood flow reflect changes at the level of the intramural resistance vessels, irrespective of the source of blood flow (i.e., antegrade or via collateral vessels).

C) SMALL ARTERIES. Active vasomotor tone in arterial segments that are not under metabolic control but which contribute substantially to total coronary resistance have the potential to alter myocardial blood flow. Chilian and co-workers (101, 105) showed that under normal conditions up to 25% of total coronary resistance can reside in arterial vessels larger than 170 μm in diameter, with as much as 40% in vessels larger than 100 μm. Metabolic vasodilation and autoregulation occur predominantly in arterioles smaller than 100 μm; under conditions of unimpeded coronary inflow, vasoconstriction of the small arteries can be compensated for by vasodilation of the arterioles (104, 299, 300). However, when hypoperfusion has already caused metabolic vasodilation of the arterioles, the ability to compensate for vasoconstriction of the small arteries is lost. Furthermore, in the presence of intense arteriolar vasodilation, an even greater fraction of total coronary resistance resides in the arteries; in this situation, vasoconstriction of small arteries can aggravate hypoperfusion.

D) INTRAMURAL PENETRATING ARTERIES. The penetrating arteries represent a special group of small arteries that traverse the left ventricular wall to deliver blood from the epicardial arteries to the subendocardial microvasculature. The penetrating arteries range from 100 to 500 μm in diameter, with most around 200 μm (64, 169). At an aortic pressure of 100 mmHg, pressure in coronary arterioles 100 μm in diameter was 80 mmHg in the subepicardium but only 60 mmHg in the subendocardium, indicating that a substantial pressure drop occurs across the penetrating arteries (99). In the presence of a coronary stenosis, which has caused the arterioles smaller than 100 μm to undergo metabolic vasodilation, the penetrating arteries can pose an important additional source of resistance to subendocardial perfusion. In this situation, variations in tone in these vessels could directly alter blood flow to the subendocardium.

E) ARTERIOLES. In the normal heart, a major fraction of coronary resistance resides in arterial segments <100 μm in diameter (arterioles). These arterioles are responsive to changing myocardial metabolic needs and are the site for metabolic vasodilation (306), autoregulation (307), and ischemic vasodilation (103, 307). Although the arterioles are the site of metabolic vasoregulation, there is evidence that vasoconstrictor tone can persist in these vessels even in the presence of myocardial ischemia (103).

3. Mediators of coronary vasodilation distal to a stenosis

A) ADENOSINE. In contrast to the normal heart where adenosine does not participate in regulation of coronary flow under physiological conditions, adenosine does contribute to coronary vasodilation when there is an insufficient supply of oxygen. During ischemia or hypoxia, ATP
breakdown leads to increased adenosine production and release from cardiac myocytes and possibly endothelial cells (39, 180, 510, 534). In this situation, adenosine does exert a significant vasodilator effect, since the increase in coronary flow in response to systemic or local myocardial hypoxia is attenuated following intracoronary administration of adenosine deaminase (205, 359, 400, 401, 595). Similarly, adenosine plays a role in ischemic coronary vasodilation. Thus intracoronary adenosine deaminase (28, 494), or adenosine receptor blockade with intravenous 8-phenyltheophylline (28) or aminophylline (204, 207, 515), caused a decrease in the total volume of excess flow during reactive hyperemia following a brief total coronary artery occlusion in open-chest and awake dogs.

Laxson et al. (356) studied the contribution of adenosine to the resistance vessel dilation that occurs when a coronary artery stenosis results in myocardial hypoperfusion during exercise. During treadmill exercise in dogs, a hydraulic occluder around the proximal left circumflex coronary artery was partially inflated to produce a constant distal coronary pressure of 40 – 42 mmHg. Mean blood flow in the region perfused by the stenotic coronary artery was decreased to 1.25 ± 0.20 compared with 2.63 ± 0.25 ml·min⁻¹·g myocardium⁻¹ in the normally perfused control region. Hypoperfusion was most severe in the subendocardium with a subendocardial/subepicardial (endo/epi) flow ratio of 0.37 ± 0.07 versus 1.21 ± 0.06 in the control region. To determine whether adenosine contributed to vasodilation of the resistance vessels in the ischemic region, exercise was repeated during blockade of adenosine receptors with 8-phenyltheophylline combined with intracoronary adenosine deaminase to augment adenosine catabolism (390). While the stenosis maintained distal coronary pressure constant at 41 ± 1 mmHg, adenosine blockade caused a further decrease in mean blood flow in the region perfused by the stenotic coronary artery to 0.92 ± 0.13 ml·min⁻¹·g⁻¹ (Fig. 31). Although there is evidence that adenosine production is positively correlated with the degree of hypoperfusion (128), the effect of adenosine was not greater in the subendocardium even though hypoperfusion was most severe in that region. The decrease in flow produced by adenosine blockade was associated with further deterioration of

FIG. 30. Schematic overview of various vasodilator (yellow text boxes) and vasoconstrictor (blue text boxes) influences in different (micro)vascular segments (epicardial artery, small intramural arteries class A and B, and arterioles) of the coronary arterial bed of the LV wall. TxA2, thromboxane A2 (receptor); 5HT, serotonin or 5-hydroxytryptamine (receptor); B2, bradykinin receptor subtype 2; ANG II, angiotensin II; ET, endothelin; β1 and β2, β1- and β2-adrenergic receptor; α1 and α2, α1- and α2-adrenergic receptors; NO, nitric oxide; PGI2, prostacyclin (receptor); EDHF, endothelium-derived hyperpolarizing factor; KATP, ATP-sensitive K⁺ channel; KCa, calcium-sensitive K⁺ channel; KV, voltage-sensitive K⁺ channel.

FIG. 31. Effect of adenosine receptor blockade with 8-phenyltheophylline (8PT, 5 mg/kg iv) and increased adenosine catabolism with adenosine deaminase (ADA; top panel) and effect of NO synthase inhibition with L-nitro-L-arginine (L-NA, 20 mg/kg iv; bottom panel) on blood flow distal to a coronary artery stenosis. Epi, outer mid; OM, outer mid; IM, inner mid; Endo, subendocardium. Data are means ± SE. * P < 0.05 vs. corresponding control. See text for further explanation. [Data from Laxson et al. (356) and Duncker and Bache (137).]
systolic segment shortening in the hypoperfused region, indicating worsening of ischemia (356). These findings indicate that adenosine does contribute to vasodilation of the coronary resistance vessels when exercise in the presence of a flow-limiting stenosis results in myocardial ischemia.

In summary, adenosine does not play a role in metabolic regulation of myocardial blood flow in the normal heart during physiological conditions. However, adenosine does contribute to coronary vasodilation under conditions of hypoxia or impaired arterial inflow, principally at the level of the arterioles <100 μm in diameter (300, 306).

B) NO. NO production increases during hypoxia, suggesting that NO-dependent vasodilator mechanisms could have increased importance during ischemia (81, 447, 455). In accordance with this concept, Smith and Canty (529) observed that inhibition of NO synthesis with L-NAME had no effect on coronary flow at normal coronary pressures, but when coronary artery pressure was reduced below the autoregulatory range, coronary flow rates were lower after L-NAME than during control conditions. As a result, the lower limb of coronary pressure-flow relation during autoregulation was shifted toward higher coronary pressures after blockade of NO synthesis. We assessed the contribution of NO to the vasodilation of coronary resistance vessels that occurs during exercise in the presence of a flow-limiting coronary stenosis (Fig. 31). Dogs underwent moderate treadmill exercise while partial inflation of a hydraulic occluder created a stenosis that maintained distal coronary pressure at 55 ± 2 mmHg (137). Inhibition of NO production with L-NA did not decrease coronary flow at rest or during exercise in the normally perfused control region (137). However, in the region perfused by the stenotic coronary artery, inhibition of NO synthesis decreased mean coronary blood flow from 1.09 ± 0.13 to 0.68 ± 0.11 ml·min⁻¹·g⁻¹ (P < 0.05). This reduction of blood flow (137, 529) could have resulted from vasoconstriction either in the small coronary arteries that are not under metabolic control (>100 μm in diameter) or in arterioles that are under metabolic control (<100 μm). Studies of isolated microvessels have demonstrated that basal release of NO does occur in canine coronary arterioles (40–80 μm) but only in the presence of flow (328, 418). In the in vivo heart, basal NO release occurs in both arterioles (<100 μm) and in resistance arteries (>100 μm) (298, 299, 323), and vessels of both size dilate in response to acetylcholine (323). The observation by Jones et al. (299) that in the normal heart inhibition of NO production resulted in vasoconstriction of small arteries but (compensatory) vasodilation of the arterioles suggests that constriction of the small arteries was principally responsible for aggravation of hypoperfusion distal to a coronary artery stenosis. Thus, in the normal heart, vasoconstriction resulting from inhibition of NO production is compensated for by metabolic vasodilator factors acting at the arteriolar level. However, when a coronary stenosis has already caused metabolic vasodilation of the arterioles, the ability to compensate for inhibition of NO production is lost. In this situation, NO inhibition can aggravate hypoperfusion by causing constriction of the resistance arteries.

It is unclear whether constriction of the resistance vessels produced by inhibition of NO synthesis in hypoperfused myocardium is the result of unmasking of normal levels of NO release when other vasodilator mechanisms have been exhausted, or whether it is due to an actual increase of NO production in response to myocardial hypoperfusion. Impaired tissue oxygenation has been proposed to result in increased NO release from the endothelium (455) or erythrocytes (527, 536). Oxygen tensions are lower in the walls of arterioles and even small arteries than in the central aorta (136), suggesting that conditions exist that could allow the vascular wall to serve as a tissue oxygen sensor (454). Alternatively, decreases in oxygen tension can stimulate the release of NO from red blood cells (527, 536). There is evidence that the vasoconstrictor response to α₁- and postjunctional α₂-adrenoceptor stimulation is augmented in hypoperfused myocardium distal to a coronary artery stenosis during exercise (355, 518). Since endothelial α₂-adrenoceptors can stimulate NO production, sympathetic nervous system activation during exercise could potentially augment NO production distal to a flow-limiting stenosis. In this situation, inhibition of NO production would aggravate hypoperfusion by leaving α₁- and α₂-adrenergic coronary vasoconstriction unopposed. This is supported by the finding that coronary microvessel constriction in response to norepinephrine is enhanced following the administration of L-NA (298) and that after inhibition of NO synthesis exercise in the presence of a coronary stenosis unmasked an α₂-mediated vasoconstrictor response (287).

