Metabolic flow regulation in human coronary artery disease
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Chapter 2

Mediators in coronary flow control
A review
1. Introduction

The purpose of this chapter is to review several physiological pathways that may play a role in the control of coronary blood flow. These pathways are either based on the release of endogenous substances related to metabolism, or based on the neurohumoral system and/or the vascular endothelium.

Below, the endogenous substances are arranged according to the adaptation of flow to changes in metabolism, referred to as metabolic control of flow, and to the adaptation of coronary vascular tone to changes in perfusion pressure, referred to as autoregulation [1,2]. In addition, the neurohumoral system and the endothelium have an effect on coronary vascular tone, and thus coronary blood flow, but their role is more difficult to classify in specific metabolic control or autoregulatory effects. Hence, these systems will be discussed in more general terms.

2. Metabolic control of coronary flow

As has been demonstrated experimentally, coronary blood flow is closely coupled to myocardial metabolism. The present line of thought is that an alteration in the balance of oxygen supply and demand leads to the production of vasodilatory substances that may restore the supply/demand balance through a change in coronary blood flow. In this context, several substances and ion channels that may be involved in the metabolic control of coronary flow have been identified. These include adenosine, ATP sensitive K+ channels and nitric oxide.

2.1 Adenosine in the metabolic control of coronary flow

Adenosine, a metabolite of adenine nucleotides is a widespread biological compound found in every cell of the human body. Since the identification of adenosine as an endogenous coronary vasodilator, it was hypothesized to be a regulator of coronary blood flow [3]. According to the ‘adenosine hypothesis’, this substance was primarily released in conditions of reduced myocardial oxygen supply or increased myocardial oxygen demand, in order to maintain the balance between myocardial oxygen supply and demand. In this way, adenosine might contribute to the homeostatic regulation of coronary blood flow.

In the heart, adenosine is produced in cardiomyocytes and the coronary endothelium by two major pathways: (1) dephosphorylation of AMP to adenosine and phosphate and (2) the hydrolysis of S-adenosylhomocysteine to adenosine and homocysteine (figure 2.1). The relative importance of both pathways varies under different conditions and possibly also in different tissues. The conversion of AMP to adenosine is regulated by the activity of the enzyme 5'-nucleotidase which is greatly increased by stimuli that lower energy levels (including hypoxia, ischemia, and exercise) and is decreased by adenosine, ATP and α,-adrenergic receptor stimulation. Adenosine inactivation can occur via three different mechanisms: (1) phosphorylation to AMP by adenosine kinase, which is the preferential pathway, (2) degradation to inosine by adenosine deaminase or (3) washout in the circulation. Furthermore,
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Figure 2.1: Schematic presentation of the synthesis and degradation of adenosine. SAH, S-adenosylhomocysteïne; ADO, adenosine. (From Mubagwa et al. [4])

Methylxanthines (e.g. aminophylline, 8-phenyltheophylline (8-PT)) may act as competitive inhibitors of adenosine.

Adenosine causes its various effects by interacting with specific cell surface adenosine receptors, of which the myocardial A₁r and the vascular A₂ receptor are the most important. Coupling of adenosine with its A₂ receptor, present on coronary vascular smooth muscle and endothelial cells, produces potent vasodilation in most vascular beds and several mechanisms for this effect have been proposed (for review see [4]).

Since adenosine levels in the interstitial fluid and coronary sinus increase when myocardial metabolism is increased, either by catecholamine infusion [5-9], pacing [10], sympathetic stimulation [9,11], or exercise [8,12,13], adenosine has been postulated as a possible mediator of metabolic coronary flow regulation. In addition, it was shown that adenosine levels correlated positively with coronary blood flow [12]. However, these findings do not necessarily imply that the release of adenosine is the cause for the associated increase in coronary blood flow.

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A large number of studies revealed that administration of adenosine receptor blockers or adenosine deaminase had little effect on the increase in coronary blood flow during metabolically induced changes in myocardial oxygen consumption (MVO$_2$) [11,14-22]. In addition, it was shown that the estimated interstitial adenosine concentration remained well below the threshold for coronary vasodilation, both at control, during paired-pulse pacing [15], and during exercise [23,24]. The few studies in humans also demonstrated that adenosine receptor blockade did not alter the decrease in coronary resistance or the increase in coronary blood flow in response to exercise [25], and pacing [26], respectively, despite substantial antagonism of adenosine-induced coronary dilation. Thus, adenosine is probably not involved in the metabolic control of coronary flow under normal conditions.

