MINIREVIEW

Control of Coronary Blood Flow during Exercise

JOHNATHAN D. TUNE,*[,1] KEITH NEU RICHMOND,† MARK W. GORMAN,‡ AND ERIC O. FEIGL‡

Department of Integrative Physiology, University of North Texas Health Science Center, Fort Worth, Texas 76107; †Division of Cardiovascular Biology, Shen Nippon Biomedical Laboratories, Ltd., USA, Redmond, Washington 98052; and ‡Department of Physiology and Biophysics, University of Washington School of Medicine, Seattle, Washington 98195

Under normal physiological conditions, coronary blood flow is closely matched with the rate of myocardial oxygen consumption. This matching of flow and metabolism is physiologically important due to the limited oxygen extraction reserve of the heart. Thus, when myocardial oxygen consumption is increased, as during exercise, coronary vasodilation and increased oxygen delivery are critical to preventing myocardial underperfusion and ischemia. Exercise coronary vasodilation is thought to be mediated primarily by the production of local metabolic vasodilators released from cardiomyocytes secondary to an increase in myocardial oxygen consumption. However, despite various investigations into this mechanism, the mediator(s) of metabolic coronary vasodilation remain unknown. As will be seen in this review, the adenosine, K^+_{ATP} channel and nitric oxide hypotheses have been found to be inadequate, either alone or in combination as multiple redundant compensatory mechanisms. Prostaglandins and potassium are also not important in steady-state coronary flow regulation. Other factors such as ATP and endothelium-derived hyperpolarizing factors have been proposed as potential local metabolic factors, but have not been examined during exercise coronary vasodilation. In contrast, norepinephrine released from sympathetic nerve endings mediates a feed-forward β-adrenoceptor coronary vasodilation that accounts for ~25% of coronary vasodilation observed during exercise. There is also a feed-forward α-adrenoceptor-mediated vasoconstriction that helps maintain blood flow to the vulnerable subendocardium when heart rate, myocardial contractility, and oxygen consumption are elevated during exercise. Control of coronary blood flow during pathophysiological conditions such as hypertension, diabetes mellitus, and heart failure is also addressed.

[Exp Biol Med Vol. 227(4):238–250, 2002]

[1] To whom requests for reprint should be addressed at Department of Integrative Physiology, University of North Texas Health Science Center, 3500 Camp Bowie Boulevard, Fort Worth, TX 76107-2699. E-mail: jtune@hsc.unt.edu

1535-3702/02/2274-0238$15.00

Key words: adenosine; nitric oxide; K^+_{ATP} channels; β-feed-forward vasodilation; α-adrenoceptor vasoconstriction

The anaerobic capacity of the mammalian heart is very limited and if the oxygen supply is interrupted, the affected myocardium quickly stops beating. During normal resting conditions, the heart extracts ~75% of the oxygen delivered by coronary blood flow, therefore the oxygen extraction reserve is quite limited (1–3). Thus, myocardial function is dependent on an adequate coronary blood flow on a moment-to-moment basis.

Despite these seeming constraints at rest, the heart is capable of increasing myocardial oxygen consumption 5-fold or more above resting values when there is tachycardia, augmented contractility, and increased cardiac afterload, as occurs during exercise (1–4). For this reason, exercise is frequently used to test the physiological mechanisms that control coronary blood flow and thus oxygen delivery to the heart.

The dominant determinant of coronary blood flow is the rate of myocardial oxygen consumption, and the central question in coronary physiology is how coronary flow is coupled to myocardial oxygen consumption by a local metabolic mechanism (1–4). As will be seen, the adenosine, K^+_{ATP} channel, and nitric oxide hypotheses for the local metabolic control of coronary blood flow during exercise have been found inadequate individually and in combination. Therefore, the mechanism of local metabolic control of coronary blood flow remains unknown, with no strong alternative hypothesis available at this time.

In contrast to the negative results on identifying the local metabolic vasodilator mechanism in the coronary circulation, there have been positive findings on the neural control of coronary blood flow during exercise. A feed-forward β-adrenoceptor-mediated coronary vasodilation

due to norepinephrine released from sympathetic nerve endings has been documented. The feed-forward mechanism operates without an error signal whereby increases in heart rate and myocardial contractility due to activation of the sympathetic nerves to the heart and coronary vasculature also result in a parallel coronary vasodilation. The feed-forward β-adrenoceptor vasodilation acts primarily on small coronary arterioles and accounts for ~25% of the coronary vasodilation observed during exercise. There is also evidence for a feed-forward norepinephrine α-adrenoceptor-mediated vasoconstriction in large- and medium-size coronary arteries during exercise. The α-adrenoceptor-mediated vasoconstriction upstream from small arterioles has the effect of reducing vessel compliance and thus lessening wasteful systolic-diastolic flow oscillations in the coronary arterial tree. This has the beneficial result of maintaining blood flow to the vulnerable inner layer of the left ventricle when heart rate, myocardial contractility, and myocardial oxygen consumption are all high during exercise.

The experimental details for the interpretations concerning local metabolic and neural control of coronary blood flow during exercise are given below.

Adenosine Hypothesis

For many years, adenosine has been thought to be the vasodilatory metabolite that links coronary blood flow to myocardial metabolism (1, 5–7). The adenosine hypothesis predicts that an increase in myocardial oxygen consumption decreases myocardial tissue oxygen tension to stimulate the release of adenosine from cardiomyocytes. The resulting increase in cardiac interstitial adenosine concentration activates adenosine receptors on coronary vascular smooth muscle cells, which increases coronary vascular conductance and augments oxygen delivery. The increase in coronary blood flow and oxygen delivery act to restore myocardial oxygen tension to a normal operating level, thereby decreasing cardiac adenosine production in a negative feedback manner. Thus, the interstitial concentration of adenosine would control coronary blood flow to match myocardial oxygen delivery with myocardial oxygen consumption, and maintain myocardial oxygen tension within the normal physiologic range (8, 9).

Adenosine and Local Metabolic Coronary Vasodilation. Many investigations have examined the role of adenosine in local metabolic coronary vasodilation during increases in myocardial oxygen consumption (10–28). Results from these studies are inconsistent in that indices of interstitial adenosine concentration were increased during increases myocardial oxygen consumption (10, 11, 13, 15, 16, 18, 20), but blockade of endogenous adenosine receptors did not alter functional coronary hyperemia during increases in myocardial oxygen consumption (12, 17, 24, 26–28). One potential reason for these conflicting findings could be that the adenosine measurements reported in early investigations did not reliably estimate the cardiac interstitial concentration of adenosine (28, 29). An alternative explanation for these discrepant results is that the interstitial adenosine concentration increases sufficiently to overcome the competitive adenosine receptor blockade, as would be predicted if adenosine were part of a high gain negative feedback system (21, 30, 31). In other words, the failure of adenosine receptor blockade to limit coronary vasodilation during increases in myocardial oxygen consumption is due to a sufficient compensatory increase in cardiac adenosine production. Therefore, to adequately test the adenosine hypothesis, it is essential to have an estimate of cardiac interstitial adenosine concentration.

Despite avid uptake of adenosine by coronary vascular endothelial cells, cardiac interstitial adenosine concentration may be estimated (32, 33). The method for estimating the interstitial concentration of adenosine uses measurements of coronary blood flow, hematocrit, and arterial and coronary venous plasma adenosine concentrations in an axially distributed mathematical model. Experiments using this model determined the relationship between interstitial adenosine concentration and coronary blood flow and found that the threshold for adenosine-mediated coronary vasodilation was ~117 n*M* (33).

Recently, Tune *et al.* (28) quantitatively examined the adenosine hypothesis by combining measurements of coronary venous adenosine concentration with adenosine receptor blockade during exercise in chronically instrumented dogs. This is important because if, as postulated, adenosine is part of a high-gain negative feedback system, then adenosine levels will increase to overcome the competitive receptor blockade and little change in coronary blood flow will be observed. Interstitial adenosine concentration was estimated using the mathematical model described above (32, 33). Tune *et al.* (28) found that adenosine receptor blockade did not alter coronary blood flow at rest or during graded treadmill exercise, which is consistent with earlier studies in dogs (17) and pigs (26). Coronary venous plasma adenosine concentration was little changed when myocardial oxygen consumption was increased over 4-fold during exercise. The slope of the estimated interstitial adenosine concentration versus myocardial oxygen consumption relationship did not differ significantly from zero, and the interstitial adenosine concentration remained well below the threshold concentration necessary for coronary vasodilation (117 n*M*; Fig. 1). Furthermore, coronary venous and estimated interstitial adenosine concentrations did not increase to overcome the competitive receptor blockade of either 8-phenyltheophylline or 8-*p*-suflophenyltheophylline. In order for adenosine to have increased sufficiently to overcome the receptor blockade would have required a 12-fold increase in adenosine concentration for 8-phenyltheophylline and a 5-fold increase for 8-*p*-suflophenyltheophylline (28). This clearly did not occur (Fig. 1). These findings demonstrate that adenosine is not required for local metabolic coronary vasodilation during exercise-induced increases in myocardial oxygen consumption.

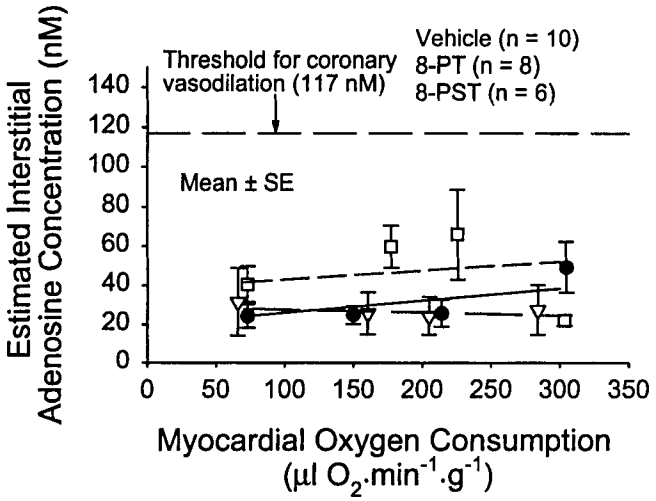

Figure 1. Relationship between estimated interstitial adenosine concentration and myocardial oxygen consumption during control vehicle and adenosine receptor blockade with 8-phenyltheophylline (8-PT) or 8-sulfophenyltheophylline (8-PST). The slopes of the regression lines do not differ significantly ($P = 0.63$, $R^2 = 0.4$), and the average slope did not differ significantly from zero ($P = 0.23$, $R^2 = 0.4$). The estimated interstitial adenosine concentration remained well below the threshold for coronary vasodilation and did not increase to overcome the competitive receptor blockade. This figure was reproduced with the permission of the American Physiological Society from Ref. 28.