NO-dependent vasodilator responses are impaired in patients with atherosclerosis, hyperlipidemia (187), or hypertension (368, 442). The experimental evidence demonstrating that inhibition of NO production can aggravate myocardial hypoperfusion distal to a coronary artery stenosis supports the clinical observation that endothelial dysfunction of the coronary resistance vessels can render patients more vulnerable to hypoperfusion in myocardial regions perfused by a stenotic coronary artery (497, 622).

C) PROSTAGLANDINS. In early studies, inhibitors of cyclooxygenase were reported to depress coronary reactive hyperemia and hypoxic coronary vasodilation (1, 3). However, these results were likely influenced by experimental preparations in which acute surgical trauma had caused activation of the prostaglandin system (437), since subsequent studies in intact animals have generally found little effect of these agents (269, 437). In anesthetized swine in which an intraluminal hollow plug was used to produce
an 80% reduction in coronary artery cross-sectional area, cyclooxygenase blockade with indomethacin did not alter coronary blood flow (428), suggesting that vasodilator prostaglandins do not contribute to resistance vessel dilation distal to a flow-limiting coronary stenosis. Conversely, in patients with coronary artery disease, inhibition of cyclooxygenase resulted in coronary vasoconstriction (135, 198), suggesting that vasodilator prostaglandins assume greater importance in regulation of coronary vasomotor control in chronic ischemia. However, in those studies, it cannot be excluded that vasoconstriction occurred not only in the distal microvasculature but also in proximal stenotic segments.

D) K<sub>ATP</sub> CHANNELS. Opening of K<sub>ATP</sub> channels contributes to coronary vasodilation during reactive hyperemia (21, 150, 153) and hypoxia (124). Studies in which coronary microvessels were directly visualized using intravital microscopy in open-chest dogs demonstrated that K<sub>ATP</sub> channels become progressively more activated as coronary artery pressure is decreased. Thus Komaru et al. (322) observed that superfusion of the subepicardial vasculature with the K<sub>ATP</sub> blocker glibenclamide had no effect on arteriolar diameter (<100 μm) at coronary artery pressures of 90–100 mmHg, but abolished the arteriolar dilation that occurred in response to progressive reductions of coronary pressure. In contrast, small coronary artery (>100 μm) diameter decreased as perfusion pressure (distending pressure) was decreased, and this was not modified by glibenclamide. These findings indicate that K<sub>ATP</sub> channels in arterioles are important mediators of the vasodilator response that accounts for coronary autoregulation. In extracorporeally perfused dog hearts, intracoronary glibenclamide (10 μg·kg<sup>-1</sup>·min<sup>-1</sup>) had no effect on coronary flow when perfusion pressures were equal to or greater than aortic pressure (>100 mmHg), but caused a decrease in flow when pressures were below 80 mmHg (422). We studied coronary flow responses over a range of perfusion pressures produced by progressively inflating a hydraulic occluder in dogs running on a treadmill (heart rates ~200 beats/min) (152). K<sub>ATP</sub> channel blockade with glibenclamide produced similar decreases in blood flow both at perfusion pressures below the autoregulatory range and at normal pressures, so that the absolute decrease in flow was similar at all coronary artery pressures, but the relative flow reduction became progressively greater as coronary pressure decreased (152). Furthermore, the selective K<sub>ATP</sub> channel opener pinacidil increased coronary blood flow at normal perfusion pressures but not at pressures below the autoregulatory range (152), indicating that K<sub>ATP</sub> channels became progressively activated as coronary pressures decreased, so that most of the channels were open when perfusion pressures reached the lower limit of autoregulation. Thus the available evidence indicates that K<sub>ATP</sub> channels located in coronary arterioles (<100 μm) contribute importantly to coronary metabolic vasodilation and autoregulation.

E) K<sub>Ca</sub> CHANNELS. A possible role for K<sub>Ca</sub> channel activity in regulation of coronary vasomotor tone distal to a coronary artery stenosis during exercise has not been investigated to date. However, in extracorporeally perfused hearts of open-chest dogs, the K<sub>Ca</sub> channel antagonist charybdotoxin had no effect on coronary flow during normal arterial inflow conditions, but caused a decrease of coronary flow during myocardial hypoperfusion at a constant coronary artery perfusion pressure of 42 ± 2 mmHg (429). It cannot be determined from that study whether the constriction of resistance vessels produced by K<sub>Ca</sub> channel blockade was the result of unmasking of normal K<sub>Ca</sub> channel activity because other vasodilator mechanisms had been exhausted in the hypoperfused region, or whether it was due to an actual increase in K<sub>Ca</sub> channel activity in response to myocardial hypoperfusion.

F) SUMMARY AND INTEGRATION. The increased delivery of oxygen and metabolic substrate which is essential for the cardiac response to an increased work load involves a number of parallel mechanisms that produce coronary vasodilation. In the dog, blockade of any one of these vasodilator mechanisms fails to blunt the increase in coronary blood flow in response to exercise in the normal heart, suggesting that adenosine, K<sub>ATP</sub> channel opening, prostacyclin, or NO either do not contribute to exercise-induced coronary vasodilation or that redundancy of these vasodilator mechanisms allows compensation when one mechanism is blocked. In contrast, when exercise in the presence of a coronary artery stenosis has caused all vasodilator mechanisms to become activated, blockade of any of these vasodilator mechanisms aggravates myocardial hypoperfusion.

4. Is coronary vasodilation maximal in ischemic myocardium?

Systolic wall stress and hence oxygen demands are highest in the subendocardial layers of the left ventricular wall. The need for greater blood flow in the subendocardium requires a transmural gradient of vasomotor tone, with vascular resistance being lower in the inner than in the outer left ventricular wall. Since extravascular compressive forces are greatest in the subendocardium, vasodilator reserve is exhausted first in the subendocardium when perfusion pressure falls (186, 273). As a result, vasodilator reserve can still exist in the subepicardial layers of the left ventricle at a time when reduced blood flow indicates loss of vasodilator reserve in the subendocardium (203, 206). Myocardial ischemia has traditionally been viewed to produce maximal vasodilation of the coronary resistance vessels and to override any competing vasoconstrictor influences. However, a number of investigators have demonstrated that subendocardial vasodila-
Coronary blood flow can exist distal to a coronary artery stenosis that results in subendocardial hypoperfusion (19, 91, 213, 218, 441). Thus, with coronary artery pressure distal to a stenosis maintained at a fixed level, intracoronary infusion of adenosine increased subendocardial blood flow by >50%, sometimes with an improvement in myocardial contractile performance (441). The presence of vasodilator reserve in ischemic myocardial regions may have been the result of increased sympathetic drive in anesthetized open-chest animals, since a study in closed-chest sedated dogs failed to observe recruitable vasodilator reserve in ischemic myocardium (92). During treadmill exercise when sympathetic activity is high, intravenous infusion of the L-type Ca$^{2+}$ channel antagonist nifedipine increased blood flow and contractile performance of ischemic myocardium perfused by a stenotic coronary artery or by collateral vessels (265). Laxson et al. (354) exercised dogs on a treadmill while a stenosis was produced with a hydraulic occluder. While distal coronary artery pressure was maintained constant at 43 ± 2 mmHg, an intracoronary infusion of adenosine increased subendocardial blood flow by 50% (Fig. 32) and improved regional systolic segment shortening. In contrast to other studies in which vasodilator reserve was found in only the subepicardium (186, 203, 206, 273), vasodilator reserve was present in both the subendocardium and the subepicardium (354). It is important to note that in this study coronary artery pressure distal to the coronary stenosis was maintained constant to prevent passive redistribution of flow due to changes in poststenotic pressure, whereas distal coronary perfusion pressure was not controlled in the earlier studies (186, 203, 206, 273). These findings demonstrate that vasodilator reserve can exist in coronary resistance vessels within hypoperfused myocardium. In vivo studies directly observing subepicardial microvessels in open-chest dogs, coronary arterioles (<100 μm in diameter) dilated in response to progressive decreases in perfusion pressure while small arteries >100 μm showed either no change (103) or a decrease (307) in vessel diameter. At a coronary pressure of 40 mmHg, which produced a significant decrease in blood flow to the subepicardium, local intra-arterial infusion of adenosine caused dilation of the arterioles but not of the small arteries (103). These findings support the concept that vasodilator reserve can persist in coronary arterioles within acutely ischemic myocardium.

Whereas adenosine is a potent vasodilator of coronary arterioles <100 μm in diameter (103, 140, 306), it is a weak dilator of arterial vessels >100 μm in diameter (103, 306). In contrast, nitrovasodilators are known to preferentially dilate arteries >100 μm in diameter (520, 607). To assess vasodilator reserve at the level of the small coronary arteries within acutely ischemic myocardium, we investigated the effects of intravenous nitroglycerin, isosorbide dinitrate, and the NO donors ITF 296 and ITF 1129 on blood flow distal to a coronary artery stenosis during treadmill exercise in dogs (144, 289). During normal arterial inflow, these agents had no effect on coronary blood flow either at rest or during exercise, which can be explained by the small artery dilation being countered by an autoregulatory increase in arteriolar tone to maintain blood flow commensurate with the needs of the myocardium (103, 300). In contrast, in the presence of a coronary artery stenosis that maintained distal perfusion pressure constant, the nitrovasodilators (Fig. 32) increased blood flow to the hypoperfused region, an effect that was most pronounced in the deeper myocardial layers. Improvement in blood flow to hypoperfused regions by nitrovasodilators could involve several mechanisms. First, in patients with an eccentric atherosclerotic narrowing of a coronary artery, nitrovasodilators can dilate the artery at the site of the stenosis (199, 466). However, in our experimental model, this effect was prevented by using an occluder that maintained a constant distal coronary perfusion. Second, nitrates cause venodilation, which can lower left ventricular diastolic pressure, thereby reducing extravascular forces that compress the intramyocardial vasculature. However, even nitrate doses that had no effect on left ventricular end-diastolic pressure or dimensions enhanced myocardial perfusion distal to the stenosis, indicating that a decrease of extravascular compressive forces could not account for the improved perfusion (144, 287). In the normal dog heart, intravascular pressure in coronary arterioles is substantially lower in the subendocardium than in the subepicardium (99), indicating that a significant pressure drop occurs across the penetrating arteries (diameter ~200 μm) which traverse the left ven-

![Fig. 32. Effect of adenosine (50 μg·kg$^{-1}$·min$^{-1}$ iv) (A) and the nitrovasodilator ITF 296 (2 μg·kg$^{-1}$·min$^{-1}$ iv) (B) on blood flow distal to a coronary artery stenosis. Epi, subepicardium; OM, outer mid; IM, inner mid; Endo, subendocardium. Data are means ± SE. Note that while adenosine produces similar increases in flow to all myocardial layers, ITF increases flow selectively to the subendocardial layers. *P < 0.05 vs. corresponding control. See text for further explanation. [Data from Laxson et al. (354) and Duncker et al. (144).]
tricular wall to deliver blood to the subendocardium. Since nitrovasodilators are known to dilate vessels larger than 100 μm in diameter (520, 607), vasodilation of the penetrating arteries by nitrovasodilators would preferentially enhance flow to the innermost myocardial layers. In the presence of a flow-limiting stenosis, the arterioles <100 μm have already undergone metabolic vasodilation so that a disproportionate fraction of resistance resides in the small arteries >100 μm, which includes the penetrating arteries. In this situation, dilation of the penetrating arteries by nitrovasodilators could increase blood flow to the inner layers of the left ventricle. Although the small arteries that supply the subepicardial microvasculature will also be dilated by nitrovasodilators, these arteries travel a much shorter distance (64, 169). Hence, their contribution to subepicardial resistance is less than the contribution of the penetrating arteries to subendocardial resistance.