Under conditions of hypoperfusion, however, coronary blood flow may be determined by other factors, than the factors responsible for metabolic flow regulation. Duncker et al. [27] showed that after coronary vasoconstriction with glibenclamide, the vasodilatory response to exercise was blunted by adenosine receptor blockade with 8-PT. Thus, under conditions of relative hypoperfusion, adenosine was suggested to have contributed to the exercise-induced increase in coronary blood flow. That the role of adenosine gets more important in conditions of hypoperfusion may be related to the fact that it is released at a higher rate and therefore is present at higher concentrations than found under physiological conditions [28,29]. Headrick et al. [29] observed progressively greater increases in interstitial adenosine concentrations in isovolumically beating hearts (MVO$_2$ 73 µl/min/g) than in empty beating hearts (MVO$_2$ 51 µl/min/g) when both underwent similar reductions in coronary blood flow. Thus, the release of adenosine appeared to be directly and inversely related to the oxygen supply-demand balance. However, the question remains whether the observed increase in adenosine concentration contributed to the overall coronary vasodilation in response to pacing or exercise. In this context, Richmond et al. [28,30] recently showed that estimated interstitial adenosine did not increase sufficiently to reach vasoactive levels, suggesting that adenosine did not mediate a compensatory mechanism for metabolic coronary vasodilation under conditions of hypoperfusion.

In conclusion, adenosine does not appear to be the primary mediator of the close coupling between coronary blood flow and metabolism during metabolic coronary flow control. However, under conditions of hypoperfusion, there are indications that coronary blood flow may be dependent on the increased levels of adenosine.

### 2.2 ATP sensitive K+ channels in the metabolic control of coronary flow

ATP sensitive K+ channels (K+ATP channels) identified in vascular smooth muscle cells may contribute to the regulation of coronary blood flow. When these channels open, K+ leaves the cell resulting in hyperpolarisation of the cell membrane. This leads to vasorelaxation by reduced Ca$^{2+}$ entry through closing of voltage-dependent calcium channels. By definition, these channels are sensitive to ATP, which reduces the open-state probability of these channels. In contrast, the open-state probability is enhanced by a decrease in ATP, as in hypoxia or severe ischemia. In addition to
metabolic factors, these channels can also be opened by receptor activation (for example by adenosine) [31].

Drugs that modulate the open-state probability include the anti-diabetic sulfonylurea compounds, e.g. glibenclamide and tolbutamide, agents that may block the K+ATP channels specifically [32-34]. In contrast, a number of vasodilator substances causing hyperpolarisation of coronary vascular cell membranes, such as cromakalim, pinacidil, and nicorandil, supposedly exert their effect by selectively opening K+ATP channels [34,35].

Figure 2.2: Graphs showing the effect of intracoronary glibenclamide on the percent changes in coronary blood flow (CBF) (A), and on the ratio of the percent increase in CBF and myocardial oxygen consumption (MVO2) in response to pacing (B). Data are mean (SEM). (From Katsuda et al. [39])
Besides their presence in vascular smooth muscle cells, these channels have also been described in various other tissues, including cardiac muscle [36], skeletal muscle [37], and pancreatic beta-cells [38].

There is evidence that opening of K+ATP channels contributes to metabolic coronary vasodilation. In dogs, Katsuda et al. [39] demonstrated that K+ATP channel blockade with intracoronary infusion of glibenclamide significantly attenuated metabolic coronary vasodilation in response to pacing by ~40%, whereas basal flow and the pacing-induced increase in myocardial oxygen consumption remained unaffected. (figure 2.2).

However different observations were reported by Duncker et al. [27,40,41] who studied the effect of K+ATP channel blockade on metabolic coronary vasodilation in response to exercise in chronically instrumented dogs. In these studies, glibenclamide did not impair the increase in coronary blood flow with exercise. However, glibenclamide reduced basal coronary blood flow and myocardial oxygen consumption both at rest as well as during exercise [40]. Consequently, they concluded that the coronary vasculature retains the capacity to dilate in response to increases in oxygen demand when K+ATP channels are blocked.

The reason for the difference between the studies by Duncker et al. [40] and Katsuda et al. [39] is not clear, but it may be related to the different doses of glibenclamide that were used. In the study by Duncker et al. [40], glibenclamide induced a substantial decrease in basal coronary blood flow, which lead to an impairment in myocardial function. Thus, in response to the deterioration of myocardial function other vasodilatory mechanisms may have been activated with exercise (e.g. adenosine), so that the effect of glibenclamide may have been blunted (see below).

K+ATP channels have also been reported to play a role in metabolic coronary vasodilation induced by β-adrenoceptor stimulation. In anesthetized open chest dogs, Narishige et al. [42] showed that glibenclamide dose-dependently attenuated isoproterenol-induced increases in coronary blood flow, whereas the inotropic and chronotropic responses were not affected by K+ATP channel blockade (figure 2.3, A). The remaining vasodilation was completely attributable to direct stimulation of vascular β2-receptors, since β1 blockade with bisoprolol completely abolished the isoproterenol induced inotropic and chronotropic response, without preventing the remaining isoproterenol-induced increase in coronary blood flow. This vascular β2-receptor-mediated vasodilation was unaffected by glibenclamide (figure 2.3, B). Compared to isoproterenol, selective β1-receptor activation with denopamine induced a similar increase in myocardial oxygen consumption and a smaller increase in coronary blood flow. Glibenclamide almost completely abolished this β1-receptor mediated increase in flow, again without affecting the increase in myocardial oxygen consumption (figure 2.3, C). To maintain adequate myocardial oxygenation, myocardial oxygen extraction increased during infusion of glibenclamide. However, the reduction by glibenclamide of denopamine-induced increases in percentage systolic segment shortening, suggests that myocardial oxygen supply may not have increased sufficiently. Based on these observations, Narishige et al. [42] concluded that metabolic coronary vasodilation by β1-adrenoceptor stimulation, was mediated
by opening of K+ATP channels of coronary vascular smooth muscle and that these channels play a crucial role in maintaining adequate blood flow under conditions in which myocardial oxygen requirements are enhanced.