Adenosine and Coronary Vasodilation during Ischemia. Although studies indicate that adenosine is not responsible for functional exercise hyperemia under normal physiological conditions, adenosine most likely contributes significantly to coronary vasodilation during exercise-induced ischemia (34). Studies in chronically instrumented dogs with a coronary stenosis (coronary perfusion pressure = 40 mm Hg) found that coronary vasodilation in response to exercise was significantly reduced by combined blockade of endogenous adenosine production with adenosine deaminase and adenosine receptors with 8-phenyltheophylline (34, 35). These findings indicate that cardiac adenosine release occurs during ischemia (5, 36–38). The critical oxygen tension for adenosine release in isolated cardiomyocytes was estimated to be ~3 mm Hg (37). Therefore, as long as changes in myocardial oxygen delivery adequately match changes in the rate of myocardial metabolism, adenosine release is not elevated and thus does not contribute to functional coronary hyperemia. However, if an imbalance between oxygen delivery and consumption is significant, such as in patients with a critical coronary stenosis, adenosine is released by the ischemic myocytes in an attempt to augment coronary blood flow and oxygen delivery.

In summary, experimental evidence does not support adenosine as the physiologic local metabolic vasodilatory metabolite that links coronary blood flow to myocardial metabolism. This evidence includes: i) Adenosine receptor blockade does not alter the relationship between coronary blood flow and myocardial oxygen consumption (17, 26, 28); ii) Coronary venous plasma adenosine concentration is little changed with exercise-induced increases in myocardial oxygen consumption (28, 39–41); iii) The estimated interstitial adenosine concentration remains well below the threshold value necessary for coronary vasodilation both at rest and during increases in myocardial oxygen consumption (27, 28); and iv) Adenosine receptor blockade does not augment coronary venous or estimated interstitial adenosine concentration to overcome the receptor blockade (27, 28). However, adenosine does act as a coronary vasodilator during pathophysiological conditions when the myocardium is ischemic.

K^+_{ATP} Channels

There is a class of potassium channels that can be regulated by intracellular ATP that are present in many tissues, including pancreatic β cells, skeletal muscle, brain, and smooth muscle (42). These channels are commonly identified by their response to the blocking agent glibenclamide. Glibenclamide is a member of the sulfonylurea class of compounds that have a high selectivity for K^+_{ATP} channels, and it has been shown to have a K_i for the channels found in cardiac and smooth muscle in the range of 5–20 μ*M* (48–50). These ATP-sensitive potassium (K^+_{ATP}) channels were identified in smooth muscle from mesenteric arteries by Standen *et al.* in 1989 (44). In 1992, Miyoshi *et al.* (45) identified K^+_{ATP} channels in cultured smooth muscle cells from porcine coronary arteries. Since that time, the role of these channels in the regulation of vessel diameter, particularly in coronary vessels, has been examined by numerous investigators.

K^+_{ATP} channels have been found to play a role in hypoxic coronary vasodilation (46, 47). Daut *et al.* (46) found that hypoxic coronary vasodilation in isolated perfused guinea pig hearts was blunted by glibenclamide. Coronary reactive hyperemia is also reduced during K^+_{ATP} channel blockade with glibenclamide (48–50). K^+_{ATP} channels are involved in adenosine-induced coronary vasodilation as shown by the ability of glibenclamide to inhibit this response (46, 49, 50, 51, 53–55). However, K^+_{ATP} channels are not necessary for coronary autoregulation (relatively constant flow with altered arterial perfusion pressure) as shown by Stepp *et al.* (55). Because hypoxia and ischemia result in adenosine release from the myocardium, as reviewed above, the blunting of hypoxic or ischemic coronary vasodilation by glibenclamide probably represents an inhibition of adenosine vasodilation.

The evidence for involvement of K^+_{ATP} channels in the maintenance of basal coronary blood flow is strong (50, 55–60). When K^+_{ATP} channels are inhibited by glibenclamide, coronary blood flow at rest is reduced between 12% and 25%, suggesting that these channels are at least partly responsible for maintaining vessel diameter during steady-state conditions.

However, the regulation of coronary blood flow during exercise or cardiac pacing is not dependent upon K^+_{ATP} channels (40, 50, 59, 61, 62). Although flow is reduced at rest when K^+_{ATP} channels are blocked by glibenclamide,

Richmond *et al.* (40) found that during exercise, the increase in flow is the same (3.5-fold) with or without K^+_{ATP} channel blockade. This is consistent with the results from Duncker *et al.* (50, 61, 62) who found a decrease in resting coronary blood flow in dogs but not an attenuation of flow during exercise. The combination of these results suggest that another factor must be responsible for the increase in coronary blood flow during exercise.

In summary, there is strong evidence that adenosine causes coronary vasodilation during ischemia or hypoxia and that K^+_{ATP} channels mediate the vasodilation. Although K^+_{ATP} channels are involved in regulating coronary vessel diameter at rest, they are not required during coronary autoregulation or for the increase in coronary blood flow that occurs during exercise.

Nitric Oxide

The coronary vascular endothelium modulates vascular resistance through the production of various vasoactive agents, including the endothelium-derived relaxing factor nitric oxide (63). Nitric oxide is formed from L-arginine by nitric oxide synthase and is continuously released by endothelial cells (64). Nitric oxide release is augmented by agonists such as acetylcholine and bradykinin (64–66) and also by mechanical stimulation such as shear stress (67–73), pulsatile flow (74), and axial strain (75).

Endothelial-derived nitric oxide is thought to be one of the factors controlling coronary blood flow both at rest and during exercise. However, inhibition of nitric oxide synthesis with arginine analogues results in either no change (39, 74, 76–85) or a small decrease (86–90) in coronary blood flow at rest and when myocardial oxygen consumption is elevated. Studies also consistently show that blockade of nitric oxide synthesis does not attenuate exercise-induced coronary vasodilation, but does decrease coronary venous oxygen tension at a given level of myocardial oxygen consumption (Fig. 2) (39, 76, 77, 79, 80, 83, 85). These findings are consistent with studies using either systemic (39, 77, 83, 85) or intracoronary infusions of arginine analogs (76, 79, 80) to inhibit nitric oxide synthesis, indicating that nitric oxide is not required for exercise-induced coronary vasodilation. However, these findings do indicate that nitric oxide exerts a tonic coronary vasodilator influence both at rest and during exercise-induced increases in myocardial oxygen consumption.

Nitric oxide has been shown to contribute to epicardial coronary dilation at rest in dogs (91–95) and humans (96, 97), and during increases in myocardial oxygen consumption in dogs (74, 85, 87, 8) and humans (86, 99). This effect of nitric oxide has been demonstrated by a significant reduction in epicardial coronary diameter when nitric oxide synthesis is inhibited. However, it is important to note that although epicardial coronary diameter was decreased in these studies by nitric oxide synthesis inhibition, coronary blood flow was not significantly altered, suggesting that a compensatory, downstream arteriolar dilation adequately

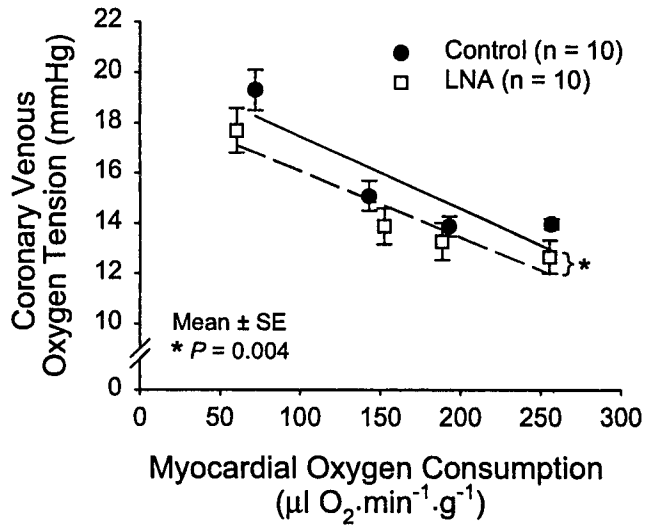

Figure 2. Relationship between coronary venous oxygen tension and myocardial oxygen consumption during control and nitric oxide synthesis inhibition with LNA. The slope of the relationship was unchanged by LNA ($P = 0.79$), indicating that nitric oxide is not required for local metabolic coronary vasodilator during exercise. The average coronary venous oxygen tension was significantly reduced by LNA ($P = 0.004$), indicating that nitric oxide exerts a tonic coronary vasodilator influence both at rest and during exercise. This figure was reproduced with the permission of Lippincott, Williams & Wilkins from Ref. 39.

compensated for the upstream, epicardial coronary constriction (100).

The findings of Bernstein *et al.* (77) and Traverse *et al.* (101) indicate that exercise-induced epicardial coronary vasodilation is mediated by an increase in endothelial-mediated nitric oxide production at high levels of myocardial oxygen consumption. The increased nitric oxide produced when myocardial oxygen consumption is significantly elevated is probably due to augmented shear stress that results from the high coronary flow rates (67–73). This hypothesis is supported by the findings of Van Bibber *et al.* (102) who found that nitric oxide synthesis inhibition attenuated norepinephrine-induced coronary vasodilation when coronary perfusion pressure was held constant, but did not affect coronary vasodilation to norepinephrine when coronary blood flow was held constant.

In summary, nitric oxide does not act as a local metabolic vasodilator in the usual sense because blockade of nitric oxide synthesis does not steepen the relationship between coronary venous oxygen tension and myocardial oxygen consumption (Fig. 2). However, nitric oxide does exert physiological effects within the coronary vascular tree, notably upstream dilation of epicardial coronary arteries, which acts to prevent excessive shear stress on coronary endothelial cells when flow is increased by downstream, arteriolar dilation.

Compensatory Control and Its Implications

A recurring theme in recent coronary literature is that there are multiple mechanisms of local metabolic coronary

blood flow control, and that when one mechanism is inhibited, another may increase in compensation (50, 62, 80, 103–105). The suggestion is that cardiac adenosine levels increase in compensation when either K^+_{ATP} channels or nitric oxide synthesis is inhibited. The reason for postulating multiple compensating mechanisms was the observation that the addition of an adenosine receptor antagonist to a prior K^+_{ATP} channel inhibition (50, 62, 80) or nitric oxide synthesis inhibition (103, 105) decreased coronary blood flow and/or depressed the relationship between coronary venous oxygen tension and myocardial oxygen consumption.

The hypothesis that adenosine increases to mediate local metabolic coronary vasodilation when either K^+_{ATP} channels (40, 59) or nitric oxide synthesis is inhibited (39) has been examined. Graded treadmill exercise was used to increase myocardial oxygen consumption in chronically instrumented dogs before and during inhibition of K^+_{ATP} channels with glibenclamide (40) or nitric oxide synthesis with *N*ω-nitro-L-arginine (LNA) (39). Cardiac interstitial adenosine concentration was estimated from arterial and coronary venous measurements using a previously tested mathematical model (32, 33). Inhibition of either K^+_{ATP} channels or nitric oxide synthesis at rest and during exercise did not result in a significant increase in coronary venous or estimated interstitial adenosine concentration. Furthermore, the estimated interstitial adenosine concentration remained well below the threshold necessary for coronary vasodilation with or without K^+_{ATP} channel (40, 59) or nitric oxide synthesis inhibition (39). These findings indicate that adenosine does not increase to mediate a compensatory local metabolic coronary vasodilation during exercise-induced increases in myocardial oxygen consumption.