In summary, myocardial ischemia that occurs during exercise in the presence of a flow-limiting coronary artery stenosis does not cause maximal vasodilation of the coronary resistance vessels so that substantial vasodilator reserve exists in the terminal vascular bed of the hypoperfused region. This reserve can be recruited with both small artery dilators (e.g., nitrovasodilators) and arteriolar dilators (e.g., adenosine), indicating persistent vaso- motor tone throughout the coronary microcirculation.

5. Mediators of persistent vasoconstrictor tone in ischemic myocardium

A) α-ADRENERGIC CONTROL. α-Adrenergic vasoconstriction not only opposes metabolic coronary vasodilation during exercise in the normal heart, but also limits coronary vasodilation in regions of ischemic myocardium. Thus, when a coronary artery stenosis resulted in subendocardial underperfusion and impaired regional systolic segment shortening during treadmill exercise (heart rates ~200 beats/min), local blockade of α1-adrenoceptors with intracoronary prazosin significantly increased blood flow to the hypoperfused region (Fig. 33) and caused improvement of contractile performance with no change in coronary artery pressure distal to the stenosis (355). A similar increase in flow to the hypoperfused region was observed when prazosin was administered intravenously (227). Selective blockade of α2-adrenoceptors caused variable results with either no change (287, 355) or an increase (228, 518) in blood flow in the ischemic region. The differing results may be related to the severity of the coronary artery stenosis; α2-adrenoceptor activation appears to be of greater importance during more severe ischemia. In open-chest dogs, cardiac nerve stimulation caused resistance vessel constriction in myocardium perfused by a stenotic coronary artery, which appeared to be mediated by α2-adrenoceptors (264). Postfunctional α2-adrenergic vasoconstriction in ischemic myocardial regions is opposed by simultaneous stimulation of endothelial α2-receptor-mediated release of NO. Thus, in the presence of a coronary stenosis which resulted in myocardial hypoperfusion during treadmill exercise, blockade of α2-adrenoceptors had no effect on blood flow in the ischemic region. However, after inhibition of NO production with l-NA, selective blockade of α2-adrenoceptors caused an increase in coronary flow (287). This indicates that α2-adrenergic activation during exercise did exert a vasoconstrictor effect on the coronary resistance vessels, but this effect was opposed by simultaneous release of NO by the endothelium. When the NO effect was blocked, then the direct α2-adrenergic vasoconstrictor effect was revealed. These findings suggest that in patients with impaired endothelial function, unopposed α2-adrenergic constriction could contribute to hypoperfusion during exercise in myocardial regions perfused by a stenotic coronary artery (622).

Feigl and colleagues (183, 282) proposed that adrenergic coronary vasoconstriction can augment subendocardial blood flow during exercise. However, α-adrenoceptor blockade caused a transmurally uniform increase of blood flow in myocardial regions perfused by a stenotic coronary artery (355), as well as in the pressure over-loaded hypertrophied left ventricles of dogs (155), indicating transmurally uniform α-adrenergic coronary vasoconstriction. Furthermore, the relative vasoconstriction produced by α-adrenergic activity was greater during hypoperfusion (355) than during normal arterial inflow (31, 123), suggesting that hypoperfusion amplified the vasoconstrictor response. In agreement with this finding, Chilian (98) observed that while α1- and α2-adrenoceptor stimulation had no effect on vessels smaller than 100 μm during normal arterial inflow, myocardial hypoperfusion...
resulted in unmasking of both \( \alpha_1 \)- and \( \alpha_2 \)-adrenoceptor-mediated vasoconstriction in these vessels. The results suggest that the capacity of the coronary arterioles to escape from vasoconstrictor influences becomes impaired at the low perfusion pressures that exist distal to a flow-limiting coronary artery stenosis.

B) ANG II. The role of ANG II in the residual coronary vasomotor tone that exists distal to a coronary artery stenosis during exercise has not been investigated. However, in open-chest dogs with extracorporeal perfusion of the left anterior descending coronary artery, Kitakaze et al. (315) demonstrated that the AT\(_1\) receptor antagonist CVL1974 improved coronary flow and regional segment systolic shortening in ischemic myocardium while coronary artery perfusion pressure was maintained constant. These findings suggest that endogenous ANG II can exert a vasoconstrictor influence on the coronary microcirculation of normal and ischemic myocardium via AT\(_1\) receptor activation. It is likely that the vasoconstriction produced by endogenous ANG II is in part due to increased norepinephrine release from the sympathetic nerve endings (493).

C) ET. A role for ET in the residual coronary vasomotor tone that exists distal to a flow-limiting stenosis during exercise has not been investigated. Clozel and Sprecher (108) studied the influence of coronary perfusion pressure on the response of myocardial blood flow and wall motion to ET in extracorporeally perfused dog hearts. At a coronary artery pressure of 100 mmHg, intracoronary bolus injections of ET-1 in doses of 1 and 3 \( \mu g \) produced transmurally homogeneous decreases of blood flow (up to 60%) and systolic segment shortening (up to 80%). A reduction of coronary artery pressure to 40 mmHg resulted in a 60% decrease of myocardial blood flow, which was associated with a 25% decrease of systolic segment shortening. At this perfusion pressure, ET-1 (1–3 \( \mu g/kg \)) nearly abolished myocardial blood flow (85% flow reduction) and resulted in dyskinesis of the hypoperfused region. In contrast, intracoronary injections of ANG II were not enhanced by the hypoperfusion, suggesting that the increased vasoconstrictor response to ET-1 was not simply a dilution effect, i.e., a higher concentration as a result of a lower flow. The observation that the vasoconstrictor response to ET-1 was potentiated at lower perfusion pressures supports the concept that hypoperfusion can augment the response of the coronary microvasculature to vasoconstrictor influences.

D) PLATELET PRODUCTS. Thromboxane \( A_2 \) is a product of prostaglandin endoperoxide metabolism, which is liberated during platelet aggregation. Plasma levels of its metabolites, thromboxane \( B_2 \) and urinary 2,3-dinor thromboxane \( B_2 \), are increased in patients with unstable angina and in some patients with postinfarction angina (230, 270). Furthermore, transcardiac serotonin concentrations can be increased in patients with occlusive coronary artery disease, especially those with irregular eccentric atherosclerotic lesions (575). These findings suggest the presence of intravascular platelet activation, which is in agreement with angiographic and angioscopic studies that have documented thrombus formation at the site of a ruptured atherosclerotic plaque (216, 526). Thromboxane \( A_2 \) and serotonin can aggravate myocardial ischemia by accelerating platelet aggregation, thereby increasing the degree of local mechanical obstruction and causing platelet microemboli. In addition, these platelet products have the potential to aggravate ischemia by causing vasoconstriction. Thromboxane \( A_2 \) constricts both small and large vessel segments; serotonin constricts epicardial arteries but dilates coronary resistance vessels (334, 380). These compounds exert both direct vascular smooth muscle constriction and indirect endothelium-dependent dilator influences so that arterial vasoconstriction is enhanced when endothelial function is impaired (333, 335, 609).

1) Serotonin. Serotonin (5-hydroxytryptamine, 5-HT) has the interesting property of causing vasodilation of coronary arterial vessels smaller than 100 \( \mu \)m in diameter while simultaneously causing constriction of larger coronary artery segments (334). As a result of the microvascular dilation, serotonin causes an increase in coronary blood flow in the normal heart (65, 284, 334). The increase in coronary flow is endothelium dependent (605) and is mediated principally via NO (304, 564). During normal treadmill exercise, intracoronary infusion of serotonin into a coronary artery of dogs caused a doubling of coronary blood flow, even when exercise had already resulted in substantial vasodilation of the coronary resistance vessels (33). In contrast to the dilating effect of serotonin on microvessels, in vivo studies have demonstrated that serotonin caused 25–45% reductions in cross-sectional area of epicardial arteries 2–3 mm in diameter (284, 335). The arterial constriction produced by serotonin was enhanced by removal of the endothelium (335), since serotonin causes both direct (109, 117) and flow-mediated (335) endothelium-dependent vasodilation, which opposes its direct vascular smooth muscle constriction action. Serotonin-induced coronary artery and arteriolar vasodilation is mediated by endothelial 5-HT receptors (likely the 5-HT\(_{2B}\) receptor, although a 5-HT\(_{1B,1D}\) receptor may also be involved Ref. 280), while large epicardial artery constriction involves either 5-HT\(_{1B}\) receptors (116, 284) or 5-HT\(_{2A}\) receptors (75, 576) located on vascular smooth muscle cells.

The effect of serotonin on coronary blood flow in the presence of an arterial stenosis has been studied in anesthetized and in awake animals. In open-chest dogs, Ichikawa et al. (284) employed a coronary artery stenosis that caused a 30-mmHg reduction in distal coronary artery pressure and a 15% decrease in coronary flow. Intracoronary infusion of serotonin, which produced a doubling of blood flow in the absence of a stenosis, caused a 20%
increase in blood flow in the presence of a stenosis. In contrast, Woodman (609) reported that an intracoronary bolus injection of serotonin, which caused a 70% increase in flow under normal inflow conditions in open-chest dogs, resulted in a 12% decrease of flow in the presence of a critical coronary stenosis. Ruocco et al. (488) failed to observe a significant effect of serotonin on blood flow or the transmural distribution of perfusion distal to an 80% coronary artery stenosis in closed-chest sedated swine.