**Adenosine mediated K+ATP channel activation.** Both the observation that after blockade of K+ATP channels metabolic vasodilatory capacity is only partially inhibited [39], and the observation that metabolic vasodilation is restored when K+ATP channels are blocked to such an extent that basal coronary blood flow is reduced [40], suggest that other mechanisms contribute to metabolic coronary vasodilation and that these mechanisms may become more important when myocardial oxygenation is jeopardized.

In conscious dogs, Duncker et al. [27] suggested that in the presence of K+ATP channel blockade and consequent ischemia-induced contractile dysfunction, increased endogenous adenosine production was responsible for the remaining coronary vasodilation produced by exercise, whereas under normal coronary flow conditions adenosine had no effect on coronary blood flow at rest or during exercise. The mechanism behind this adenosine-mediated vasodilation during exercise may be related to the effect of adenosine on K+ATP channels. When intracellular mechanisms to open K+ATP channels are inhibited by glibenclamide and myocardial dysfunction develops, a compensatory increase in interstitial adenosine concentrations may cause an adenosine receptor-mediated activation of the K+ATP channel.

However, studies by Richmond et al. [28,30] plead against the hypothesis that an increase in adenosine release may compensate for the loss of K+ATP channel function, because they found that interstitial adenosine concentrations did not
increase sufficiently to overcome the inhibition of K+ATP channels by glibenclamide when oxygen consumption was increased, either by paired pacing [28] or exercise [30].

Alternatively, adenosine may have counteracted the vasoconstrictive effects of glibenclamide in part via another vasodilator pathway which does not involve the K+ATP channel, e.g. by activating adenylate cyclase. This is supported by the observation that the glibenclamide-induced inhibition of the vasodilation produced by administration of adenosine is not complete [27]. Thus, adenosine can also exert its effects through other routes than the K+ATP channel.

2.3 Nitric oxide in the metabolic control of coronary flow

Nitric oxide is a potent vasodilator substance that is produced by the endothelium (see paragraph 5.1). There is much controversy about nitric oxide’s role in the response of coronary resistance vessels to metabolic stimuli. Based on a study in anesthetized dogs, Katsuda et al. [43] concluded that nitric oxide did not modulate metabolic coronary vasodilation induced by tachycardia, since inhibition of nitric oxide synthesis with \( N^\text{G}-\text{nitro-L-arginine-methyl-ester} \) (L-NAME) did not alter the pacing-induced increases in coronary blood flow, myocardial oxygen consumption or regional myocardial blood flow. Others [24,44,45] also concluded that blockade of nitric oxide synthesis did not influence the increase in coronary blood flow produced by exercise. In chronically instrumented dogs, Berdaux et al. [46] indeed showed that the endothelium was not essential for metabolic vasodilation of coronary resistance arteries, because in vivo balloon endothelial denudation did not change the coronary blood flow responses to exercise. In another study, Domenech et al. [47] showed that inhibition of nitric oxide production did not change the linear relation between myocardial oxygen consumption and coronary flow. Thus, based on these studies in animals, nitric oxide does not seem to be essential for the metabolic regulation of coronary vascular resistance.

In contrast to the consistent results of these experimental studies, studies in humans have yielded more conflicting conclusions. Whereas some authors [48,49] showed that inhibition of nitric oxide with intracoronary administration of \( N^\text{G}-\text{monomethyl-L-arginine} \) (L-NMMA) attenuated the pacing-induced increases in coronary blood flow (figure 2.4), others [50-52] found that pacing induced increases in coronary blood flow were similar before and after nitric oxide inhibition. They concluded that other microvascular signals may have acted to overcome L-NMMA induced vasoconstriction when faced with an increase in myocardial oxygen demand [52]. So far, a satisfactory explanation for these inconsistent observations regarding the role of nitric oxide in human metabolic coronary flow control has not been given yet.

3. Autoregulation

Coronary autoregulation has been defined as the intrinsic ability of the heart to maintain coronary blood flow constant despite changes in coronary perfusion pressure. The precise mechanism(s) responsible for maintaining coronary blood flow
Figure 2.4: Effect of inhibition of nitric oxide synthesis on metabolic vasodilation. The graphs show the percent change in coronary vascular resistance, coronary blood flow, and proximal and distal epicardial coronary diameters during control pacing and on pacing after \( \text{NG} \)-mono-methyl-L-arginine (L-NMMA). Open circles indicate patients with risk factors for coronary atherosclerosis (hypercholesterolemia, hypertension, diabetes), and hatched circles indicated those patients without risk factors. Values are expressed as mean (SEM). *, \( p < 0.05 \) Control Pacing vs. L-NMMA + Pacing; †, \( p < 0.05 \) no risk factors vs. risk factors. (From Quyyumi et al. [48])
in the presence of decreasing coronary perfusion pressure remain(s) controversial, although coronary autoregulation is probably linked to myocardial metabolism through perfusion pressure induced changes in metabolic substrates or metabolites (see chapter 1).