An additional study by Tune *et al.* (106) examined the hypothesis of multiple compensating mechanisms of coronary flow control by combined inhibition of K^+_{ATP} channels (glibenclamide), nitric oxide synthesis (LNA), and adenosine receptors (8-phenyltheophylline). This triple blockade did not alter the myocardial oxygen consumption or coronary blood flow response to exercise, but it did significantly lower the coronary venous oxygen tension at a given level of myocardial oxygen consumption (Fig. 3). These results indicate that combined inhibition of K^+_{ATP} channels, nitric oxide synthesis, and adenosine receptors lowers the balance between myocardial oxygen delivery and consumption under resting conditions, but they also indicate that these factors are not required for local metabolic coronary vasodilation during exercise. In contrast, Ishibashi *et al.* (80) found that functional exercise coronary hyperemia and myocardial oxygen consumption were limited during exercise with triple blockade. The major differences between these studies are that glibenclamide and LNA were infused intravenously in the Tune *et al.* (106) study, and intracoronary infusion was used in the Ishibashi *et al.* (80) study. Intravenous infusion avoids direct intracoronary injection of the harsh alkaline vehicle that is required to get glibenclamide into solution and provides time for equilibration of the blocking agents in the circulation. A continuous intracoronary infusion is not suitable for steady-state measurements because recirculation of the blocking agents would result in ever increasing coronary concentrations, which might confound the measurement of myocardial oxygen consumption, a critical measurement in coronary studies. Aside from these methodological differences, it is unclear what may account for the differences between these investigations.

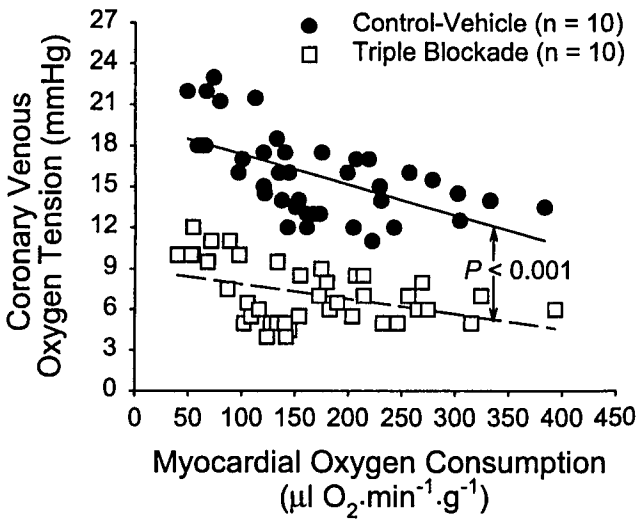

Figure 3. Relationship between coronary venous oxygen tension and myocardial oxygen consumption with and without triple blockade of K^+_{ATP} channels, nitric oxide synthesis, and adenosine receptors. Triple blockade significantly reduced coronary venous oxygen tension at rest and during exercise in a parallel manner ($P < 0.001$), but did not make the slope more negative. These findings indicate that inhibition of K^+_{ATP} channels, nitric oxide synthesis, and adenosine receptors lowers the balance between coronary blood flow and myocardial metabolism at rest, but that these factors are not required for exercise-induced coronary vasodilation. This figure was reproduced with the permission of the American Physiological Society from Ref. 106.

Although triple blockade did not decrease functional coronary exercise hyperemia in the Tune *et al.* (106) study, it did significantly elevate coronary venous and estimated interstitial adenosine concentrations when coronary venous oxygen tension fell to ~6 mm Hg during exercise (Fig. 4). The coronary venous oxygen tension of 6 mm Hg is consistent with a critical oxygen tension of 3 mm Hg for adenosine release observed in isolated *in vitro* cardiomyocytes (37), remembering that there must be an *in vivo* oxygen tension gradient from blood to tissue for diffusion to occur. Therefore, the triple blockade decreased resting coronary blood flow and the increase in myocardial oxygen consumption induced by exercise most likely resulted in subendocardial ischemia, thereby increasing cardiac adenosine release. However, the increase in adenosine levels was not sufficient to overcome the competitive receptor blockade and thus did not contribute to local metabolic coronary vasodilation.

In summary, K^+_{ATP} channels, nitric oxide, and adenosine do not act as local metabolic vasodilators in the usual

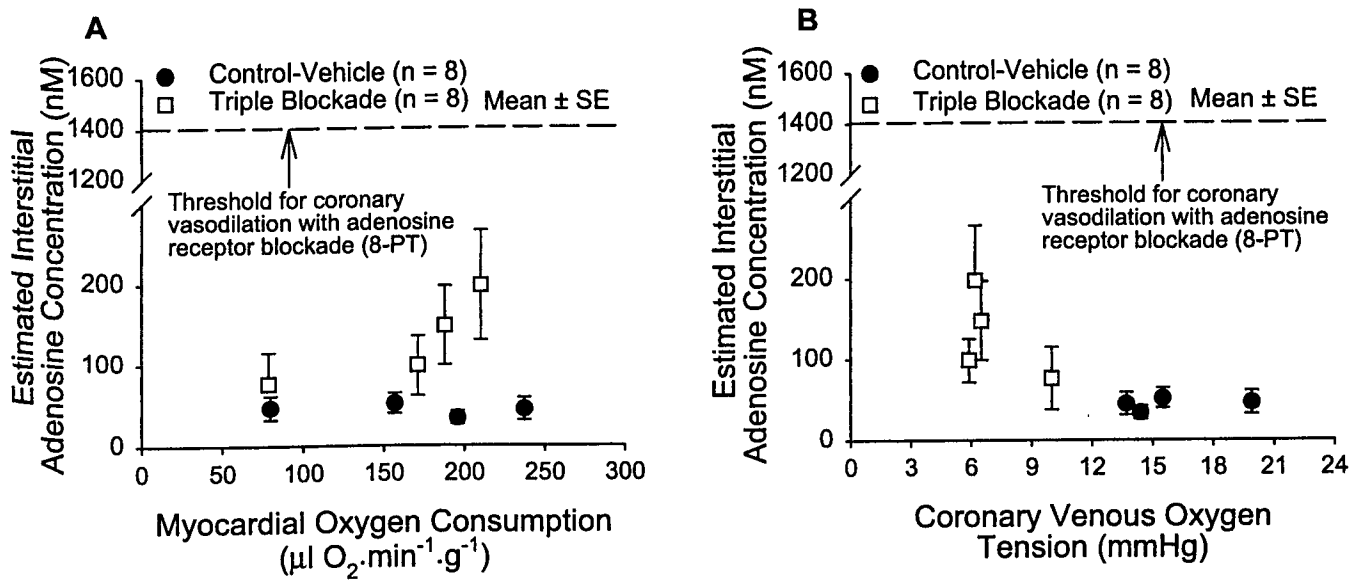

Figure 4. Effects of myocardial oxygen consumption (A) and coronary venous oxygen tension (B) on estimated interstitial adenosine concentration with and without triple blockade of K^+_{ATP} channels, nitric oxide synthesis, and adenosine receptors. Triple blockade increased the estimated interstitial concentration of adenosine as myocardial oxygen consumption was increased and as coronary venous oxygen tension was reduced. However, the estimated interstitial adenosine concentration remained well below the threshold concentration necessary for coronary vasodilation in the presence of adenosine receptor blockade with 8-phenyltheophylline (8-PT). This figure was reproduced with the permission of the American Physiological Society from Ref. 106.

sense of coupling coronary blood flow to myocardial metabolism and thus do not act as multiple compensating mechanisms of coronary flow control. However, K^+_{ATP} channels and nitric oxide do regulate the balance between oxygen supply and consumption under resting conditions.

Other Potential Mediators of Local Metabolic Vasodilation

Prostaglandins. Prostaglandins are metabolites of arachidonic acid that have been implicated as potential mediators of coronary blood flow control. Prostaglandins have been shown to be released into the coronary circulation during episodes of hypoxia (107), anoxia (108), and coronary artery occlusion (109). However, an important role of prostaglandins in local metabolic coronary vasodilation under normal physiological conditions has not been demonstrated. Inhibition of prostaglandin synthesis with indomethacin does not significantly affect resting coronary blood flow or attenuate exercise-induced coronary vasodilation (110). In addition, the relationship between coronary venous oxygen tension and myocardial oxygen consumption is unaltered by indomethacin, demonstrating that prostaglandins do not mediate functional coronary exercise hyperemia.

Other Potential Vasodilators. Other potential factors that may contribute to local metabolic coronary vasodilation include oxygen, carbon dioxide, potassium, ATP, and endothelium-derived hyperpolarizing factors (EDHFs). However, none of these factors have been examined during exercise-induced increases in myocardial oxygen consumption.

A depletion of oxygen or the accumulation of carbon dioxide are both stimuli for coronary vasodilation (111, 112). Broten *et al.* (113) developed a model of oxygen and carbon dioxide tension-induced changes in coronary vascular resistance and concluded that ~40% of the change in coronary blood flow during modest, pacing-induced increases in myocardial oxygen consumption could be accounted for by changes in coronary venous oxygen and carbon dioxide tensions. However, coronary venous carbon dioxide tension is little changed with exercise (28, 39–41), and the typical 4–6 mm Hg decrease in coronary venous oxygen tension observed during exercise cannot by itself account for the ~4-fold increase in coronary blood flow.

Potassium has been shown to be transiently elevated during pacing-induced increases in myocardial oxygen consumption (114) and may account for ~33% of the initial coronary vasodilator response to this stimulus. However, this transient elevation of potassium makes it an unlikely mechanism for steady-state increases in coronary blood flow associated with increased myocardial metabolism.

ATP and EDHFs have recently been the focus of several investigations of coronary flow regulation. ATP has been shown to be a potent vasodilator in a number of different experimental models, including isolated arteries and veins (115), coronary arteries (116), hamster cheek pouch (117), and isolated working rat hearts (118). ATP is most likely released locally by cardiomyocytes (119) and by red blood cells (120, 121) during reductions in oxygenation. EDHFs are released by coronary endothelial cells and they mediate vasodilation by hyperpolarizing underlying vascular smooth muscle cells (122, 125). It appears that a component of EDHFs are cytochrome P450-metabolites of arachidonic acid, epoxyeicosatrienoic acids (EETs) and hy-

droxyeicosatetraenoic acids (HETEs), both of which regulate coronary vascular tone (126–128). Although several studies have shown that ATP and EDHFs mediate coronary vascular relaxation, their role in local metabolic vasodilation during increases in myocardial metabolism has not been defined.

Adrenergic Control of Coronary Blood Flow

Activation of the sympathetic nervous system increases heart rate, cardiac contractility, and cardiac afterload. The resulting increase in myocardial oxygen consumption produces metabolic coronary vasodilation, which has been discussed above. This local metabolic vasodilation obscures the direct effects of sympathetic activation on coronary blood vessels. A further complication is that coronary vessels contain both α- and β-adrenoceptors, giving rise to the possibility for both adrenergic vasoconstriction and vasodilation.