When we exercised dogs on a treadmill (heart rates ~190 beats/min), in the presence of a coronary artery stenosis which maintained a constant distal coronary pressure of 42 ± 1 mmHg, serotonin tended to increase flow to the subepicardium but caused a significant decrease in flow to the subendocardium with no change in total blood flow to the ischemic region (Fig. 34) (33). It might be argued that the transmurally heterogeneous response to serotonin was the result of ischemia in the inner but not the outer layer so that autoregulatory reserve existed in the subepicardial arterioles but not in the subendocardium. However, blood flow in the poststenotic region was reduced in all myocardial layers, which would have caused metabolic arteriolar vasodilation. Moreover, earlier studies using a similar experimental model revealed that intracoronary adenosine produced an increase in blood flow which was essentially uniform in all transmural layers, suggesting that once endogenous metabolic vasodilator reserve is exhausted, vasodilator reserve in response to exogenous dilators is uniformly distributed across the left ventricular wall. Since both serotonin (334) and adenosine (103, 306) dilate isolated arterioles with diameters smaller than 100 μm, serotonin might be expected to also increase flow in all transmural layers. Although serotonin caused the expected increase in flow in the subepicardium, the stenosis unmasked an unexpected vasoconstrictor action of serotonin in the subendocardium. The results can be explained by vasoconstriction of the penetrating arteries by serotonin which would selectively increase resistance to blood flow to the subendocardium (334). In the normal heart, dilation of the resistance vessels by serotonin outweighs the effect of constriction of the penetrating arteries (33). However, in the presence of a flow-limiting coronary artery stenosis, which has caused the arterioles to undergo metabolic vasodilation, vasoconstriction of the penetrating arteries cannot be counterbalanced by additional arteriolar vasodilation. Although the arteries which supply the subepicardium would also be constricted by serotonin, these vessels travel a much shorter distance (64, 169), so that their contribution to subepicardial resistance is less important than the contribution of the penetrating arteries to subendocardial resistance.

II) Thromboxane A2. Thromboxane A2 (TxA2) receptor activation (using the stable analog U46619) produces vasoconstriction of epicardial coronary arteries and coronary resistance vessels under conditions of normal coronary artery inflow (83, 380). In vivo studies failed to demonstrate a decrease in coronary flow in the normal heart in response to U46619, although a relatively low dose of the agonist was used (83, 488).

Ruocco et al. (489) examined the interaction between endogenous prostacyclin and TxA2 in sedated swine in which an intraluminal hollow plug had been placed into the anterior descending coronary artery to cause an 80% decrease in luminal cross-sectional area. The stenosis resulted in a slight but significant decrease in myocardial blood flow with a mean distal coronary artery pressure of 78 mmHg. Infusion of U46619 caused a 20% further decrease in blood flow in the region perfused by the stenotic coronary artery with a change from lactate consumption to lactate production. Similar results were obtained after inhibition of cyclooxygenase activity with indomethacin, indicating that endogenous prostacyclin did not oppose the vasoconstriction produced by U46619. In the presence of a coronary artery stenosis that resulted in subendocardial hypoperfusion and ischemic contractile dysfunction in exercising dogs (heart rates ~190 beats/min), U46619 produced vasoconstriction that resulted in a 20–25% further decrease in myocardial blood flow with aggravation of the contractile dysfunction (25, 141). Of particular interest was the observation that the dose of U46619 (0.01 μg·kg⁻¹·min⁻¹, intracoronary) decreased blood flow only in the presence of myocardial ischemia (Fig. 32) but not during unimpeded coronary arterial inflow (34).

Thus, instead of opposing vasoconstriction, the decreased blood flow and ischemia produced by the coronary artery stenosis appeared to facilitate vasoconstriction by U46619. It is possible that the normal metabolic vasodilator mech-

![Fig. 34](https://example.com/fig34.png)
anisms are maximally activated in ischemic myocardium and therefore cannot respond to a further decrease in blood flow. TXA2 constricts coronary arterial microvessels of all sizes. In the presence of normal arterial inflow, constriction of the resistance arteries (>100 μm) can be compensated for by metabolic vasodilation of the arterioles (104, 290, 300). However, when a coronary artery stenosis has already caused metabolic arteriolar vasodilation, the ability to compensate for vasoconstriction by thromboxane in segments larger than 100 μm is lost. In agreement with this hypothesis, we observed that while endogenous adenosine contributed to coronary vasodilation during myocardial ischemia produced by exercise in the presence of a coronary artery stenosis, adenosine failed to attenuate the vasoconstriction produced by thromboxane in segments larger than 100 μm, in hypoperfused myocardium (141). The inability of endogenous adenosine to attenuate the vasoconstrictor response in hypoperfused myocardium can be explained by differing vasoactive profiles of TXA2 and adenosine in coronary arterial segments of different sizes. Whereas adenosine predominantly dilates arterioles smaller than 100 μm in diameter, thromboxane constricts coronary arterial vessels of all sizes (308, 380). Thus vasoconstriction by thromboxane of the resistance arteries (>100 μm), which are minimally responsive to the vasodilator actions of adenosine, can aggravate hypoperfusion of ischemic myocardium. In addition, thromboxane has been shown to cause constriction in the arteriolar segments that are dilated by adenosine, so that competition between thromboxane and adenosine can also occur in vessels smaller than 100 μm in diameter. Chilian and Layne (103) reported that even during severe hypoperfusion, exogenous adenosine caused further vasodilation of the coronary arterioles. This implies that residual vasomotor tone is present in ischemic myocardium and lends support to the hypothesis that vasoconstrictors can directly compete with endogenous vasodilator substances within a given vascular segment.

6. Integrated control of resistance vessel tone in ischemic myocardium

In contrast to the classical concept that myocardial hypoperfusion would cause the coronary microvasculature distal to the stenosis to become unresponsive to vasoconstrictor influences, it has become clear that residual vasomotor tone is present in the coronary resistance vessels within myocardium that becomes ischemic during exercise in the presence of a coronary artery stenosis. The residual vasomotor tone can be the result of vasoconstrictor influences of α-adrenoceptor activity, the platelet products TXA2 and serotonin, and the neurohormones ANG II and endothelin. This vasoconstriction can occur in small arteries (>100 μm) that account for a significant fraction of total coronary resistance but are not under metabolic control (α1-adrenoceptors, ANG II, TXA2, serotonin, endothelin), as well in arterioles (<100 μm) which are under metabolic control (α1- and α2-adrenoceptors, ANG II, TXA2, endothelin) (Fig. 35). These vasoconstrictor influences can compete with endogenous substances such as adenosine, bradykinin, NO, prostanooids, and EDHF which cause vasodilation through activation of KATP and KCa channels that are recruited during ischemia (Fig. 35). In support of this concept, clinical evidence is emerging that demonstrates residual coronary vasomotor tone in ischemic myocardium distal to a coronary artery stenosis (458, 497, 622).

7. Myocardial responses to chronic ischemia

Ischemia elicits local vasodilator responses that result in decreased vascular resistance and an increase in the number of open capillaries within the ischemic region, thereby augmenting blood flow and minimizing the diffusion distance for oxygen and metabolic substrate (138, 277). In addition to these vascular effects, hypoperfusion (coronary hypotension) can elicit responses within the cardiac myocytes that act to decrease energy demands, thereby reducing metabolic markers of ischemia despite persistently decreased blood flow. Short-term changes of coronary blood flow (increases or decreases) can result in directionally similar changes of myocardial oxygen consumption, termed the Gregg effect (219). Sustained limitation of blood flow in myocardial regions perfused by a stenotic coronary artery or collateral vessels can result in a state termed "hibernation" in which contractile activity, and metabolic demands, are decreased to accommodate the persistently reduced perfusion. Myocardial hibernation has been observed both in patients with occlusive coronary artery disease (88, 467) and in experimental animal models (172, 389, 404). Although a comprehensive discussion of the myocardial responses to reduced blood flow is beyond the scope of this review, the ability of the myocardium to reduce contractile activity, and thus energy demands, in response to limited blood flow deserves brief comment. It should be mentioned that myocardial hibernation appears to be fundamentally different from "stunning," in which a transient period of ischemia results in hypokinesis with normal myocardial blood flow rates, although it is likely that repetitive stunning can coexist with or lead to hibernation over time (89, 90, 554). Regions of hibernating myocardium in which blood flow is limited either by a proximal coronary stenosis or by collateral vessels have been reported to have resting blood flow rates 10–20% less than remote normally perfused myocardium, with a parallel decrease in contractile function (88, 170, 171, 317, 462, 523, 561). The response to catecholamine stimulation is blunted in hibernating regions, providing some degree of protection against the development of demand-induced ischemia (171, 375).
There are few studies examining coronary responses to exercise in chronically hypoperfused regions. In a canine model of coronary artery occlusion with moderate collateral vessel development (blood flow in the collateralized region 15–20% less than in remote normally perfused myocardium), exercise caused an increase in blood flow to the collateral-dependent region (317, 462, 561). With the use of measurements of aortic pressure and pressure in the collateral-dependent artery, it was possible to separately calculate resistance of the collateral vessels and small vessel resistance in the collateralized region. Exercise did not cause dilation of the collateral vessels (transcollateral resistance did not decrease during exercise). Rather, the increase in blood flow during exercise resulted from vasodilation of the resistance vessels in the collateral-dependent region. Exercise did not cause dilation of the collateral vessels (transcollateral resistance did not decrease during exercise). Rather, the increase in blood flow during exercise resulted from vasodilation of the resistance vessels in the collateral-dependent region (462). Preservation of vasodilator capacity in the collateral zone demonstrates that the reduced resting blood flow and persistent vasomotor tone did not result from absence of vasodilator reserve. It appears rather that energy requirements were decreased, inasmuch as such relatively hypoperfused collateral-dependent regions do not demonstrate evidence for ischemia during resting conditions (172, 404). It should be emphasized that although alterations of both the supply and demand sides of the energy equation can contribute to maintenance of metabolic equilibrium in the heart, during physiological conditions the predominant sequence is that changes in hemodynamic demands (as during exercise) result in changes in contractile work (and oxygen requirements) that drive parallel changes in blood flow.

B. Regulation of Coronary Blood Flow to Collateral-Dependent Myocardium During Exercise

Coronary artery occlusion can result in development of an effective intercoronary collateral circulation. If occlusion proceeds gradually, sufficient collateral vessel recruitment and growth may occur to allow progression to total arterial occlusion with little or no infarction of the dependent myocardium. In this situation, the collateral vessels are able to provide adequate arterial inflow to maintain myocardial integrity during resting conditions, but the ability to augment blood flow in response to exercise or other stress may be limited and develop only gradually. This section will consider studies of the coronary vascular system in the intact heart that contains a region of collateral-dependent myocardium. Emphasis
will be placed on studies in which the response of the coronary collateral system is integrated into the overall response of the heart to exercise.