3.1 Oxygen and carbon dioxide tension in coronary autoregulation

Changes in myocardial oxygen and carbon dioxide tensions may mediate coronary autoregulation. In goats, when varying coronary perfusion pressure at different levels of heart rate, Drake-Holland et al. [53] found a linear relation between coronary venous pO$_2$ and coronary vascular resistance, which supports the theoretical oxygen control model discussed in chapter 1 (figure 2.5). In addition, it illustrates that the dominant mechanism of coronary autoregulation is probably metabolic.

Studying the relation between coronary venous pO$_2$ and the 'quality of autoregulation', Dole et al. [54] found an inverse relationship between coronary venous pO$_2$ and the quality of coronary autoregulation; good autoregulation was observed when coronary venous pO$_2$ was 25 mmHg, while autoregulation was lost when coronary venous pO$_2$ was more than 32 mmHg. However, their definition of autoregulatory quality has been disputed, since this definition automatically yielded a better quality of autoregulation at high baseline flow rates (high baseline flow rates are expected at high levels of myocardial oxygen consumption, which by itself is associated with low coronary venous pO$_2$ tensions).

Although possibly involved in the phenomenon of autoregulation, the effect of carbon dioxide tension is probably small. Changes in carbon dioxide tension are too slow to explain the rapid changes in vascular resistance which occur during coronary autoregulation; after a 50 % step decrease in coronary flow, coronary venous carbon dioxide tension reached 90 % of its change in 58 seconds, whereas coronary venous oxygen tension completed this change in only 13 seconds [54]. Because the effect of oxygen tension on coronary blood flow is twice as strong as compared to the effect of carbon dioxide tension [55,56], it is generally accepted that carbon dioxide is not an important mediator of coronary autoregulation.

3.2 Adenosine in coronary autoregulation

Because adenosine was postulated to play a role in the metabolic control of coronary blood flow, adenosine might also contribute to coronary autoregulation. However, in a large number of studies, adenosine deaminase or adenosine receptor antagonists did not affect coronary flow over the autoregulatory pressure range [57-59]. In addition, interstitial adenosine levels did not change with decreases in coronary perfusion pressure [57]. Therefore, adenosine was reported a poor candidate as mediator of coronary autoregulation in the normal heart.

In contrast, when coronary pressure was reduced below the lower autoregulatory breakpoint of 50 mmHg, adenosine receptor blockade with 8-PT resulted in a small but significant decrease in coronary blood flow [41]. Similarly, adenosine receptor blockade reduced coronary blood flow distal to a coronary artery stenosis, whereas coronary blood flow in regions of myocardium supplied by the nonstenotic coronary artery remained unchanged [60,61]. Thus, reductions in coronary artery pressure
Coronary vascular resistance (mmHg/ml/min)

Coronary venous pO₂ (mmHg)

Figure 2.5: Relation between coronary vascular resistance and coronary venous pO₂, studied at constant heart rates (HR), while varying coronary perfusion pressure (Pp). ○ = HR 100/min; □ = HR 140/min; ● = HR 180/min. (From Drake Holland et al. [53])

sufficient to cause myocardial hypoperfusion, result in an augmented adenosine production, which may contribute to coronary vasodilation.

3.3 Nitric oxide in coronary autoregulation

In conscious dogs, Smith and Canty [62] found that inhibition of nitric oxide synthesis with L-NAME had no effect on resting flow or coronary flow adjustments over the autoregulatory plateau (figure 2.6). Closed loop autoregulatory gain\(^1\) at control (0.84 ± 0.09) was unchanged after inhibition of nitric oxide (0.78 ± 0.07). Although Smith and Canty could not study the effect of nitric oxide on autoregulation at pressures exceeding aortic pressure, their findings indicate that the role of nitric oxide in mediating resistance changes over the autoregulatory plateau is probably limited and suggest that either metabolic and/or myogenic mechanisms are predominant [62].