α-Adrenoceptor-Mediated Coronary Vasoconstriction. One way to demonstrate direct α-adrenoceptor coronary vasoconstriction has been to activate sympathetic nerves while preventing metabolic vasodilation by blocking β-adrenoceptors. Sympathetic stimulation under these conditions results in a decrease in coronary blood flow (129–132), which can be blocked by α-adrenoceptor antagonists (130). Further proof that this is a direct vascular effect rather than a consequence of decreased metabolism is the observation that coronary venous oxygen tension falls under these conditions (133).

An alternate approach is to block coronary α-adrenoceptors during sympathetic activation. Under these conditions, one sees higher coronary blood flow or lower coronary vascular resistance at a given level of myocardial oxygen consumption compared with control conditions (134, 135). Comparing flow at the same oxygen consumption is essential because this controls for the degree of metabolic vasodilation. The α-adrenoceptor blockade experiment has been particularly useful in demonstrating α-adrenoceptor coronary vasoconstriction during exercise (136–141).

At first glance, α-adrenoceptor vasoconstriction during exercise seems to be potentially deleterious because it competes with metabolic coronary vasodilation at a time when myocardial oxygen consumption is greatly increased. The beneficial effect becomes apparent during periods of high coronary blood flow and tachycardia (such as during strenuous exercise). Under these conditions, the highly vasodilated subendocardium (which is only perfused during diastole) is vulnerable to underperfusion due to high myocardial compressive forces and short diastoles. Regional coronary α-adrenoceptor blockade during strenuous exercise in dogs increases total transmural coronary blood flow, but reduces subendocardial flow (139). The postulated mechanism is that α-adrenoceptor vasoconstriction stiffens the medium-sized intramyocardial coronary vessels, causing a decrease in intramyocardial vascular capacitance. This mechanism is supported by the observation that α-adrenoceptor activation by norepinephrine decreases wasteful antegrade-retrograde flow oscillation during the cardiac cycle (142).

An interesting aspect of α-adrenoceptor coronary vasoconstriction is that it seems to be confined to vessels greater than 100 μm in diameter both *in vitro* (143, 144) and *in vivo* (145). Recent studies suggest that vasoconstriction in vessels smaller than this might result not from stimulation of coronary α-adrenoceptors, but from α-receptor-mediated endothelin release from cardiac myocytes (146, 147). To date, the endothelin mechanism has only been demonstrated *in vitro* or during intracoronary infusion of high doses of α-adrenoceptor agonists. It remains to be determined whether it is active under physiological conditions such as exercise.

β-Adrenoceptor-Mediated Coronary Vasodilation. In the case of coronary α-adrenoceptors, it is possible to separate their influence from metabolic vasodilation via selective blockade of either α- or β-adrenoceptors. Direct sympathetic vasodilation of coronary vessels is difficult to separate from metabolic vasodilation because β-adrenoceptors on coronary vessels and cardiac cells are responsible for both actions. In terms of control theory, this means that coronary β-adrenoceptor vasodilation is a feed-forward mechanism that does not require an error signal. The same stimulus that increases myocardial oxygen consumption (sympathetic activation to increase heart rate and contractility) in this case simultaneously causes vasodilation. The term 'feed-forward' is often used when describing this process in order to distinguish it from local metabolic feedback vasodilation secondary to sympathetic activation.

The most direct way to separate feed-forward sympathetic vasodilation from metabolic vasodilation is to use isolated blood vessels. Small coronary arteries *in vitro* relax in response to catecholamines even without prior α-adrenoceptor blockade (143, 144). In the presence of α-adrenoceptor blockade, intracoronary norepinephrine injections during long diastoles (to avoid cardiac inotropic and chronotropic effects) produce vasodilation in anesthetized dog hearts (148). These results demonstrate the possibility for feed-forward β-adrenoceptor-mediated vasodilation, but demonstrating its presence in a beating heart is difficult. Testing for this phenomenon *in vivo* would be simple if it were possible to selectively block either coronary or myocardial β-adrenoceptors. However, studies have found both β_2- and β_1-adrenoceptors on coronary vessels (148–154), making this approach problematic.

Feed-forward sympathetic coronary vasodilation *in vivo* was first clearly demonstrated in anesthetized dogs using pacing tachycardia as a stimulus to produce a relatively pure metabolic vasodilation (148). This was compared with an intracoronary infusion of norepinephrine during α-adrenoceptor blockade, which produced both metabolic and feed-forward β-adrenoceptor vasodilation. Because these two interventions produced the same increase in myocardial oxygen consumption, the metabolic components were presumably equal and any differences were due

to feed-forward β-adrenoceptor vasodilation. Norepinephrine plus α-adrenoceptor blockade resulted in significantly higher coronary sinus oxygen tension and coronary blood flow than pacing, demonstrating the presence of a feed-forward vasodilation. This approach has subsequently been adapted to demonstrate feed-forward sympathetic coronary vasodilation during exercise (41, 155). In this case, the 'metabolic only' vasodilation is produced by exercise during combined α- and β-adrenoceptor blockade. This is compared with exercise with only α-adrenoceptor blockade. When coronary venous oxygen tension is plotted versus myocardial oxygen consumption, oxygen tension does not fall significantly during α-adrenoceptor blockade, but it does fall steeply during α+β-receptor blockade. The large difference in slopes under these two conditions demonstrates the presence of feed-forward sympathetic coronary vasodilation during exercise (Fig. 5).

A drawback to these pharmacologic demonstrations of feed-forward β-adrenoceptor vasodilation (and α-adrenoceptor vasoconstriction) is that blockade of either α- or β-adrenoceptors tends to increase circulating catecholamine concentrations, particularly during exercise. Exercise during α-adrenoceptor blockade, for example, leads to higher norepinephrine concentrations that may exaggerate feed-forward β-adrenoceptor coronary vasodilation (156–158). One way around this problem is to estimate the vascular effects of the cardiac catecholamine concentrations measured during normal exercise without adrenergic blockade. In the case of epinephrine, this approach is relatively straightforward because epinephrine from the adrenal glands reaches the heart via the arterial plasma. When epinephrine is infused into resting dogs to mimic arterial epinephrine concentrations achieved during strenuous exercise, there is little increase (6%) in myocardial oxygen consumption and no change in coronary sinus oxygen tension (158). Therefore, circulating epinephrine has little direct coronary vascular effect during exercise.

In the case of norepinephrine, the plasma concentrations are not immediately informative because the sympathetic nerves deliver norepinephrine directly into the cardiac interstitial space. The interstitial norepinephrine concentration acting on coronary arterioles can be estimated from arterial and coronary venous plasma concentrations, coronary plasma flow, and the coronary capillary permeability to norepinephrine (159). In strenuously exercising dogs, the interstitial concentration was estimated to be 12 n*M* (158). Norepinephrine dose-response data in isolated coronary resistance vessels (144) indicate that this concentration should increase arteriolar conductance by ~67%, which means that feed-forward β-adrenoceptor vasodilation can account for ~25% of the increase in coronary blood flow in exercising dogs (158).

Integrating α-Adrenoceptor Vasoconstriction with β-Adrenoceptor Vasodilation. It is apparent that both α-vasoconstriction and β-vasodilation occur simultaneously in the coronary circulation during sympathetic ac-

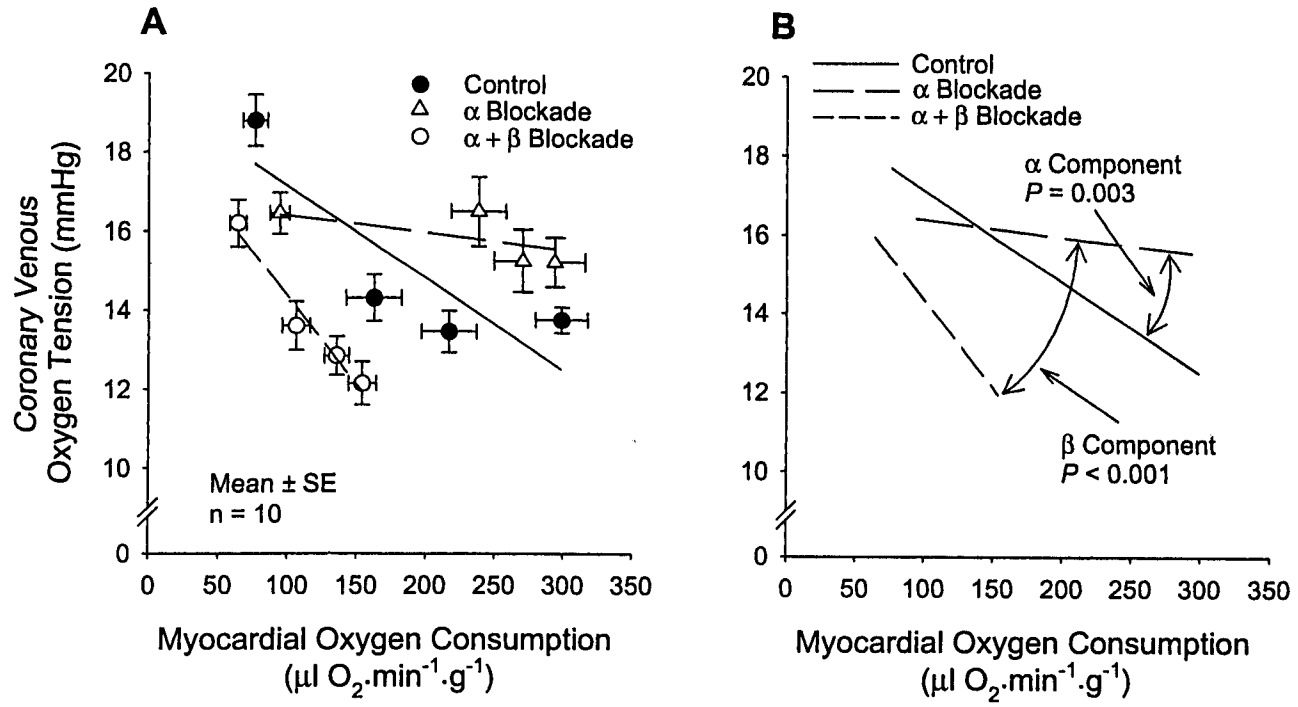

Figure 5. Mean values of coronary venous oxygen tension at rest and during three levels of exercise plotted as a function of myocardial oxygen consumption with individual regression lines for control, α-blockade with phentolamine, and α+β blockade with phentolamine and propranolol (A). Regression lines are repeated with significant differences in slopes indicated (B). The steep slope of combined α+β blockade indicates a modest match by local metabolic factors in the absence of adrenergic mechanisms. The difference in the slopes between α+β blockade and α-blockade alone demonstrates feed-forward β-adrenoceptor-mediated coronary vasodilation. The difference in the slopes between control and α-blockade demonstrates the well-established feed-forward α-adrenoceptor-mediated coronary vasoconstriction. This figure was reproduced with the permission of the American Physiological Society from Ref. 41.

tivation. These effects may not be as antagonistic as they at first appear. α-Adrenoceptor vasoconstriction is predominantly a large vessel (>100 μm) phenomenon, whereas small vessels only relax in response to norepinephrine (143–145). This may be explained by the distribution of α- and β-adrenoceptors along the coronary arterial tree (160, 161). This reciprocal gradient in adrenoceptors favors sympathetic vasodilation in resistance vessels and vasoconstriction in distribution vessels. Therefore, α-adrenoceptor vasoconstriction and β-adrenoceptor vasodilation appear to be spatially distributed so as to increase coronary blood flow (β) and at the same time improve transmural flow distribution (α). The feed-forward β-adrenoceptor vasodilation accounts for ~25% of the increase in coronary blood flow observed during exercise.