1. Coronary collateral blood flow during exercise

Several investigators have examined the ability of blood flow in collateral-dependent myocardial regions to increase in response to exercise. These studies have commonly used the ameroid constrictor technique to induce collateral vessel growth (370). Coronary artery occlusion is produced by surgically implanting a ring of casein plastic material ("ameroid") around a proximal coronary artery. The hygroscopic ameroid material slowly swells as it comes in contact with tissue fluid; external expansion is prevented by a stainless steel backing incorporated into the ring, so the inward expansion of the material causes progressive arterial narrowing. The arterial narrowing and accompanying inflammation generally results in total arterial occlusion within 3–4 wk, often in association with local thrombus formation during the final stages of occlusion. Since occlusion occurs gradually, sufficient growth of collateral vessels generally occurs to allow progression to total occlusion with little or no infarct in dogs, although in swine, a species with negligible innate collateral vessels, some subendocardial necrosis is often present (433).

Fedor et al. (179) measured myocardial blood flow with radioactive microspheres during moderate treadmill exercise 11–12 wk after placement of ameroid constrictors on both the right and left circumflex coronary arteries of adult dogs. During resting conditions, myocardial blood flow was similar in the normally perfused and collateral-dependent regions. During moderate treadmill exercise, blood flow in the collateral region increased normally in 6 of 11 dogs. In the remaining five animals, blood flow in the subepicardial half of the collateral-dependent region increased normally during exercise, but the increase in blood flow to the subendocardium was markedly impaired, resulting in a prominent decrease of the subendocardial-to-subepicardial flow ratio.

Since collateral vessel development is a time-dependent process, the heterogeneous response to exercise might be related to differences in the rate of collateral vessel growth between animals. This question has been examined by measuring the exercise-induced increase in collateral blood flow relatively early (1 mo) and late (up to 8 mo) after coronary artery occlusion in dogs (32, 329). One month after ameroid placement, myocardial blood flow measured with microspheres during resting conditions was similar in the collateral-dependent and normally perfused regions, but the response of blood flow to exercise in the collateral-dependent region was highly variable (32). Approximately one-third of the animals had sufficient collateralization to allow a completely normal response of myocardial blood flow during both light and heavy levels of exercise (group 1). In a second group of animals (group 2), mean myocardial blood flow was normal at rest and demonstrated a normal increase during light exercise, but a further increase in exercise intensity resulted in no further increase in mean blood flow. In the third group of animals (group 3), blood flow was normal at rest but failed to increase or underwent a subnormal increase even during light exercise with no additional change in response to a further increase of exercise intensity. Animals grouped according to the ability of mean blood flow in the collateral-dependent region to increase in response to exercise are shown in Figure 36. The distribution of blood flow across the left ventricular wall from epicardium to endocardium is shown for the collateral-dependent region; data from a group of normal animals undergoing similar exercise are shown for comparison. For animals in group 1, not only was the mean blood flow rate normal in the collateral-dependent region during both stages of exercise, but the transmural distribution of perfusion was also normal. For the animals in group 2, the normal increase in blood flow in response to light exercise was associated with a normal transmural distribution of perfusion. However, when the exercise level was further increased, mean flow failed to increase and a transmural redistribution of perfusion away from the subendocardium occurred. Finally, for the animals in group 3, any exercise resulted in a prominent redistribution of perfusion so that subepicardial flow increased, while blood flow to the inner half of the left ventricular wall did not change or decreased compared with resting values.

Minipigs studied 4–16 wk after ameroid placement on the left circumflex coronary artery had responses to exercise similar to those of the dogs in group 3 (481, 602). Exercise which increased heart rates to 245 beats/min caused a ~200% increase in blood flow in the normal region, while mean blood flow to the collateral-dependent region increased only ~50%. The subnormal increase in blood flow to the collateral-dependent region during exercise was associated with redistribution of perfusion away from the subendocardium, with the ratio of subendocardial/subepicardial flow falling to 0.39. The findings indicate that even in the pig, in which coronary collateralization is notoriously poor, there is some ability to increase blood flow to the collateral-dependent region during exercise relatively early after coronary occlusion. As in the dog, the limited blood flow in the collateral-dependent region is delivered primarily to the outer myocardial layers, resulting in preferential underperfusion of the subendocardium.

The transmural distribution of blood flow away from the subendocardium that occurs when the collateral vessels are unable to provide a normal increase in blood flow during exercise is similar to the subendocardial underperfusion that occurs when an arterial stenosis limits myocardial blood flow during exercise (36, 500). The ability to
maintain a normal transmural distribution of perfusion is likely related to the degree of vasodilation of the resistance vessels within the collateralized region. When collateral vessels are poorly developed, the resistance vessels in the collateral-dependent region must maintain a substantial degree of vasodilation even during resting conditions to compensate for the resistance of the collateral vessels. Furthermore, the poorly developed collateral vessels impose a limit beyond which blood flow cannot increase. When myocardial demands are below this limit, the resistance vessels are able to maintain a normal transmural distribution of perfusion in the collateral-dependent region. However, when myocardial demands exceed the capacity of the collateral vessels to deliver blood flow, intense vasodilation of the resistance vessels impairs their ability to maintain a normal transmural distribution of blood flow.

The observed wide variation in the ability of the collateral vessels to increase blood flow in response to exercise could be due to intrinsic differences between animals in the ability to develop collateral vessels, or differences in the rate of collateral vessel development between animals. If the latter were true, then allowing additional time after coronary occlusion would permit all animals to develop sufficient collateralization to undergo a uniform increase in blood flow during exercise. To examine this hypothesis, myocardial blood flow was measured at rest and during two exercise stages 8 mo after implantation of an ameroid constrictor on the left circumflex coronary artery in dogs (329). Both the increase in mean myocardial blood flow and the transmural distribution of perfusion were normal at rest and during both levels of exercise in the collateral-dependent region. Similar findings were reported by Longhurst et al. (373) in dogs studied 2–3 mo after ameroid occlusion of the left circumflex coronary artery. These findings demonstrate that the marked heterogeneity of perfusion in the collateral-dependent region during exercise 1 mo after ameroid implantation did not result from differences in the intrinsic ability for ultimate collateral vessel development, but rather from differences in the rate of collateral vessel growth between animals. When sufficient time was allowed, all animals developed sufficient collateralization to permit a normal increase in blood flow in response to a moderate level of treadmill exercise.

In summary, if the coronary collateral vessels can conduct sufficient arterial inflow to meet the needs of the dependent myocardium, then the volume and distribution of blood flow will be determined by the normal autoregulatory responses of the microvasculature in the dependent myocardium. However, if the collateral vessels cannot deliver sufficient arterial inflow to meet the needs of the dependent myocardium, then the volume of flow will be determined by the conductance of the collateral system and the transmural distribution of perfusion will be similar to that observed when flow is limited by an arterial stenosis.

2. Influence of infarct in the collateral region

A) COLLATERAL FLOW DURING RESTING CONDITIONS. Gradual application of a coronary occlusion to produce a region of

![Graph showing myocardial blood flow to four transmural layers from epicardium to endocardium at rest and during two levels of treadmill exercise.](http://phyx6physiology.org/2008/07/0662062062.html)
collateral-dependent myocardium without infarct allows study of the collateral circulation uninfluenced by infarcted myocardium. In the clinical setting, however, collateral-dependent regions frequently include areas of infarcted myocardium. In this situation, blood flow to the collateral-dependent region is influenced not only by the structure and function of the collateral vessels, but also by abnormalities resulting from the presence of infarcted tissue. In both human subjects suffering acute myocardial infarction and experimental canine models of abrupt coronary occlusion, the area of infarcted myocardium is smaller than the region of tissue normally perfused by the coronary artery (“risk region”) (505). Survival of a portion of myocardium normally perfused by an occluded artery is dependent on delivery of a limited inflow of arterial blood by preexisting coronary collateral vessels. The fraction of myocardium surviving acute coronary occlusion is quantitatively related to the volume of collateral blood flow available early after coronary occlusion (476).

Several reports have examined blood flow to collateral-dependent myocardium, which included regions of infarct studied ~2 wk after acute coronary artery occlusion (259–261). Regional myocardial blood flow was measured with radioactive microspheres in multiple myocardial specimens; the percent infarct in each myocardial specimen was determined using quantitative microscopy. When blood flow to collateral-dependent myocardial specimens was plotted against percent infarct during resting conditions, an inverse linear relationship was found, with myocardial blood flow decreasing in direct proportion to the fraction of infarct within a myocardial specimen.

b) Collateral Flow During Exercise. The above studies indicate that during resting conditions, blood flow to collateral-dependent regions that include infarct is proportional to the volume of residual viable myocardium. To examine whether the presence of infarct influences the response collateral flow during exercise, myocardial blood flow was measured during three levels of treadmill exercise (heart rates of 164, 205, and 242 beats/min) in dogs 2 wk after abrupt total occlusion of the left anterior descending coronary artery (261). The degree of infarcted myocardium importantly influenced the response of collateral flow during exercise. In specimens that contained <50% infarct, blood flow during resting conditions was depressed in direct proportion to the degree of infarct, but the proportionate increase in blood flow in response to exercise was not different from a normally perfused myocardial region. Thus the presence of infarct did not impair the increase in blood flow in the collateral-dependent noninfarcted myocardium. However, when more than 50% of a myocardial specimen was occupied by infarct, not only was resting flow depressed, but the relative increase in flow during exercise was also reduced. It is likely that impairment of perfusion in regions containing >50% infarct resulted from the high resistance to blood flow offered by the poorly developed collateral vessels. Regions with the largest percent infarct were those with the sparsest native collateral vessels; even 2 wk after coronary occlusion, collateral vessel development was insufficient to allow a normal increase in flow to the residual viable myocardium during exercise. In addition, the presence of infarct might directly influence blood flow to the residual viable myocardium, or metabolic alterations in the residual myocardium (such as hibernation) might blunt the increase in oxygen demands during exercise (178).