Smith and Canty also showed that inhibiting nitric oxide synthase with L-NAME increased the lower autoregulatory breakpoint from 45 ± 3 mmHg under control

\(^1\) Autoregulatory gain = 1 – (ΔF/ΔP ∙ Pᵢ/Fᵢ), where ΔF/ΔP is the slope of the autoregulatory plateau, Pᵢ is the resting coronary pressure and Fᵢ is the resting coronary flow.
Figure 2.6: Effect of inhibition of nitric oxide synthesis on coronary autoregulation. Shown are the pressure flow relationships under control conditions (open circles) and following inhibition of nitric oxide synthesis with $N^\omega$-nitro-L-arginine-methyl-ester (L-NAME) (hatched triangles). L-NAME had no significant effect on flow regulation over the autoregulatory plateau. The lower autoregulatory break point (arrows) as well as the pressure flow relationship during hypoperfusion were, however, shifted to the right after inhibition of nitric oxide production. (From Smith et al. [62])

conditions, to $61 \pm 2$ mmHg after L-NAME. In addition, both the slope of the coronary pressure-flow relation below the autoregulatory breakpoint and the peak reactive hyperemic flow were reduced, reflecting an impaired capability to minimize coronary vascular resistance in this condition. Thus, it appears that under conditions of hypoperfusion, production of nitric oxide may play a role in minimizing coronary vascular resistance.

In contrast to Smith’ study, Ueeda et al. [63] reported that coronary autoregulation improved after inhibition of nitric oxide in the non-working isolated guinea pig heart. This discrepancy with the study by Smith and Canty [62] may be related to the intrinsic ability of the vasculature to autoregulate flow. Ueeda et al. [63] reported an autoregulatory gain of 0.16, which indicates a relatively vasodilated circulation that may have been due to high levels of nitric oxide. Since nitric oxide may attenuate the myogenic component of autoregulation, this may explain the improved autoregulation after inhibition of nitric oxide. In contrast, under conditions in which the intrinsic ability of the heart to autoregulate flow is high (high autoregulatory gain), autoregulation is not affected by inhibition of nitric oxide.

The relative contribution of the myogenic and metabolic components of autoregulation may vary in different vascular beds. In vascular beds with almost no autoregulation (e.g. the skin), nitric oxide may completely oppose the myogenic component of the autoregulatory responses. In these vascular beds, autoregulation will improve after abolishment of the opposing nitric oxide factor. However, in vascular beds suggested to have predominantly metabolic autoregulation with little
myogenic activity, the effect of nitric oxide inhibition on the myogenic autoregulatory responses will hardly influence the total process of autoregulation.

3.4 ATP sensitive K+ channels in coronary autoregulation
Since autoregulation is supposedly controlled by the same basic flow regulatory mechanisms that play a role in metabolic coronary flow regulation, the involvement of K+ATP channels in coronary autoregulation has also been determined. Studying anesthetized dogs, Komaru et al. [64] reported that coronary epicardial microvascular dilation distal to a coronary artery stenosis, was abolished by topical administration of glibenclamide. Using an extracorporeal circuit for pressure controlled perfusion of the left anterior descending coronary artery, Narishige et al. [65] confirmed that intracoronary glibenclamide abolished coronary autoregulation in the canine heart at coronary pressures between 50 and 110 mmHg. These results indicate that progressively more K+ATP channels are activated as coronary pressure decreases, which is supported by the finding that pinacidil increased coronary flow at normal pressures, but not at pressures below the lower autoregulatory breakpoint, suggesting that, as perfusion pressure reaches this lower breakpoint, most of the K+ATP channels have become activated [41]. Therefore it is likely that K+ATP channels play a significant role in the coronary microvascular response to reductions in coronary perfusion pressure, determining coronary autoregulation.

In contrast, Stepp et al. [59] found that K+ATP channels were not necessary for coronary autoregulation. In closed-chest dogs, they demonstrated that autoregulation was preserved during infusion of glibenclamide, although glibenclamide reduced coronary blood flow by 19 % at each perfusion pressure, over the autoregulatory range from 100 to 60 mmHg. However, in their study, coronary venous carbon dioxide tension rose progressively with decreasing coronary pressures after glibenclamide, which indirectly suggests that carbon-dioxide-mediated vasodilation may have compensated for the loss of K+ATP channel function, thereby masking the effect of glibenclamide on coronary autoregulation.

The mechanism by which a decrease in coronary perfusion pressure may activate K+ATP channels is at present unknown, although it may be related to changes in metabolites. For example, a reduction in myocardial tissue oxygen concentration with decreases in coronary perfusion pressure may be a signal that (indirectly) regulates the activation of K+ATP channels in vascular smooth muscle cells, leading to vasodilation [66] and restoration of coronary blood flow to the previously existing level. In this respect, it is interesting that coronary autoregulation has been shown strongly coupled to tissue oxygen tension [53,54]. However, other metabolites, such as ADP, lactate and extracellular cations, might also contribute to the activation of K+ATP channels [67].

4. Neurohumoral control
The coronary circulation is richly innervated by both sympathetic and parasympathetic nerves and their activation can exert important influences on
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coronary vasomotor tone. Both circuits are assumed to maintain equilibrium and homeostasis by functionally counteracting each other.

4.1 Sympathetic control

Regarding the sympathetic nervous system, both alpha and β-adrenergic receptors have been identified in the coronary circulation. Whereas alpha-receptors are predominantly present in the epicardial arteries [68], β-receptors are located in the smaller transmural vessels and small coronary arteries [69,70].