Pathophysiology

Studies indicate that control of coronary blood flow is altered at rest and during exercise under pathophysiological conditions such as hypertension, diabetes, and heart failure. However, it is unclear whether these conditions lead to any imbalance between oxygen delivery and myocardial oxygen consumption. In addition, the specific mechanism(s) underlying this impairment remain to be elucidated.

Hypertension. Hypertension may be accompanied by increased sympathetic nerve activity and/or alterations in adrenergic receptor sensitivity, which may adversely affect coronary flow regulation (162). Increased vascular reactivity to vasoconstrictor substances has been observed in clinical hypertension (163, 164) and in animals models of hypertension (165, 166). Gwirtz (162) determined that enhanced α_1-adrenoceptor-mediated coronary vasoconstriction limits coronary blood flow at rest and during exercise in dogs with renovascular hypertension. However, whether this enhanced adrenergic constriction is sufficient to limit the balance between coronary blood flow and myocardial metabolism is presently unknown. In addition, it is also unclear if vasodilator mechanisms are altered or impaired by chronic hypertension.

Diabetes Mellitus. Dysfunction of the coronary circulation could, in part, be responsible for the increased incidence of myocardial ischemia, infarction, and sudden cardiac death among patients with diabetes mellitus (167, 168). Coronary flow reserve (169–171) and pacing-induced coronary vasodilation (170) are reduced in diabetic patients with no evidence of coronary artery disease. Pharmacologic and pacing-induced increases in coronary blood flow are also attenuated in experimental diabetes (172–174). However, there has not been an examination of whether coronary blood flow control is impaired sufficiently to decrease the balance between coronary blood flow and myocardial oxygen consumption during exercise-induced increases in myocardial metabolism.

Heart Failure. The literature on coronary blood flow control in heart failure is discordant. Studies have reported a decrease (175) or no change (176, 177) in resting coronary blood flow from patients with dilated cardiomyopathy and/or congestive heart failure. Investigations in animals with experimental, pacing-induced heart failure have reported both increased (178–180) and decreased (181–184) coronary blood flow. These conflicting results are most likely due to differing levels of myocardial oxygen consumption, the primary determinant of coronary flow. Traverse *et al.* (184) reported that pacing-induced heart failure in dogs decreased myocardial oxygen consumption and coronary blood flow both at rest and during exercise, but did not appear to result in an imbalance between myocardial oxygen delivery and metabolism. This finding is consistent with an earlier study in patients with congestive heart failure in which myocardial oxygen consumption was increased by dobutamine (185). These studies suggest that mechanisms that regulate coronary control in response to increases in myocardial metabolism appear to be intact during heart failure, and that the diminished coronary blood flow per gram observed during heart failure is secondary to a decreased myocardial oxygen consumption.

Conclusions

The mediator or mediators of local metabolic coronary vasodilation remain unknown. Numerous studies that have examined the role of adenosine, K^+_{ATP} channels, and nitric oxide in coronary flow control have produced little evidence that any of these factors contribute to metabolic vasodilation during increases in myocardial oxygen consumption. However, nitric oxide and K^+_{ATP} channels do contribute to the regulation of coronary vascular tone under normal, resting conditions. Taken together, these factors do not result in a redundant compensating mechanism of coronary blood flow control during exercise. Prostaglandins and potassium are not important in steady-state coronary flow regulation during exercise. Other factors such as ATP and EDHFs have been implicated as possible local metabolic coronary vasodilators, but have not been examined during exercise hyperemia.

Feed-forward β-adrenoceptor-mediated coronary vasodilation has been shown to account for ~25% of coronary vasodilation observed during exercise. This dilation is a direct effect of norepinephrine's action on small coronary arterioles. Norepinephrine-induced α-adrenoceptor-mediated coronary vasoconstriction reduces upstream vessel compliance and lessens wasteful to-and-fro flow in the coronary arterial tree. This paradoxical effect of proximal coronary artery vasoconstriction during exercise helps to maintain blood flow to the vulnerable subendocardium when heart rate, myocardial contractility, and oxygen consumption are elevated.

The fact that β-adrenoceptor-mediated coronary vasodilation accounts for approximately one-quarter of exercise hyperemia means that local metabolic and/or endothelium-dependent dilation must account for the other three-quarters of exercise-induced vasodilation. This distribution of coronary flow regulation may be altered under pathophysiologic

conditions such as in hypertension, diabetes mellitus, or heart failure.

1. Berne RM. Regulation of coronary blood flow. Physiol Rev **44:**1–29, 1964.
2. Feigl EO. Coronary Physiology. Physiol Rev **63:**1–205, 1983.
3. Laughlin MH, Korthuis RJ, Duncker DJ, Bache RJ. Control of coronary blood flow to cardiac and skeletal muscle during exercise. In: Rowell LB, Shepherd JT, Eds. Exercise, Regulation and Integration of Multiple Systems. Bethesda, MD: American Physiological Society 705–769, 1996.
4. Gorman MW, He M-X, Sparks HV. Control of the coronary circulation. In: Sperelakis N, Ed. Physiology and Pathophysiology of the Heart (3rd ed). Dordrecht, The Netherlands: Kluwer Academic Publishers, pp1087–1107, 1995.
5. Berne RM. Cardiac nucleotides in hypoxia: possible role in regulation of coronary blood flow. Am J Physiol **204:**317–322, 1963.
6. Gerlach E, Beuticke B, Dreisbach RH. Der nucleotide-abbau im herzmuskel bei sauerstoffmangel und seine mogliche bedeutung fur die coronardurchbluntung. Naturwissenschaften **50:**228–229, 1963.
7. Berne RM. The role of adenosine in the regulation of coronary blood flow. Circ Res **47:**807–813, 1980.
8. Bröten TP, Romson JL, Fullerton DA, Van Winkle DM, Feigl EO. Synergistic action of myocardial oxygen and carbon dioxide in controlling coronary blood flow. Circ Res **68:**531–542, 1991.
9. Drake-Holland AJ, Laird JD, Noble MIM, Spaan JAE, Vergoesen I. Oxygen and coronary vascular resistance during autoregulation and metabolic vasodilation in the dog. J Physiol **348:**285–300, 1984.
10. Watkinson WP, Foley DH, Rubio R, Berne RM. Myocardial adenosine formation with increased cardiac performance in the dog. Am J Physiol Heart Circ Physiol **236:**H13–H21, 1979.
11. Bacchus AN, Ely SW, Knabb RM, Rubio R, Berne RM. Adenosine and coronary blood flow in conscious dogs during normal physiological stimuli. Am J Physiol Heart Circ Physiol **243:**H628–H633, 1982.
12. Jones CE, Hurst TW, Randall JR. Effect of aminophylline on coronary functional hyperemia and myocardial adenosine. Am J Physiol Heart Circ Physiol **243:**H480–H487, 1982.
13. McKenzie JE, Steffen RP, Haddy FJ. Relationships between adenosine and coronary resistance in conscious exercising dogs. Am J Physiol Heart Circ Physiol **242:**H24–H29, 1982.
14. Manfredi JP, Sparks HV. Adenosine's role in coronary vasodilation induced by atrial pacing and norepinephrine. Am J Physiol Heart Circ Physiol **243:**H536–H545, 1982.
15. Knabb RM, Ely SW, Bacchus AN, Rubio R, Berne RM. Consistent parallel relationships among myocardial oxygen consumption, coronary blood flow, and pericardial infusate adenosine concentration with various interventions and β blockade in the dog. Circ Res **53:**33–41, 1983.
16. Ely SW, Knabb RM, Bacchus AN, Rubio R, Berne RM. Measurements of coronary plasma and pericardial infusate adenosine concentrations during exercise in conscious dogs: relationship to myocardial oxygen consumption and coronary blood flow. J Mol Cell Cardiol **15:**673–683, 1983.
17. Bache RJ, Dai X-Z, Schwartz S, Homans DC. Role of adenosine in coronary vasodilation during exercise. Circ Res **62:**846–853, 1988.
18. Gidday JM, Hill HE, Rubio R, Berne RM. Estimates of left ventricular interstitial fluid adenosine during catecholamine stimulation. Am J Physiol Heart Circ Physiol **254:**H207–H216, 1988.
19. Edlund A, Sollevi A, Wennmalm A. The role of adenosine and prostacyclin in coronary flow regulation in healthy man. Acta Physiol Scand **135:**39–46, 1989.
20. Deussen A, Walter C, Borst M, Schrader J. Transmural gradient of adenosine in canine heart during functional hyperemia. Am J Physiol Heart Circ Physiol **260:**H671–H680, 1991.
21. Headrick JP, Ely SW, Matherne GP, Berne RM. Myocardial adenosine, flow, and metabolism during adenosine antagonism and adrenergic stimulation. Am J Physiol Heart Circ Physiol **264:**H61–H70, 1993.
22. Edlund A, Sollevi A. Theophylline increases coronary vascular tone in humans: evidence for a role of endogenous adenosine in flow regulation. Acta Physiol Scand **155:**303–311, 1995.
23. Edlund A, Conradsson T, Sollevi A. A role for adenosine in coronary vasoregulation in man. Effects of theophylline and enprofylline. Clin Physiol **15:**623–636, 1995.
24. Mallet RT, Lee S-C, Downey HF. Endogenous adenosine increases oxygen utilization efficiency in isoprenaline-stimulated canine myocardium. Cardiovasc Res **31:**102–116, 1996.
25. Van Bibber R, Stepp DW, Kroll K, Feigl EO. The role of adenosine in norepinephrine-induced coronary vasodilation. Am J Physiol Heart Circ Physiol **273:**H557–H565, 1997.
26. Duncker DJ, Stubenitsky R, Verdouw PD. Role of adenosine in the regulation of coronary blood flow in swine at rest and during treadmill exercise. Am J Physiol Heart Circ Physiol **275:**H1663–H1672, 1998.
27. Yada T, Richmond KN, Van Bibber R, Kroll K, Feigl EO. Role of adenosine in local metabolic coronary vasodilation. Am J Physiol Heart Circ Physiol **276:**H1425–H1433, 1999.
28. Tune JD, Richmond KN, Gorman MW, Olsson RA, Feigl EO. Adenosine is not responsible for local metabolic control of coronary blood flow in dogs during exercise. Am J Physiol Heart Circ Physiol **278:**H74–H84, 2000.
29. Bassingthwaighte JB. Interstitial adenosine: the measurement, the interpretation. J Mol Cell Cardiol **24:**337–346, 1992.
30. Heller LJ, Dole WP, Mohrman DE. Adenosine receptor blockade enhances isoproterenol-induced increases in cardiac interstitial adenosine. J Mol Cell Cardiol **23:**887–898, 1991.
31. McKenzie JE, Steffen RP, Haddy FJ. Effect of theophylline on adenosine production in the canine myocardium. Am J Physiol Heart Circ Physiol **252:**H204–H210, 1987.
32. Kroll K, Stepp DW. Adenosine kinetics in the canine coronary circulation. Am J Physiol Heart Circ Physiol **270:**H1469–H1483, 1996.
33. Stepp DW, Van Bibber R, Kroll K, Feigl EO. Quantitative relation between interstitial adenosine concentration and coronary blood flow. Circ Res **79:**601–610, 1996.
34. Laxson DD, Homans DC, Bache RJ. Inhibition of adenosine-mediated coronary vasodilation exacerbates myocardial ischemia during exercise. Am J Physiol Heart Circ Physiol **265:**H1471–H1477, 1993.
35. Duncker DJ, Laxson DD, Lindstrom P, Bache RJ. Endogenous adenosine and coronary vasoconstriction in hypoperfused myocardium during exercise. Cardiovasc Res **27:**1592–1597, 1993.
36. Bardenheuer H, Schrader J. Supply-to-demand ratio for oxygen determine formation of adenosine by the heart. Am J Physiol Heart Circ Physiol **250:**H173–H180, 1986.
37. Stumpe T, Schrader J. Phosphorylation potential, adenosine formation, and critical PO_2 in stimulated rat cardiomyocytes. Am J Physiol Heart Circ Physiol **273:**H756–H766, 1997.
38. Zhang J, Ugurbil K, From AH, Bache RJ. Myocardial oxygenation and high-energy phosphate levels during graded coronary hypoperfusion. Am J Physiol Heart Circ Physiol **280:**H318–H326, 2001.
39. Tune JD, Richmond KN, Gorman MW, Feigl EO. Role of nitric oxide and adenosine in control of coronary blood flow in exercising dogs. Circulation **101:**2942–2948, 2000.
40. Richmond KN, Tune JD, Gorman MW, Feigl EO. Role of K^+_{ATP} channels and adenosine in the control of coronary blood flow during exercise. J Appl Physiol **89:**529–536, 2000.
41. Gorman MW, Tune JD, Richmond KN, Feigl EO. Feedforward sympathetic coronary vasodilation in exercising dogs. J Appl Physiol **89:**1892–1902, 2000.
42. Ashcroft SJH, Ashcroft FM. Properties and functions of ATP-sensitive K-channels. Cell Signal **2:**197–214, 1990.
43. Nichols CG, Lederer W. Adenosine triphosphate-sensitive potassium channels in the cardiovascular system. Am J Physiol Heart Circ Physiol **261:**H1675–H1686, 1991.
44. Standen NB, Quayle JM, Davies NW, Brayden JE Huang Y, Nelson MT. Hyperpolarizing vasodilators activate ATP-sensitive K^+ channels in arterial smooth muscle. Science **245:**177–180, 1989.
45. Miyoshi Y, Nakaya Y, Wakalsuki T, Nakaya S, Fugino K, Saito K, Inoue I. Endothelin blocks ATP-sensitive K^+ channels and depolarizes smooth muscle cells of porcine coronary artery. Circ Res **70:**612–616, 1992.
46. Daut J, Maier-Rudolph W, Beckerath NV, Mehrke G, Gunther K, Goedel-Meinen L. Hypoxic dilation of coronary arteries is mediated by ATP-sensitive potassium channels. Science **247:**1341–1344, 1990.
47. Nakhostine N, Lamontagne D. Contribution of prostaglandins in hyp-