3. Influence of Collateral Vessel Tone

Studies using isolated vessel segments and in vivo studies performed in open-chest animals have demonstrated that well-developed collateral vessels are capable of active vasomotion (243, 249). This suggests that collateral vessels do not behave as fixed conduits with a constant upper limit for conductance of blood to the dependent myocardium, but that vasomotor tone of collateral vessels can modulate the availability of blood to the dependent myocardium. This hypothesis was tested by infusion of arginine vasopressin in dogs in which a collateral-dependent myocardial region was produced using the repetitive coronary occlusion technique of Franklin et al. (195); this technique uses repeated 2-min coronary artery occlusions to stimulate collateral vessel development. An intra-arterial microcatheter was implanted distal to the occluder to allow measurement of the coronary pressure perfusing the collateralized region and calculation of collateral resistance (192). With the use of this model, distal occlusion pressures gradually increase as collateralization occurs; when the distal pressure increases to 35–40 mmHg (~3 wk of repetitive 2-min occlusions), permanent coronary occlusion can be produced without causing infarct. Following permanent occlusion, distal coronary pressures increase even more rapidly so that within 1 wk mean distal pressure increases to ~75 mmHg. At this time, myocardial blood flow was measured with microspheres at rest and during treadmill exercise. After completion of control measurements, arginine vasopressin was infused (0.01 mg·kg⁻¹·min⁻¹ iv) and blood flow was again measured at rest and during exercise. Arginine vasopressin was used because it causes constriction of isolated segments of collateral vessels (243) but does not constrict epicardial coronary arteries, since constriction of arteries proximal to the origin of the collateral vessels could also impair collateral blood flow (243, 308). Myocardial blood flow in the normal and collateral-dependent regions are shown in Figure 37. During resting conditions, blood flow was slightly but significantly lower in the collateral zone than in the normal zone. Exercise increased blood flow in both the normal and collateral-dependent regions, although the increase was subnormal in the collateralized region. When exercise was repeated
4. Control of coronary blood flow in collateralized hearts

A) α-ADRENERGIC CONTROL. α-Adrenergic vasoconstrictor influences can restrain the increase in coronary blood flow that occurs in response to the increased myocardial oxygen demands during exercise in the normal heart (31, 232) and in the presence of a coronary stenosis that results in myocardial hypoperfusion (82, 227, 297, 354, 518). A study was performed to determine whether α-adrenergic vasoconstriction also limits blood flow to collateral-dependent myocardium during exercise (260). Myocardial blood flow was measured at rest and during two levels of treadmill exercise in dogs 2 wk after acute coronary occlusion that produced a collateralized region that included a variable degree of subendocardial infarct. The increase in subendocardial blood flow in response to exercise was impaired in the collateral-dependent region, while subepicardial flow was not different from that in the remote normally perfused region. During resting conditions, selective α1-adrenergic blockade with prazosin caused no change in either mean blood flow or the transmural distribution of perfusion in either the normal or the collateral-dependent regions. However, at comparable levels of exercise, prazosin caused a 27% increase in mean blood flow in the normally perfused region and a 35% increase in mean flow in the collateral-dependent region (P < 0.01). Prazosin caused increases in blood flow in all transmural layers in the collateral-dependent region from epicardium to endocardium, although the absolute increase in flow was most marked in the subepicardium. Since previous studies have failed to document α-adrenergic vasoconstriction in coronary collateral vessels stud-
ied either in vitro or in vivo, it is unlikely that the increase in blood flow to the collateral-dependent region produced by prazosin was the result of interruption of α-adrenergic vasoconstriction in the collateral vessels (30, 243, 249). More likely, α-adrenergic blockade increased blood flow by interrupting vasomotor tone of the resistance vessels in the collateral-dependent myocardium. This is analogous to studies demonstrating that resistance vessels in regions distal to a flow-limiting coronary stenosis that result in myocardial ischemia during exercise also retain vasomotor tone (354). It appears that α-adrenergic vasoconstriction of the resistance vessels can also limit myocardial blood flow in region perfused by collateral vessels.

B) β-ADRENERGIC CONTROL. β-Adrenergic stimulation has been found to cause relaxation of isolated rings of well-developed canine coronary collateral vessels (184). Furthermore, norepinephrine infusion caused a decrease in collateral resistance in dogs studied 2–3 mo after implantation of an ameroid constrictor on the left circumflex coronary artery (384). These findings of adrenergic collateral vessel dilation suggest that β-adrenergic blockade might have the potential to decrease collateral flow. However, arterioles isolated from collateral-dependent myocardium are reported to have blunted β-adrenergic responsiveness (522). The influence of β-adrenergic activity on collateral flow was studied in dogs in which acute coronary occlusion had resulted in a collateral-dependent myocardial region containing infarct (259). During resting conditions, selective β1-adrenergic blockade with timolol caused no change in blood flow to either the normally perfused or collateral-dependent myocardium, indicating minimal adrenergic activity at rest. However, during exercise, timolol decreased blood flow in both collateralized and remote regions, largely due to the negative chronotropic effect of β-adrenergic blockade. To correct for changes resulting from alterations of myocardial oxygen demands, results were compared at similar rate-pressure products. At comparable rate-pressure products, timolol significantly decreased blood flow in both the subepicardium and subendocardium of the normally perfused region. In the collateral region, timolol caused a decrease of subepicardial blood flow comparable to that in the normally perfused region. However, in the subendocardium of the collateral region (in which blood flow during exercise was substantially less than normal), β-adrenergic blockade did not cause a further reduction of blood flow. The effect of β-adrenergic blockade on subepicardial flow could have resulted from vasoconstriction of either the collateral vessels or the resistance vessels in the collateral zone. To further examine this question, Traverse et al. (559) studied the effect of β-adrenergic activity on collateral blood flow during treadmill exercise using the non-selective β-blocker propranolol. Pressure in the coronary artery distal to the occlusion was measured to separate the effects of propranolol on collateral resistance and small-vessel resistance in the collateral zone. Collateral vessel growth was stimulated with repetitive 2-min coronary occlusions so that myocardial infarction was avoided. During control exercise, blood flow in the collateral zone was 38 ± 5% less than in the normal zone. At identical levels of exercise, with heart rate maintained constant by atrial pacing, propranolol decreased mean blood flow in the collateralized myocardium by ~20%; this occurred principally in the subepicardium with no significant effect on flow in the subendocardium. The decrease in collateral zone blood flow in response to propranolol resulted from a 40% increase in transcollateral resistance and a ~50% increase in small-vessel resistance in the collateral-dependent region. The decrease in subepicardial flow in the collateral region following β-adrenergic blockade was proportionately similar to the decrease in flow in the normally perfused region. Thus the decrease in subepicardial blood flow in the collateral region in response to β-adrenergic blockade resulted from vasoconstriction of the coronary resistance vessels with a smaller effect on the collateral vessels.

In summary, adrenergic nervous system activity can influence blood flow to collateral-dependent myocardium during exercise. The available data suggest that the influence of the adrenergic nervous system on blood flow in the collateral zone results principally from altered vasomotor activity of the microvasculature within the collateral-dependent region rather than from direct vasomotor effects on the collateral vessels.

C) NO. In vitro studies using isolated vessel rings have demonstrated that collateral vessels acquire a functionally competent endothelium and muscular media early in their development and are responsive to NO-dependent agonists, such as bradykinin and acetylcholine (5, 10, 188). Furthermore, inhibition of NO synthesis has been shown to decrease retrograde blood flow from a cannulated collateral-dependent coronary artery in anesthetized open-chest dogs (188) and to significantly increase collateral vessel vascular resistance in awake dogs (194), demonstrating that tonic production of NO contributes to maintenance of collateral vasodilation. Conversely, arterioles isolated from collateral-dependent myocardium demonstrate blunted endothelium-dependent vasodilator responses to acetylcholine and ADP in dogs (521), and ADP and bradykinin in swine (222, 519). To determine whether endogenous NO contributes to maintenance of blood flow in collateral-dependent myocardium, Traverse et al. (561) exercised dogs on a treadmill (heart rate 230 beats/min) before and after NO synthase inhibition with L-NA (20 mg/kg iv). During resting conditions, L-NA tended to decrease blood flow to the collateral region with no change in normal zone blood flow. During exercise, L-NA caused a decrease in mean blood flow to the collateral region (from 2.24 ± 0.19 to 1.78 ± 0.26 ml·min⁻¹·g myocardium⁻¹ after L-NA, P < 0.05), which occurred in both
the subendo- and subepicardium (Fig. 38). This decrease resulted from a near doubling of the collateral vascular resistance, with a trend toward an increase in small vessel resistance in the collateral zone. Interestingly, L-NA also decreased blood flow to the normal myocardial region during exercise (from 2.99 ± 0.24 to 2.45 ± 0.28 ml·min⁻¹·g myocardium⁻¹) as the result of a 44 ± 13% increase in coronary vascular resistance. These findings indicate that, in contrast to the normal heart (7) or normal regions in hearts with an acute coronary artery stenosis (137), endogenous NO is important in maintaining flow to regions of normally perfused myocardium during exercise in a model of single-vessel coronary artery occlusion.

In view of the observation that endogenous NO contributes to maintenance of perfusion in collateral-dependent myocardium, the question arises as to whether exogenous NO can increase blood flow during exercise in a collateralized region. Studies in open-chest animals with well-developed coronary collateral vessels demonstrated that nitroglycerin increased blood flow and improved contractile function in collateral-dependent myocardium (113, 173, 249). However, nitroglycerin did not increase blood flow to collateral-dependent myocardium of exercising dogs with a chronic coronary occlusion (462). The lack of effect of nitroglycerin on either coronary collateral resistance or small-vessel resistance in the collateral zone suggests that the endogenous NO system is already maximally recruited during exercise in the canine model of single-vessel coronary artery occlusion. This is supported by the observation that after inhibition of NO synthase with L-NA, nitroglycerin did increase blood flow to the collateral zone, and this was associated with an improvement of regional systolic wall thickening (317). This observation suggests that in patients in whom dyslipidemia and atherosclerosis have resulted in endothelial dysfunction and impaired NO bioavailability, nitroglycerin would be able to increase collateral blood flow.