Stimulation of alpha-receptors unequivocally leads to vasoconstriction, due to increased levels of calcium intracellularly. This vasoconstrictive response limits vasodilation in the subepicardial vessels and prevents coronary steal by favorably influencing the transmural distribution of blood flow to the subendocardium [71]. It can be blocked by the simultaneous administration of alpha-receptor blockers such as phentolamine.

However, the response to stimulation of β-receptors is less clear. This is due to the concomitant effect of β-agonists on the β-receptors of the myocardium, causing an inotropic and chronotropic response, which by itself leads to metabolic coronary vasodilation. There are however indications that when the β-receptor-induced inotropic and chronotropic responses are blocked, β-agonists also have the ability to produce coronary vasodilation directly [72]. This direct β-adrenergic coronary vasodilation of resistance vessels is possibly mediated by an endothelium dependent mechanism that is linked to the nitric oxide pathway [73].

Adrenergic stimulation. Adrenergic stimuli may influence coronary vasomotor tone during interventions that activate the sympathetic nervous system, such as exercise, the cold pressor test and mental stress. The net effect of the increased sympathetic activity is dilation of coronary resistance vessels and an increase in coronary blood flow, which is mainly related to the norepinephrine content of the cardiac sympathetic-nerve terminals rather than the level of circulating catecholamines [74]. The exact mechanism behind the activation of cardiac sympathetic-nerve terminals and coronary vasodilation however remains complex, especially since Zeiher et al. [75] showed that the increase in coronary blood flow in response to sympathetic stimulation with the cold pressor test remained unchanged after intracoronary β-adrenergic blockade with propranolol.

Basal coronary vessel tone. There is conflicting evidence regarding the contribution of the sympathetic nervous system to resting coronary vasomotor tone. Acute surgical denervation of the heart had been shown to reduce coronary vascular resistance and arteriovenous oxygen extraction [71]. In addition, some studies reported that coronary vascular resistance decreased after blockade of α-adrenergic receptors, suggesting the presence of a tonic α-adrenergic vasoconstrictive effect [76]. However, Di Carlì et al. [74] showed that basal coronary flow in transplant recipients was similar in different coronary territories, despite apparent differences in the sympathetic innervation between these territories. This finding was in line with studies by Hodgson et al. [77] who showed that intracoronary infusion of phentolamine induced minimal changes in epicardial diameter and coronary resistance, in both normally innervated and denervated, cardiac transplant patients.
indicating that resting α-adrenergic tone was negligible. Furthermore, in healthy volunteers without signs or risk factors of coronary artery disease, no difference in resting perfusion (measured with PET) before and after ten days of oral treatment with the selective α₁-antagonist doxazosin was found [78]. Finally, Van der Stroom et al. [79] found no change in coronary sinus blood flow following the intracoronary administration of increasing doses of urapidil in patients with coronary artery disease. Julius et al. [80] reported similar findings in a comparable group of patients, demonstrating that cross sectional areas of both normal and stenotic vessel segments were unaffected by intracoronary infusion of phenolamine. Thus, it appears that α-adrenergic coronary constrictor tone does not contribute to resting coronary vessel tone [81,82].

**Metabolic control.** The role of α-adrenergic mechanisms in the coronary response to dynamic exercise was studied in patients given an α-adrenergic receptor blocker and in control patients without α-adrenergic blockade. In response to exercise, coronary cross-sectional areas of normal vessel segments increased similarly in both groups, indicating that in these normal segments metabolic coronary vasodilation was not influenced by an α-adrenergic mechanism [80]. However, while in the control patients the stenotic coronary segments constricted in response to exercise, this response was blunted and reversed to vasodilation in the patients taking phenolamine (figure 2.7). Similarly, in dogs it was shown that the exercise-induced vasoconstriction of the left circumflex artery after endothelial denudation, was alleviated after the blockade of α₁-adrenoceptors with prazosin [46]. Thus, the mechanical removal of the endothelium unmasked the vasoconstrictor effect of the
exercise-induced catecholamine release at the level of epicardial coronary α₁-adrenoceptors [83].

These findings strongly suggest that α-adrenergic activation contributes to the exercise-induced vasoconstriction of stenotic coronary artery segments, whereas normal segments remain unresponsive to the increased levels of circulating catecholamines during exercise. Thus, it appears that exercise induced vasoconstriction of stenosed coronary arteries is mediated not only by endothelial dysfunction, but also by α-adrenergic mechanisms.

In summary, at rest there appears to be no α-adrenergic coronary constrictor tone in the normal coronary circulation. In the presence of coronary atherosclerosis however, α-adrenergic constriction is unmasked in response to sympathetic activation. This latter mechanism also contributes to the observed exercise-induced vasoconstriction of coronary stenoses.

4.2 Parasympathetic control

Historically, when studying the effect of the autonomic nervous system on coronary dynamics, much emphasis has been laid on the sympathetic circuit of the autonomic nervous system, whereas little attention has been paid to the parasympathetic system. This may be due to the fact that it is notoriously difficult to obtain quantitative information on parasympathetic neuronal activity in vivo, because the neurotransmitter of this system, acetylcholine is degraded extremely rapidly by acetylcholine esterases. Therefore, information about the effect of the parasympathetic system on the coronary vasculature is often obtained by studying the coronary response to muscarinic receptor agonists such as acetylcholine and carbachol.