oxia-induced vasodilation in isolated rabbit hearts. Relation to adenosine and KATP channels. Pflugers Arch **428:**526–532, 1994.
48. Aversano T, Ouyang P, Silverman H. Blockade of the ATP-sensitive potassium channel modulates reactive hyperemia in the canine coronary circulation. Circ Res **69:**618–622, 1991.
49. Clayton FC, Hess TA, Smith MA, Grover GJ. Coronary reactive hyperemia and adenosine-induced vasodilation are mediated partially by a glyburide-sensitive mechanism. Pharmacology **44:**92–100, 1992.
50. Duncker DJ, Van Zon NS, Pavek TJ Herlinger SK, Bache RJ. Endogenous adenosine mediates coronary vasodilation during exercise after K^+_{ATP} channel blockade. J Clin Invest **95:**285–295, 1995.
51. Akatsuka Y, Egashira K, Katsuda Y, Narishige T, Ueno H, Shimokawa H, Takeshita A. ATP-sensitive potassium channels are involved in adenosine A(2) receptor mediated coronary vasodilation in the dog. Cardiovasc Res **28:**906–911, 1994.
52. Belloni FL, Hintze TH. Glibenclamide attenuates adenosine-induced bradycardia and coronary vasodilation. Am J Physiol Heart Circ Physiol **261:**H720–H727, 1991.
53. Niiya K, Uchida S, Tsuji T, Olsson RA. Glibenclamide reduces the coronary vasoactivity of adenosine receptor agonists. J Pharmacol Exp Ther **271:**14–19, 1994.
54. Orito K, Satoh K, Taira N. Involvement of ATP-sensitive K^+ channels in the sustained coronary vasodilator response to adenosine in dogs. Eur J Pharmacol **231:**183–198, 1993.
55. Stepp DW, Kroll K, Feigl EO. K^+_{ATP} channels and adenosine are not necessary for coronary autoregulation. Am J Physiol Heart Circ Physiol **273:**H1299–H1308, 1997.
56. Dankelman J, Van der Ploeg DPB, Spaan JAE. Glibenclamide decelerates the responses of coronary regulation in the goat. Am J Physiol Heart Circ Physiol **266:**H1715–H1721, 1994.
57. Imamura Y, Tomoike H, Narishige T, Takahashi T, Kasuya H, Takeshita A. Glibenclamide decreases basal coronary blood flow in anesthetized dogs. Am J Physiol Heart Circ Physiol **263:**H399–H404, 1992.
58. Mori H, Chujo M, Tanaka E, Yamakawa A Shinozaki Y, Mohamed M-U, Nakazawa H. Modulation of adrenergic coronary vasoconstriction via ATP-sensitive potassium channels. Am J Physiol Heart Circ Physiol **268:**H1077–H1085, 1995.
59. Richmond KN, Tune JD, Gorman MW, Feigl EO. Role of K^+_{ATP} channels in local metabolic coronary vasodilation. Am J Physiol Heart Circ Physiol **277:**H2115–H2123, 1999.
60. Samaha FF, Heineman FW, Ince D, Fleming J, Balaban RS. ATP-sensitive potassium channel is essential to maintain basal coronary vascular tone in vivo. Am J Physiol Cell Physiol **262:**C1220–C1227, 1992.
61. Duncker DJ, Van Zon NS, Altman JD, Pavek TJ, Bache RJ. Role of K^+_{ATP} channels in coronary vasodilation during exercise. Circulation **88:**1245–1253, 1993.
62. Duncker DJ, Van Zon NA, Ishibashi Y, Bache R. Role of K^+_{ATP} channels and adenosine in the regulation of coronary blood flow during exercise with normal and restricted coronary blood flow. J Clin Invest **97:**996–1009, 1996.
63. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature **288:**373–376, 1980.
64. Moncada S, Palmer RMJ, Higg EA. Nitric oxide: Physiology, pathophysiology, and pharmacology. Pharmacol Rev **43:**109–142, 1991.
65. Amezcua JL, Palmer RMJ, de Souza BM, Moncada S. Nitric oxide synthesis from L-arginine regulates vascular tone in the coronary circulation of the rabbit. Br J Pharmacol **97:**1119–1124, 1989.
66. Pelc LR, Gross GJ, Warltier DC. Mechanism of coronary vasodilation produced by bradykinin. Circulation **83:**2048–2056, 1991.
67. Hintze TH, Vatner SF. Reactive dilation of large coronary arteries in conscious dogs. Circ Res **84:**50–57, 1984.
68. Busse R, Pohl U, Luckhoff A. Mechanisms controlling the production of endothelial autocoids. Z Kardiol **78:**64–69, 1989.
69. Kuo L, Davis MJ, Chilian WM. Endothelium-dependent, flow-induced dilation of isolated coronary arterioles. Am J Physiol Heart Circ Physiol **259:**H1063–H1070, 1990.
70. Buga GM, Gold ME, Fukuto JM, Ignarro LJ. Shear stress-induced release of nitric oxide from endothelial cells grown on beads. Hypertension **17:**187–193, 1991.
71. Lamontagne D, Pohl U, Busse R. Mechanical deformation of vessel wall and shear stress determine the basal release of endothelium-derived relaxing factor in the intact rabbit coronary vascular bed. Circ Res **70:**123–130, 1992.
72. Koller A, Kaley G. Role of shear stress and endothelial prostaglandins in flow- and viscosity-induced dilation of arterioles in vitro. Circ Res **72:**1276–1284, 1993.
73. Stepp DW, Nishikawa Y, Chilian WM. Regulation of shear stress in the canine coronary microcirculation. Circulation **100:**1555–1561, 1999.
74. Canty JM Jr, Schwartz JS. Nitric oxide mediates flow-dependent epicardial coronary vasodilation to changes in pulse frequency but not mean flow in conscious dogs. Circulation **89:**375–384, 1994.
75. Awolesi MA, Sessa WC, Sumpio BE. Cyclic strain upregulates nitric oxide synthase in cultured bovine aortic endothelial cells. J Clin Invest **96:**1449–1454, 1995.
76. Altman JD, Kinn J, Duncker DJ, Bache RJ. Effect of inhibition of nitric oxide formation on coronary blood flow during exercise in the dog. Cardiovasc Res **28:**119–124, 1994.
77. Bernstein RD, Ochoa FY, Xu X, Forfia P, Shen W, Thompson CI, Hintze TH. Function and production of nitric oxide in the coronary circulation of the conscious dog during exercise. Circ Res **79:**840–848, 1996.
78. Davis CAI, Sherman AJ, Yaroshenko Y, Harris KR, Hedjbeli S, Parker MA, Klocke FJ. Coronary vascular responsiveness to adenosine is impaired additively by blockade of nitric oxide synthesis and a sulfonylurea. J Am Coll Cardiol **31:**816–822, 1998.
79. Duncker DJ, Bache RJ. Inhibition of nitric oxide production aggravates myocardial hypoperfusion during exercise in the presence of a coronary artery stenosis. Circ Res **74:**629–640, 1994.
80. Ishibashi Y, Duncker DJ, Zhang J, Bache RJ. ATP-sensitive K^+ channels, adenosine, and nitric oxide-mediated mechanisms account for coronary vasodilation during exercise. Circ Res **82:**346–359, 1998.
81. Parent R, Al-Obaidi M, Lavallee M. Nitric oxide formation contributes to β-adrenergic dilation of resistance coronary vessels in conscious dogs. Circ Res **73:**241–251, 1993.
82. Parent R, Pare R, Lavallee M. Contribution of nitric oxide to dilation of resistance coronary vessels in conscious dogs. Am J Physiol Heart Circ Physiol **262:**H10–H16, 1992.
83. Shen W, Lundborg M, Wang J, Stewart JM, Xu X, Ochoa M, Hintze TH. Role of EDRF in the regulation of regional blood flow and vascular resistance at rest and during exercise in conscious dogs. J Appl Physiol **77:**165–172, 1994.
84. Smith TP Jr, Canty JM Jr. Modulation of coronary autoregulation responses by nitric oxide: evidence for flow-dependent resistance adjustments in conscious dogs. Circ Res **73:**232–240, 1993.
85. Wang J Wolin MS, Hintze TH. Chronic exercise enhances endothelium-mediated dilation of epicardial coronary artery in conscious dogs. Circ Res **73:**829–838, 1993.
86. Egashira K, Katsuda Y, Mohri M, Kuga T, Tagawa T, Kubota T, Hirakawa Y, Takeshita A. Role of endothelium-derived nitric oxide in coronary vasodilation induced by pacing tachycardia in humans. Circ Res **79:**331–335, 1996.
87. Embrey RP, Brooks LA, Dellsperger KC. Mechanism of coronary microvascular responses to metabolic stimulation. Cardiovasc Res **35:**148–157, 1997.
88. Maekawa K, Saito D, Obayashi N, Uchida S, Haraoka S. Role of endothelium-derived nitric oxide and adenosine in functional myocardial hyperemia. Am J Physiol Heart Circ Physiol **267:** H166–H177, 1994.
89. Matsunaga T, Okumura K, Tsunoda R, Tayama S, Tabuchi T, Yasue H. Role of adenosine in regulation of coronary flow in dogs with inhibited synthesis of endothelium-derived nitric oxide. Am J Physiol Heart Circ Physiol **270:**H427–H434, 1996.
90. Nishikawa Y, Kanki H, Ogawa S. Role of nitric oxide in coronary vasomotion during handgrip exercise. Am Heart J **134:**967–973, 1997.
91. Chu A, Chambers DE, Lin C-C, Kuehl WD, Cobb FR. Nitric oxide modulates epicardial coronary basal vasomotor tone in awake dogs. Am J Physiol Heart Circ Physiol **258:**H1250–H1254, 1990.
92. Chu A, Chanber DE, Lin C-C, Kuehl WD, Palmer RMJ, Moncada S, Cobb FR. Effects of inhibition of nitric oxide formation on basal vasomotion and endothelium-dependent responses of the coronary arteries in awake dogs. J Clin Invest **87:**1964–1968, 1991.
93. Hamdad N, Ming Z, Parent R, Lavallee M. β_2-Adrenergic dilation of