D) PROSTANOIDS. Although coronary vessels are capable of synthesizing and responding to vasoactive products of arachidonic acid (423), physiological studies have failed to demonstrate an important role for the prostaglandin system in regulation of coronary blood flow in the normal canine heart. In contrast, in open-chest dogs in which chronic coronary artery occlusion had resulted in growth of collateral vessels, cyclooxygenase blockade caused a decrease in retrograde blood flow from the collateral-dependent artery (4, 6), suggesting that basal release of prostaglandins maintains tonic vasodilation of coronary collateral vessels. However, interpretation of these findings is complicated by reports that tissue injury during acute surgical preparation of open-chest animal models can artificially increase basal prostaglandin synthesis by the heart. Altman et al. (8) addressed the role of prostaglandins in control of blood flow in collateral-dependent myocardium in chronically instrumented dogs, free from the effects of anesthesia and acute surgical trauma. Myocardial blood flow was measured with radioactive microspheres at rest and during treadmill exercise (heart rate 215 ± 7 beats/min). Cyclooxygenase blockade with indomethacin (5 mg/kg iv) caused no change in heart rate or arterial pressure, and no change in blood flow in the normal zone or the collateral zone during resting conditions. However, during exercise, indomethacin caused a 42 ± 10% increase in transcollateral resistance that was associated with a 27 ± 11% decrease in subendocardial flow in the collateral zone (both P < 0.05), but no change

FIG. 38. Effect of inhibition of NO synthase inhibition on left ventricular subendocardial and subepicardial blood flows in hearts with a collateral-dependent region due to chronic coronary artery occlusion and in hearts subjected to an acute coronary artery stenosis during treadmill exercise. Inhibition of NO synthase decreased blood in the normal as well as in the collateral-dependent regions. In contrast, while NO synthase inhibition decreased flow distal to a coronary artery stenosis, it had no effect on the normal region. Data are means ± SE. *P < 0.05 vs. corresponding control. See text for further explanation. [Data from Traverse et al. (561) and Duncker and Bache (137).]
in normal zone blood flow. Indomethacin had no effect on small vessel resistance in the collateral zone so that the decrease in blood flow was mediated entirely by constriction of the collateral vessels. Thus, in the setting of chronic coronary occlusion, the cyclooxygenase system exerts a vasodilator influence on collateral vessels that becomes apparent during exercise.

E) ADENOSINE. Acadesine (5\(^{-}\text{AICA riboside}\)) is an adenosine-regulating agent that increases adenosine production. In acutely ischemic myocardium, increased production of adenosine via activation of 5\(^{-}\text{ectonucleotidase}\) (278) can exert cardioprotective effects (225). Consequently, a study was performed to determine whether acadesine would improve blood flow to collateral-dependent myocardium during exercise (290). In dogs with moderately well-developed coronary collateral vessels but a subnormal increase in blood flow in the collateral zone during exercise, acadesine increased blood flow in the collateral-dependent region during exercise by 24 ± 5% with no change in the transmural distribution of perfusion. The increase in collateral zone blood flow produced by acadesine resulted from a 25% decrease transcollateral resistance and a 20% decrease in small-vessel resistance in the collateral region. Acadesine also increased normal zone blood flow in the collateralized dogs but had no effect on coronary flow in normal dogs. These findings suggest that adenosine metabolism is altered not only in the collateral-dependent region but also in the remote region of hearts with a chronic coronary artery occlusion. The importance of endogenous adenosine for the regulation of coronary blood flow in the collateralized heart during exercise has not been studied to date.

F) SUMMARY AND INTEGRATION. The coronary collateral system embodies a dynamic network of interarterial vessels that can undergo both long- and short-term adjustments that are capable of modulating blood flow to the dependent myocardium. Long-term adjustments including recruitment and growth of collateral vessels in response to arterial occlusion are time dependent and determine the maximum blood flow rates available to the collateral-dependent vascular bed during exercise. Rapid short-term adjustments result from active vasomotor activity of the collateral vessels. Mature coronary collateral vessels are responsive to vasodilators such as nitroglycerin (113, 173, 249) and atrial natriuretic peptide (191), to vasoconstric-

![Figure 39](http://physrev.physiology.org/) Schematic overview of various vasodilator (yellow text boxes) and vasoconstrictor (blue text boxes) influences in collateral arteries (and epicardial conduit vessels) and distal coronary microcirculation (small intramural arteries class A and B and arterioles) of the coronary arterial bed of the LV wall, during exercise in the presence of a chronic coronary artery occlusion. In solid line text boxes are shown the contribution to vasomotor control of endogenous vasoactive substances, whereas in dashed line text boxes the effects of exogenous administration of vasoactive substances have been shown. \(\beta_1\) and \(\beta_2\), \(\alpha\)-adrenergic receptor; NO, nitric oxide; Ado, adenosine (AICA-riboside); NTG, nitroglycerin; PGI\(_2\), prostacyclin; \(\alpha_1\), \(\alpha_2\)-adrenergic receptor; VP, vasopressin. See text for further explanation.
can modify collateral conductance, thereby influencing the blood supply to the dependent myocardium. In addition, vasomotor activity in the resistance vessels of the collateral perfused vascular bed can influence the volume and distribution of blood flow within the collateral zone (Fig. 39). Finally, there is evidence that vasomotor control of resistance vessels in the normally perfused regions of collateralized hearts is altered compared with normal hearts (290, 561), indicating that the coronary vascular adaptations in hearts with a coronary occlusion involve alterations in resistance vessels at a global as well as a regional level (532). These observations caution against using vessels from the remote “normally perfused” myocardial region as control vessels.

C. Exercise Training and the Coronary Collateral Circulation

Exercise training has emerged as an intervention for primary and secondary prevention of coronary artery disease (340, 369). The mechanisms that have been proposed to contribute to the beneficial effects of exercise include regression of atherosclerosis, formation of collaterals (angiogenesis), development of new vessels (angiogenesis/vasculogenesis), and improvement of endothelial function. For an overview of the effects of exercise training in patients with coronary artery disease and potential mechanisms, the reader is referred to a recent article by Linke et al. (369). Here we focus on the effects of exercise training on the collateral circulation and the coronary microcirculation within collateral-dependent myocardium.

1. Coronary collateral blood flow

A) NATIVE COLLATERAL VESSELS IN THE NORMAL HEART. The effect of exercise training on collateral function in hearts with a normal coronary circulation has been assessed by measuring retrograde flow from the cannulated collateral-dependent coronary artery opened to atmospheric pressure (84, 114, 506) or by measurement of collateral blood flow with radioactive microspheres (112, 131, 319, 321, 501, 507) (Table 4). Studies comparing collateral function in trained and sedentary control groups at the end of a training period have produced exclusively negative results (84, 114, 131, 321, 501, 506, 507). To compensate for the substantial interanimal differences in native collaterals present in the dog, Knight and Stone (319) measured collateral blood flow in chronically instrumented dogs before and after exercise training; collateral blood flow was found to increase. Cohen (112) also observed a tendency for collateral flow to increase in chronically instrumented dogs following exercise training, but a similar increase was also observed in sedentary animals, suggesting that the chronic instrumentation procedure stimulated the growth of coronary collateral vessels independent of exercise training. These findings indicate that physical conditioning does not enhance native collateral blood flow in the normal heart.

B) EXERCISE TRAINING WITH A CORONARY STENOSIS OR OCCLUSION. There is considerable interest in whether chronic exercise is capable of stimulating development of coronary collateral vessels in patients with occlusive coronary artery disease. Human studies using angiography to assess the collateral vasculature in exercise-trained patients with coronary artery disease have generally yielded negative results (195, 428). These studies are limited to anatomic assessment of coronary collateral vessels without measurement of collateral blood flow. In contrast, Belardinelli et al. (50) reported a beneficial effect of 8 wk of moderate exercise training on collateral-dependent myocardial perfusion, as assessed by thallium uptake in patients with ischemic cardiomyopathy.

Eckstein (156) was the first to report a beneficial effect of exercise training on collateral formation in dogs with a coronary artery stenosis (Table 5). The increase in retrograde blood flow from the cannulated collateral-dependent artery produced by exercise training was most striking in the presence of a mild stenosis that resulted in minimal collateral formation in the sedentary animals, suggesting that exercise produced ischemia which then acted to stimulate collateral vessel growth. Cohen et al. (115) reported similar results in chronically instrumented dogs. Thus, while exercise training under normal inflow conditions does not stimulate the formation of coronary collaterals, these studies suggest that chronic exercise resulting in or aggravating ischemia in a myocardial region distal to a coronary artery stenosis can stimulate collateral vessel growth.