Parasympathetic stimulation leads to coronary vasodilation, that can be blocked by atropine. Since the acetylcholine-induced vasodilator response is secondary to the endothelial release of nitric oxide, many of the parasympathetic effects on the coronary circulation can thus be related to the effects of nitric oxide. For example, the role of the parasympathicus in the regulation of coronary vasomotor tone will likely be reduced in the presence of endothelial dysfunction, because of the reduced nitric oxide availability in that setting. Thus, besides the well known acetylcholine-induced, nitric oxide mediated effects of the parasympathicus, very little is known about the role of the parasympathetic nervous system itself in the process of coronary flow control.

In isolated canine saphenous veins and rabbit ear arteries, stimulation of muscarinic receptors on the sympathetic nervous system attenuated the release of noradrenaline in response to electrical stimulation [84,85]. Thus, through inhibition of sympathetic outflow, parasympathetic stimulation may also affect coronary vasomotor tone.

4.3 Peptidergic control

It is generally believed that neural control depends primarily on the release of noradrenaline and acetylcholine from sympathetic and parasympathetic nerve terminals, respectively. However, it is now recognized that in addition to the classic
neurotransmitters, other putative transmitters (including several vasoactive peptides) also have vasoactive properties. These peptides identified in nerves associated with coronary vessels include calcitonin-gene-related peptide, neuropeptide Y and vasoactive intestinal peptide. Most of these compounds influence coronary tone in a dual action. Through their specific receptors on endothelial cells, they stimulate the formation of endothelium-derived nitric oxide by activating endothelial nitric oxide synthase, which leads to a reduction in vascular tone. In contrast, an increase in vascular tone is achieved by their action on specific receptors located on the vascular smooth muscle cells. The subsequent net effect on vascular tone depends on the relative strength of these two opposing actions and, under pathophysiological conditions, in particular on the functional integrity of the endothelium.

Although neuropeptide Y, which is co-stored and released with noradrenaline from sympathetic nerve terminals, has generally been regarded as a vasoconstrictor peptide, its functional significance in the regulation of coronary vasomotor tone still has to be defined [86]. This also applies to vasoactive intestinal peptide, which is present in post-ganglionic parasympathetic nerve fibers and has been shown to have a direct vasodilatory effect on coronary arteries [87]. The precise role of the neuropeptide-containing nerve fibers in the control of coronary flow is however at present still uncertain.

5. Endothelial modulation of coronary vascular tone

The luminal surface of the coronary vessels is lined by endothelial cells which are in close contact with the smooth muscle cells constituting the media. These endothelial cells play a major role in the control of coronary blood flow, since they modulate the contractile activity of the underlying smooth muscle through the secretion and synthesis of substances with different biological activities in response to a variety of pharmacological agents (e.g. acetylcholine and substance P [88]) and physical stimuli (e.g. shear stress [89] and pulsatile flow [90]).

5.1 Nitric oxide and endothelial control of coronary vasomotor tone

Of all the substances produced by the endothelium, endothelium derived relaxing factor, generally believed to be similar to nitric oxide, is probably the most important [91]. In the vascular smooth muscle cell, nitric oxide activates soluble guanylate cyclase, which increases the intracellular levels of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate [92]. This reduces the intracellular calcium concentration in the vascular smooth muscle cell, which leads to relaxation and vasodilation [93,94].

The synthesis of nitric oxide by endothelial cells requires the presence of endothelial nitric oxide synthase (eNOS), a calcium sensitive enzyme, which is constitutively expressed in endothelial cells. Under control of this enzyme, nitric oxide and the amino acid L-citrulline are formed from L-arginine and oxygen, using NADPH as a reductor. The activity of eNOS in turn is regulated by intracellular concentrations of calcium. A variety of endothelium-dependent stimuli, including serotonin, histamine, bradykinin and acetylcholine, which activate receptor-coupled
G-proteins, finally lead to increased calcium concentrations in the endothelial cells and may therefore increase the production and release of nitric oxide [95].

Analogue s of L-arginine, such as L-NITE or L-NMMA can competitively block the synthesis of nitric oxide by inhibiting eNOS [96-98]. For this reason, the arginine analogues have been used extensively to study the contribution of nitric oxide in the process of coronary flow control.

It has become clear that endothelium-derived nitric oxide plays a crucial role in the generation of the coronary vessel tone of coronary conduit arteries. This indicates that the continuous, basal release of nitric oxide from endothelial cells keeps the conduit vasculature in a dilated state. However, whether this mechanism also contributes to coronary vessel tone of coronary resistance vessels continues to be disputed. Whereas in vitro studies suggested that the basal release of nitric oxide contributed to basal coronary vasomotor tone of coronary resistance vessels [96,98,99], in vivo studies in dogs could not confirm these findings [43,62,97,100,101]. In contrast, in humans it was demonstrated that during intracoronary infusion of L-NMMA coronary blood flow decreased and coronary vascular resistance increased [48,50,52,102,103]. Thus, it appears that in humans the tonic release of nitric oxide supposedly contributes to the vascular conductance of both epicardial as well as coronary resistance vessels and that role of nitric oxide in the generation of basal coronary vasomotor tone of resistance vessels is more pronounced in man than in dogs.