conductance coronary arteries involves flow-dependent NO formation in conscious dogs. Am J Physiol Heart Circ Physiol **271:**H1926–H1937, 1996.
94. Jones CJH, DeFily DV, Patterson JL, Chilian WM. Endothelium-dependent relaxation competes with α_1- and α_2-adrenergic constriction in the canine epicardial coronary microcirculation. Circulation **87:**1264–1274, 1993.
95. Parent R, Hamdad N, Ming Z, Lavallee M. Contrasting effects of blockade of nitric oxide formation on resistance and conductance vessels in conscious dogs. Cardiovasc Res **31:**555–567, 1996.
96. Lefroy DC, Crake T, Uren NG, Davies GJ, Maseri A. Effect of inhibition of nitric oxide synthesis on epicardial coronary artery caliber and coronary blood flow in humans. Circulation **88:**43–54, 1993.
97. Nishikawa Y, Ogawa S. Importance of nitric oxide in the coronary artery at rest and during pacing in humans. J Am Coll Cardiol **29:**85–92, 1997.
98. Berdeaux A, Ghaleb B, Dubois-Rande JL Vigue B, La Rochelle CD, Hittinger L, Giudicelli JF. Role of vascular endothelium in exercise-induced dilation of large epicardial coronary arteries in conscious dogs. Circulation **89:**2799–2808, 1994.
99. Quyyumi AA, Dakak N, Andrews NP, Gilligan DM, Panza JA, Cannon RO. Contribution of nitric oxide to metabolic coronary vasodilation in the human heart. Circulation **92:**320–326, 1995.
100. Jones CJH, Kuo L, Davis MJ, DeFily DV, Chilian WM. Role of nitric oxide in the coronary microvascular responses to adenosine and increased metabolic demand. Circulation **91:**1807–1813, 1995.
101. Traverse JH, Wang YL, Du R, Nelson D, Lindstrom P, Archer SL, Gong G, Bache RJ. Coronary nitric oxide production in response to exercise and endothelium-dependent agonist. Circulation **101:**2526–2531, 2000.
102. Van Bibber R, Traub O, Kroll K, Feigl EO. EDRF and norepinephrine-induced vasodilation in the canine coronary microcirculation. Am J Physiol Heart Circ Physiol **268:**H1973–H1981, 1995.
103. Matsunaga T, Okumura K, Tsunoda R, Tayama S, Tabuchi T, Yasue H. Role of adenosine in regulation of coronary flow in dogs with inhibited synthesis of endothelium-derived nitric oxide. Am J Physiol Heart Circ Physiol **270:**H427–H434, 1996.
104. Minamino T, Kitakaze M, Node K, Funaya H, Hori M. Inhibition of nitric oxide synthesis increases adenosine production via an extracellular pathway through activation of protein kinase C. Circulation **96:**1586–1592, 1997.
105. Tayama S, Okumura K, Matsunaga T, Tsunoda R, Tabuchi T, Iwasa A, Yasue H. Influence of chronic nitric oxide inhibition of coronary blood flow regulation: a study of the role of endogenous adenosine in anesthetized, open-chest dogs. Jpn Circ J **62:**371–378, 1998.
106. Tune JD, Richmond KN, Gorman MW, Feigl EO. K^+_{ATP} channels, nitric oxide, and adenosine are not required for local metabolic coronary vasodilation. Am J Physiol Heart Circ Physiol **280:**H868–H875, 2001.
107. Afonso S, Bandow GT, Rowe GG. Indomethacin and the prostaglandin hypothesis of coronary blood flow regulation. J Physiol London **241:**299–308, 1974.
108. Block AJ, Poole S, Vane JR. Modification of basal release of prostaglandins from rabbit isolated hearts. Prostaglandins **7:**473–486, 1974.
109. Alexander RW, Kent KM, Pasano JJ, Keiser HR, Cooper T. Regulation of post-occlusive hyperemia by endogenously synthesized prostaglandins in the dog heart. J Clin Invest **55:**1174–1181, 1975.
110. Dai X-Z, Bache RJ. Effect of indomethacin on coronary blood flow during graded treadmill exercise in the dog. Am J Physiol Heart Circ Physiol **247:**H452–H458, 1984.
111. Case RB, Greenberg H. The response of canine coronary vascular resistance to local alterations in coronary arterial pCO_2. Circ Res **39:**558–566, 1976.
112. Case RB, Felix A, Wachter M, Kyriakidis G, Castellana F. Relative effect of CO_2 on canine coronary vascular resistance. Circ Res **42:**410–418, 1978.
113. Broten TP, Romson JL, Fullerton DA, Van Winkle D, Feigl EO. Synergistic action of myocardial oxygen and carbon dioxide in controlling coronary blood flow. Circ Res **68:**531–542, 1991.
114. Murray PA, Belloni FL, Spark HV. The role of potassium in the metabolic control of coronary vascular resistance of the dog. Circ Res **44:**767–780, 1979.
115. DeMay JG, Vanhoutte PM. Heterogenous behavior of canine arterial and venous wall. Importance of the endothelium. Circ Res **51:**439–447, 1982.
116. Cocks TM, Angus JA. Endothelium-dependent relaxation of coronary arteries by noradrenaline and serotonin. Nature **305:**627–630, 1983.
117. McCullough WT, Collins DM, Ellsworth ML. Arteriolar responses to extracellular ATP in striated muscle. Am J Physiol Heart Circ Physiol **272:**H1886–H1891, 1997.
118. Clemens MG, Forrester T. Appearance of adenosine triphosphate in the coronary sinus from isolated working rat heart in response to hypoxia. J Physiol **312:**143–158, 1981.
119. Borst MM, Schrader J. Adenine nucleotide release from isolated perfused guinea pig hearts and extracellular formation of adenosine. Circ Res **68:**797–806, 1991.
120. Ellsworth ML, Forrester T, Ellis CG, Dietrich HH. The erythrocyte as a regulator of vascular tone. Am J Physiol Heart Circ Physiol **269:**H2155–H2161, 1995.
121. Dietrich HH, Ellsworth ML, Sprague RS, Dacey RG. Red blood cell regulation of microvascular tone through adenosine triphosphate. Am J Physiol Heart Circ Physiol **278:**H1294–H1298, 2000.
122. Fleming I, Bauersachs J, Busse R. Paracrine functions of the coronary vascular endothelium. Mol Cell Biochem **157:**137–145, 1996.
123. Quilley J, Fulton D, McGiff JC. Hyperpolarizing factors. Biochem Pharmacol **54:**1059–1070, 1997.
124. Fisslthaler B, Popp R, Kiss L, Potente M, Harder DR, Fleming I, Busse R. Cytochrome P450 2C is an EDHF synthase in coronary arteries. Nature **401:**493–497, 1999.
125. Nishikawa Y, Stepp DW, Chilian WM. In vivo location and mechanism of EDHF-mediated vasodilation in canine coronary microcirculation. Am J Physiol Heart Circ Physiol **277:**H1252–H1259, 1999.
126. Harder DR, Campbell WB, Roman RJ. Role of cytochrome P-450 enzymes and metabolites of arachidonic acid in the control of vascular tone. J Vasc Res **32:**79–92, 1995.
127. Campbell WB, Gebremedhin D, Pratt PF, Harder DR. Identification of epoxyeicosatrienoic acids as endothelium-dependent hyperpolarizing factors. Circ Res **78:**415–423, 1996.
128. Rosolowsky M, Campbell WB. Synthesis of hydroxyeicosatetraenoic (HETEs) and epoxyeicosatrienoic acids (EETs) by cultured bovine coronary endothelial cells. Biochim Biophys Acta **1299:**267–277, 1996.
129. Ek L, Åblad B. Effects of three β-adrenergic receptor blockers on myocardial oxygen consumption in the dog. Eur J Pharmacol **14:**19–28, 1971.
130. Feigl EO. Sympathetic control of the coronary circulation. Circ Res **20:**262–271, 1967.
131. McRaven DR., Mark AL, Abboud FM, Mayer HE. Responses of coronary vessels to adrenergic stimuli. J Clin Invest **50:**773–778, 1971.
132. Nayler WG, Carson V. Effect of stellate ganglion stimulation on myocardial blood flow, oxygen consumption, and cardiac efficiency during beta-adrenoceptor blockade. Cardiovasc Res **7:**22–29, 1973.
133. Feigl EO. Control of myocardial oxygen tension by sympathetic coronary vasoconstriction in the dog. Circ Res **37:**88–95, 1975.
134. DiSalvo J, Parker PE, Scott JB, Haddy FJ. Carotid baroceptor influence on coronary vascular resistance in the anesthetized dog. Am J Physiol **221:**156–160, 1971.
135. Mohrman DE, Feigl EO. Competition between sympathetic vasoconstriction and metabolic vasodilation in the canine coronary circulation. Circ Res **42:**79–86, 1978.
136. Bache RJ, Dai X-Z, Herzog CA, Schwartz JS. Effects of nonselective and selective α_1-adrenergic blockade on coronary blood flow during exercise. Circ Res **61**(Suppl. II):II-36–II-41, 1987.
137. Gwirtz PA, Stone HL. Coronary blood flow and myocardial oxygen consumption after *alpha* adrenergic blockade during submaximal exercise. J Pharmacol Exp Ther **217:**92–98, 1981.
138. Heyndrickx GR, Muylaert P, Pannier JL. α-Adrenergic control of oxygen delivery to myocardium during exercise in conscious dogs. Am J Physiol Heart Circ Physiol **242:**H805–H809, 1982.
139. Huang AH, Feigl EO. Adrenergic coronary vasoconstriction helps maintain uniform transmural blood flow distribution during exercise. Circ Res **62:**286–298, 1988.
140. Murray PA, Vatner SF. α-Adrenoceptor attenuation of the coronary vascular response to severe exercise in the conscious dog. Circ Res **45:**654–660, 1979.