Studies of the effect of exercise training on collateral formation in response to a progressive coronary artery occlusion have yielded equivocal results (Table 5). Heaton et al. (254) and Neill and Oxendine (424) reported no differences between sedentary and trained dogs in collateral blood flow measured 6–8 wk after placement of an ameroid constrictor on a coronary artery, although a slight improvement in the ENDO/EPI blood flow ratio in the collateralized region was observed after exercise training (254). Exercise training may have failed to exert an effect because the stimulus for collateral formation was nearly maximal even in the sedentary animals. Thus blood flow to the collateral-dependent myocardium in sedentary dogs was not different from flow in the normal myocardium, so that exercise training may not have induced ischemia in these well-collateralized hearts (254, 424). In contrast, in swine, blood flow in the collateral-dependent region was <50% of blood flow in the normal myocardial segment during exercise, so that exercise-induced ischemia might have further stimulated collateral
<table>
<thead>
<tr>
<th>Investigators</th>
<th>Species, Sex</th>
<th>Age</th>
<th>Running Training Program</th>
<th>Efficacy</th>
<th>Cardiac Hypertrophy</th>
<th>Experimental Conditions</th>
<th>Study Groups</th>
<th>Retrograde Flow, ml/min</th>
<th>Normal Zone Flow, ml·min⁻¹·g⁻¹</th>
<th>Collateral Zone Flow, ml·min⁻¹·g⁻¹</th>
<th>Before Training</th>
<th>After Training</th>
<th>Before Training</th>
<th>After Training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burt and Jackson (84)</td>
<td>Dog M, F</td>
<td>?</td>
<td>8-16 km/h, 0%; 90 min/day, 5 days/ wk, 4-6 wk</td>
<td>?</td>
<td>?</td>
<td>Open chest</td>
<td>Sedentary</td>
<td>5.0</td>
<td>4.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cohen et al. (114)</td>
<td>Dog M, Y</td>
<td>6.4-9.6 km/h, 20%; 75 min/day, 5 days/wk, 12 wk</td>
<td>HR&lt;sub&gt;EX&lt;/sub&gt; ↓, SMVO&lt;sub&gt;2&lt;/sub&gt; ↑</td>
<td>LVW ↔, LVW/BW ↔</td>
<td>Open chest</td>
<td>Extracorporeal perfusion</td>
<td>Exercise</td>
<td>3.2</td>
<td>1.01</td>
<td>0.33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scheel et al. (506)</td>
<td>Dog M, A</td>
<td>5.8 km/h, 25%; 45 min/day, 7 days/ wk, 6 wk</td>
<td>?</td>
<td>HW ↔, HW/BW ↔</td>
<td>Isolated blood-perfused heart</td>
<td>Sedentary</td>
<td>0.33</td>
<td>0.19</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Knight and Stone (319)</td>
<td>Dog M, F</td>
<td>6.5-9.6 km/h, 20%; 45 min/day, 5 days/wk, 4 wk</td>
<td>?</td>
<td>No&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Awake, rest</td>
<td>Trained</td>
<td>1.48</td>
<td>1.44</td>
<td>0.71</td>
<td>1.03&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohen (112)</td>
<td>Dog M, Y</td>
<td>6.4-9.6 km/h, 20%; 75 min/day, 5 days/wk, 12 wk</td>
<td>HR&lt;sub&gt;EX&lt;/sub&gt; ↓</td>
<td>No&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Awake, rest</td>
<td>Trained</td>
<td>1.58</td>
<td>1.70</td>
<td>0.35</td>
<td>0.61&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1.55</td>
<td>2.06</td>
<td>0.26</td>
<td>0.49&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dodd-o and Gwirtz (131)</td>
<td>Dog M, F</td>
<td>6.4-9.6 km/h, 20%; 75 min/day, 5 days/wk, 12 wk</td>
<td>HR&lt;sub&gt;REST&lt;/sub&gt; ↓</td>
<td>?</td>
<td>Open chest</td>
<td>Sedentary</td>
<td>0.99</td>
<td>0.26</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sanders et al. (501)</td>
<td>Swine M, F</td>
<td>6 km/h, 0%; 60 min/day, 5 days/wk, 10 mo</td>
<td>HR&lt;sub&gt;REST&lt;/sub&gt; ↓</td>
<td>HW ↔, HW/BW ↔</td>
<td>Open chest</td>
<td>Sedentary</td>
<td>0.47</td>
<td>0.06</td>
<td></td>
<td></td>
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<tr>
<td>Scheffer and Verdouw (507)</td>
<td>Swine M, F</td>
<td>5.5 km/h, 0%; 40-60 min/day, 5 days/wk, 8 wk</td>
<td>HR&lt;sub&gt;EX&lt;/sub&gt; ↓</td>
<td>LVW 20% ↑, LVW/BW ↑</td>
<td>Open chest</td>
<td>Sedentary</td>
<td>0.95</td>
<td>0.21</td>
<td></td>
<td></td>
<td>0.79</td>
<td>0.31</td>
<td></td>
<td></td>
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<tr>
<td>Koerner and Terjung (321)</td>
<td>Rat M, Y</td>
<td>1.6 km/h, 15%; 60 min/day, 5 days/ wk, 12-24 wk</td>
<td>SMVO&lt;sub&gt;2&lt;/sub&gt; ↑</td>
<td>LVW ↔, LVW/BW 16% ↑</td>
<td>Open chest</td>
<td>Sedentary</td>
<td>6.25</td>
<td>0.39</td>
<td></td>
<td></td>
<td>4.93</td>
<td>0.43</td>
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</tbody>
</table>

Collateral zone/Normal zone myocardial blood flow ratios were measured with radioactive microspheres. <sup>a,b</sup>Not measured in that study but based on previous observations from the same laboratory ("Stone, 1980; "Liang et al., 1984; "Cohen, 1978). <sup>*</sup><i>P</i> < 0.05, after training vs. before training. <sup>†</sup><i>P</i> < 0.05, exercise group vs. sedentary group.
Table 5. Effects of exercise training on collateral blood flow in animals with impeded coronary arterial inflow

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Species, Sex, Age</th>
<th>Program</th>
<th>Start</th>
<th>Efficacy</th>
<th>Hypertrophy</th>
<th>Experimental Conditions</th>
<th>Study Groups</th>
<th>Normal Zone Flow, ml/min</th>
<th>Collateral Zone Flow, ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed Coronary Artery Stenosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Before Training</td>
<td>After Training</td>
</tr>
<tr>
<td>Eckstein (156)</td>
<td>Dog M, F</td>
<td>7.5 km/h, 30%; 70 min/day, 5 days/wk, 6-8 wk</td>
<td>1 wk</td>
<td>postplacement</td>
<td>?</td>
<td>HW ↔, HW/BW ↔</td>
<td>Open chest extracorporeal perfusion</td>
<td>Sedentary</td>
<td>34</td>
</tr>
<tr>
<td>Cohen et al. (115)</td>
<td>Dog M Y</td>
<td>6.4–9.6 km/h, 20%; 75 min/day, 5 days/wk, 12 wk</td>
<td>2 wk</td>
<td>postplacement</td>
<td>HR&lt;sub&gt;EX&lt;/sub&gt; ↓</td>
<td>No&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Rest</td>
<td>Sedentary</td>
<td>1.28</td>
</tr>
<tr>
<td>Heaton et al. (254)</td>
<td>Dog M, F A</td>
<td>9.6 km/h, 5%; 60 min/day, 5 days/wk, 6 wk</td>
<td>2 wk</td>
<td>postplacement</td>
<td>HR&lt;sub&gt;EX&lt;/sub&gt; ↓</td>
<td>?</td>
<td>Rest</td>
<td>Sedentary</td>
<td>1.33</td>
</tr>
<tr>
<td>Neill and Oxendine (424)</td>
<td>Dog M, F</td>
<td>8 km/h, 15%; 30 min/day, 5 days/wk, 5 wk</td>
<td>1 wk</td>
<td>postplacement</td>
<td>?</td>
<td>HW ↔, HW/BW ↔</td>
<td>Rest</td>
<td>Sedentary</td>
<td>1.79</td>
</tr>
<tr>
<td>Scheel et al. (506)</td>
<td>Dog M A</td>
<td>5.8 km/h, 25%; 45 min/day, 5 days/wk, 8 wk</td>
<td>3 mo</td>
<td>postplacement</td>
<td>?</td>
<td>LVW ↔, LVW/BW ↔</td>
<td>Isolated blood-perfused heart; perfusion pressure 100 mmHg; maximal vasodilation</td>
<td>Sedentary</td>
<td>128</td>
</tr>
<tr>
<td>Schaper et al. (504)</td>
<td>Dog M F</td>
<td>6 km/h, 22%; 60 min/day, 5 days/wk, 4 wk</td>
<td>2 wk</td>
<td>postplacement</td>
<td>HR&lt;sub&gt;EX&lt;/sub&gt; ↓</td>
<td>HW ↔, HW/BW ↔</td>
<td>Isolated blood-perfused heart; perfusion pressure 80 mmHg; maximal vasodilation</td>
<td>Sedentary</td>
<td>3.75</td>
</tr>
<tr>
<td>Bloor et al. (61)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Swine M, F</td>
<td>6–8 km/h, 5%; 60 min/day, 5 days/wk, 5 mo</td>
<td>2 wk</td>
<td>postplacement</td>
<td>HR&lt;sub&gt;HRT&lt;/sub&gt; ↓</td>
<td>LVW ↔, LVW/BW ↑</td>
<td>Anesthetized, open chest</td>
<td>Sedentary</td>
<td>0.48</td>
</tr>
<tr>
<td>Roth et al. (482)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Swine M, F</td>
<td>5 km/h, ≥5%; 30–50 min/day, 5 days/wk, 5 wk</td>
<td>4 wk</td>
<td>postplacement</td>
<td>HR&lt;sub&gt;EX&lt;/sub&gt; ↓</td>
<td>LVW ↔, LVW/BW ↔</td>
<td>Rest</td>
<td>Sedentary</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Normal zone flows and collateral zone flows were measured with radioactive microspheres. <sup>a</sup>In the study by Bloor et al. (61), a fixed stenosis was initially implanted; however, at the time of autopsy the stenosis had progressed into a total occlusion in all animals. <sup>b</sup>In the study of Roth et al. (482), absolute flows were not presented; the flow data in the collateral-dependent zone column represent collateral/normal zone ratios. <sup>c</sup>Not measured in that study but based on previous observations from the same laboratory (Cohen, 1978). †<sup>P</sup> < 0.05, after training vs. before training. ‡<sup>P</sup> < 0.05, exercise group vs. sedentary group.
growth (61, 482). Moreover, differences in collateral blood flow between exercised and sedentary dogs might not have been detected because maximal resistance vessel dilation was not achieved, i.e., maximal collateral conductance was not assessed (254, 424). This could explain why retrograde blood flow (which is not affected by resistance vessel tone) was increased in trained dogs (424, 506). However, Schaper et al. (504) measured collateral blood flow in isolated dog hearts perfused with blood at constant pressure during maximal coronary resistance vessel dilation with adenosine and observed no effect of exercise training on maximum collateral blood flow. Maximum blood flow in the collateral-dependent region was 45% of the maximal flow in the normal myocardium of the sedentary animals, which makes it likely that blood flow to the occluded area was sufficient to minimize ischemia during exercise training. In none of the above studies was an attempt made to maximally dilate the coronary collateral vessels, e.g., with nitroglycerin, so that differences in collateral vessel tone could have influenced the measured collateral blood flow rates (249).

C) SUMMARY AND INTEGRATION. Exercise does not stimulate growth of coronary collateral vessels in the normal heart. However, if exercise produces ischemia, which would be absent or minimal under resting conditions, there is evidence that collateral growth can be enhanced. Finally, when there is ischemia even under resting conditions, exercise may have only a modest additional effect. However, the concept that exercise-induced ischemia can enhance collateral vessel growth is not supported by two studies, exercise may have only a modest additional effect. Interestingly, exercise training had no effect on bradykinin-induced vasodilation of arterioles isolated from the remote normally perfused region of collateralized hearts (222), which contrasts with observations in arterioles obtained from exercise-trained normal hearts (414). The authors proposed that adaptive responses in the nonoccluded arterial beds (which are the source of collateral flow to the occluded territory) likely modify the response to exercise training (222). These observations exemplify the importance of including control vessels from normal hearts, rather than simply using vessels from the remote myogenic zone as controls. Exercise training also increases basal myogenic tone in collateral-dependent arterioles, similar to the effect of exercise training on arterioles in normal hearts (413). This increase in basal tone is associated with augmented vasodilator influences exerted by increased NO production and Kv channel activity (252).

In summary, exercise-induced adaptations of coronary resistance vessels within a collateral-dependent ventricular region consist of simultaneously increased basal tone and increased vasodilator influences, including increased NO production and Kv channel activity. These microvascular adaptations may provide a greater intrinsic capacity of local vascular control mechanisms to regulate blood flow to collateral-dependent myocardium and thereby contribute to the improved perfusion observed after exercise training.

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