141. Seitelberger R, Guth BD, Heusch G, Lee J-D, Katayama K, Ross J Jr. Intracoronary α_2-adrenergic receptor blockade attenuates ischemia in conscious dogs during exercise. Circ Res **62:**436–442, 1988.
142. Morita K, Mori H, Tsujioka K, Kimura A, Ogasawara Y, Goto M, Hiramatsu O, Kajiya F, Feigl EO. α-Adrenergic vasoconstriction reduces systolic retrograde coronary blood flow. Am J Physiol Heart Circ Physiol **273:**H2746–H2755, 1997.
143. Zuberbuhler RC, Bohr DF. Responses of coronary smooth muscle to catecholamines. Circ Res **16:**431–440, 1965.
144. Quillen J, Sellke F, Banitt P, Harrison D. The effect of norepinephrine on the coronary microcirculation. J Vasc Res **29:**2–7, 1992.
145. Chilian WM, Layne SM, Eastham CL, Marcus ML. Heterogeneous microvascular coronary α-adrenergic vasoconstriction. Circ Res **64:**376–388, 1989.
146. Tiefenbacher CP, DeFily DV, Chilian WM. Requisite role of cardiac myocytes in coronary α_1-adrenergic constriction. Circulation **98:**9–12, 1998.
147. DeFily DV, Nishikawa Y, Chilian WM. Endothelin antagonists block α_1-adrenergic constriction of coronary arterioles. Am J Physiol Heart Circ Physiol **279:**H1028–G1034, 1999.
148. Miyashiro JK, Feigl EO. Feedforward control of coronary blood flow via coronary β-receptor stimulation. Circ Res **73:**252–263, 1993.
149. Hamilton FN, Feigl EO. Coronary vascular sympathetic beta-receptor innervation. Am J Physiol **230:**1569–1576, 1976.
150. Murphree SS, Saffitz JE. Delineation of the distribution of β-adrenergic receptor subtypes in canine myocardium. Circ Res **63:**117–125, 1988.
151. Trivella MG, Broten TP, Feigl EO. β-Receptor subtypes in the canine coronary circulation. Am J Physiol Heart Circ Physiol **259:**H1575–H1585, 1990.
152. Nakane T, Tsujimoto G, Hashimoto K, Chiba S. Beta-adrenoceptors in the canine large coronary arteries: β-1 adrenoceptors predominate in vasodilation. J Pharmacol Exp Ther **245:**936–943, 1988.
153. O'Donnell SR, Wanstall JC. The classification of β-adrenoceptors in isolated ring preparations of canine coronary arteries. Br J Pharmacol **81:**637–644, 1984.
154. Toda N, Okamura T. β-Adrenoceptor subtype in isolated human, monkey and dog epicardial coronary arteries. J Pharmacol Exp Ther **253:**518–524, 1990.
155. Duncker DJ, Stubenitsky R, Verdouw PD. Autonomic control of vasomotion in the porcine coronary circulation during treadmill exercise: evidence for feed-forward β-adrenergic control. Circ Res **82:**1312–1322, 1998.
156. Heyndrickx GR, Vilaine JP, Moerman EJ, Leusen I. Role of prejunctional α_2-adrenergic receptors in the regulation of myocardial performance during exercise in conscious dogs. Circ Res **54:**683–693, 1984.
157. Staib AH, E. Appel E, Starey F, Lindner E, Grotsch H, Palm D, Grobecker H. Exercise induced changes of catecholamines and potassium in plasma of dogs after treatment with propranolol. Arzneimittelforschung **30:**1514–1517, 1980.
158. Gorman MW, Tune JD, Richmond KN, Feigl EO. Quantitative analysis of feedforward sympathetic coronary vasodilation in exercising dogs. J Appl Physiol **89:**1903–1911, 2000.
159. Cousineau D, Goresky CA, Bach GG, Rose CP. Effect of β-adrenergic blockade on in vivo norepinephrine release in canine heart. Am J Physiol Heart Circ Physiol **246:**H283–H292, 1984.
160. Muntz KH, Olson EG, Lariviere GR, D'Souza S, Mukherjee A, Willerson JT, Buja LM. Autoradiographic characterization of β-adrenergic receptors in coronary blood vessels and myocytes in normal and ischemic myocardium of the canine heart. J Clin Invest **73:**349–357, 1984.
161. Murphree SS, Saffitz JE. Quantitative autoradiographic delineation of the distribution of β-adrenergic receptors in canine and feline left ventricular myocardium. Circ Res **60:**568–579, 1987.
162. Gwirtz PA. Coronary α_1-constrictor tone during renovascular hypertension. Circulation **92:**1576–1581, 1995.
163. Goldenberg M, Pines KL, Baldwin EF, Greene DG, Roh CE. The hemodynamic response of man to norepinephrine and epinephrine and its relation to the problem of hypertension. Am J Med **5:**792–806, 1948.
164. Doyle AE, Black H. Reactivity to pressor agents in hypertension. Circulation **12:**974–980, 1955.
165. Johnson JA, Ichikawa S, Kurz KD, Fowler WL, Payne CG. Pressor responses to vasopressin in rabbits with 3-day renal artery stenosis. Am J Physiol Heart Circ Physiol **240:**H862–H867, 1981.
166. Shannon RP, Gelpi RF, Hittinger L, Vatner DE, Homcy CJ, Graham RM, Vatner SF. Inotropic response to norepinephrine is augmented early and maintained late in conscious dogs with perinephritic hypertension. Circ Res **68:**543–554, 1991.
167. Gaba MK, Gaba S, Clark LT. Cardiovascular disease in patients with diabetes: clinical considerations. J Assoc Acad Minor Phys **10:**15–22, 1999.
168. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC, Sowers JR. Diabetes and cardiovascular disease: a statement for healthcare professions from the American Heart Association. Circulation **100:**1134–1146, 1999.
169. Nitenberg A, Valensi P, Sachs R, Dali M, Aptecar E, Attali J-R. Impairment of coronary vascular reserve and Ach-induced coronary vasodilation in diabetic patients with angiographically normal coronary arteries and normal left ventricular systolic function. Diabetes **42:**1017–1025, 1993.
170. Nahser PJ, Brown RE, Oskarsson H, Winniford MD, Rossen JD. Maximal coronary flow reserve and metabolic coronary vasodilation in patients with diabetes mellitus. Circulation **91:**635–640, 1995.
171. Meyer C, Schwaiger M. Myocardial blood flow and glucose metabolism in diabetes mellitus. Am J Cardiol **80:**94A–101A, 1997.
172. Downing SE, Lee JC, Weinstein EM. Coronary dilator actions of adenosine and CO_2 in experimental diabetes. Am J Physiol Heart Circ Physiol **243:**H252–H258, 1982.
173. Durante W, Sunahara FA, Sen AK. Effect of diabetes on metabolic coronary vasodilation in the rat. Cardiovasc Res **23:**40–45, 1989.
174. Zhao G, Zhang X, Smith CJ, Xu X, Ochoa M, Greenhouse D, Vogel T, Curran C, Hintze T. Reduced coronary NO production in conscious dogs after the development of alloxan-induced diabetes. Am J Physiol Heart Circ Physiol **277:**H268–H278, 1999.
175. Parodi O, DeMaria R, Oltrona L, Testa R, Sambuceti G, Roghi A, Merli M, Belingheri L, Accinni R, Spinelli F, Pellegrini A, Baroldi G. Myocardial blood flow distribution in patients with ischemic heart disease or dilated cardiomyopathy undergoing heart transplantation. Circulation **88:**509–522, 1993.
176. Opherk D, Schwartz F, Mall G, Manthey J, Baller D, Kubler W. Coronary dilatory capacity in idiopathic dilated cardiomyopathy: analysis of 16 patients. Am J Cardiol **51:**1657–1662, 1983.
177. Nitenberg A, Foult JM, Blanchet F, Zouioueche S. Multifactorial determinants of reduced coronary flow reserve after dipyridamole in dilated cardiomyopathy. Am J Cardiol **55:**748–754, 1985.
178. Moe GW, Montgomery C, Howard RJ, Grima EA, Armstrong PW. Left ventricular myocardial blood flow, metabolism, and effects of treatment with enalapril: further insights into the mechanisms of canine experimental pacing-induced heart failure. J Lab Clin Med **121:**294–301, 1993.
179. Helmer GA, McKirnan MD, Shabetai R, Boss GR, Ross J, Hammond HK. Regional deficits of myocardial blood flow and function in left ventricular pacing-induced heart failure. Circulation **94:**2260–2267, 1996.
180. Shen W, Asai K, Uechi M, Mathier MA, Shannon RP, Vatner SF, Ingwall JS. Progressive loss of myocardial ATP due to a loss of total purines during the development of heart failure in dogs: a compensatory role for the parallel loss of creatine. Circulation **100:**2113–2118, 1999.
181. Spinale FG, Tanaka R, Crawford FA, Zile MR. Changes in myocardial blood flow during development of and recovery from tachycardia-induced cardiomyopathy. Circulation **85:**717–729, 1992.
182. Shannon RP, Komamura K, Shen Y-T, Bishop SP, Vatner SF. Impaired regional subendocardial coronary flow reserve in conscious dogs with pacing-induced heart failure. Am J Physiol Heart Circ Physiol **265:**H801–H809, 1993.
183. Neumann T, Heusch G. Myocardial, skeletal muscle, and renal blood flow during exercise in conscious dogs with heart failure. Am J Physiol Heart Circ Physiol **273:**H2452–H2457, 1997.
184. Traverse JH, Melchert P, Pierpont GL, Jones B, Crampton M, Bache RJ. Regulation of myocardial blood flow by oxygen consumption is maintained in the failing heart during exercise. Circ Res **84:**401–408, 1999.
185. Magorien RD, Unverferth DV, Brown GP, Leier CV. Dobutamine and hydralazine: comparative influences of positive inotropy and vasodilation on coronary blood flow and myocardial energetics in nonischemic congestive heart failure. J Am Coll Cardiol **1:**499–505, 1983.