An alternative explanation may involve the heterogeneous vasoactive properties of nitric oxide. In open-chest dogs, Jones et al. [104] measured coronary microvascular diameters by stroboscopic epi-illumination and intravital microscopy and demonstrated that L-NAMES constricted small arteries (> 100 μm), whereas arterioles (< 100 μm) dilated (figure 2.8). These findings suggest that nitric oxide causes heterogeneously distributed vasodilation of the coronary microcirculation and that it aids in the maintenance of a normal distribution of coronary microvascular resistance, by tonically dilating arteries between 100 and 300 μm in diameter. In this way, nitric oxide may preserve the vasomotor tone and vasodilator potential of the smaller microvessels (<100 μm) which are most sensitive to metabolite- and pressure-mediated dilation [104]. This heterogeneous response of the coronary microcirculation makes the interpretation of alterations in total coronary vascular resistance in response to L-NMMA very difficult. The opposing responses of small arteries and arterioles to L-NMMA may counteract each other in such a way that total coronary vascular resistance remains unaffected. Nitric oxide may thus regulate the distribution of coronary microvascular resistance, without changing total coronary vascular resistance.

In addition to basal release by the vascular endothelium, nitric oxide is also produced in response to a variety of receptor-dependent and independent pharmacological substances, including acetylcholine, bradykinin, substance P, and calcium ionophore. In fact, it was the endothelial release of nitric oxide which explained the dual action of acetylcholine: although a potent vasodilator when administered in vivo, acetylcholine elicited contractile responses in most isolated vascular smooth muscle preparations. After the discovery that relaxation induced by
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Figure 2.8: Scatterplot showing the percent changes in coronary microvascular diameters caused by inhibition of nitric oxide synthesis with L-NAM plotted against baseline diameters. L-NAM constricted small coronary arteries (> 100 micrometer) and dilated arterioles (< 100 micrometer). (From Jones et al. [104])

acetylcholine was abolished by the removal of the endothelium [91], it became clear that it was the endothelial lining which was essential for the vasodilator action of acetylcholine, because of the acetylcholine-induced endothelial release of nitric oxide.

In addition to the acetylcholine-induced release of nitric oxide, other acetylcholine-induced mechanisms may also contribute to its vasodilator activity, including the induced membrane hyperpolarisation of vascular smooth muscle cells, which by itself may cause vasodilation [105]. By some authors, nitric oxide itself was thought to be responsible for the hyperpolarisation and several explanations for the hyperpolarising effect of nitric oxide have been proposed [106-110]. However, not all the hyperpolarisation was explained by nitric oxide [111,112], and therefore, another diffusible substance capable of mediating smooth muscle cell hyperpolarisation and relaxation was suggested to be released by the vascular endothelium [113]. However, in subsequent years it appeared that the degree to which hyperpolarisation contributed to relaxation was reportedly small or even nonexistent, since, frequently, endothelium-dependent effects on the membrane potential did not coincide with the relaxation or constriction of smooth muscle cells (for review see Cohen et al. [114]).
Since nitric oxide is also released in response to physical stimuli such as shear stress, it plays an important role in the flow-induced vasodilation of coronary arteries. From animal experiments there is indeed ample evidence that the vasodilation of large epicardial arteries in response to exercise is dependent on flow-mediated relaxation, controlled by the release of endothelium-derived nitric oxide [45,46,115]. Several clinical studies [48-52,116] corroborated the animal experiments by showing that inhibition of nitric oxide uniformly resulted in impaired epicardial vasomotor responses to exercise and pacing. Thus, the endothelium is essential for epicardial coronary artery dilation in response to increased myocardial work through a nitric oxide mediated mechanism, which is likely to be related to the metabolically induced increase in coronary blood flow and shear stress.

5.2 Bradykinin and endothelial control of coronary vasomotor tone
Increased shear forces stimulate the formation of bradykinin in vascular endothelium. Bradykinin binds to two kind of receptors: the B₁ and B₂ receptor. B₂ receptors are more sensitive to bradykinin than B₁ receptors. Bradykinin-receptor stimulation activates NOS in a calcium dependent manner, which leads to increased endothelial release of nitric oxide. In addition, bradykinin receptor stimulation results in the release of another powerful vasodilator: prostacyclin.

There are indications that bradykinin does not contribute to the maintenance of coronary vasomotor tone under physiological conditions; in conscious dogs it was shown that coronary blood flow remained unchanged following the administration of the specific bradykinin-receptor antagonist HOE-140, despite a slight, but significant fall in endothelial nitric oxide production [117]. The acute effects of bradykinin on coronary vascular tone thus appear to be minimal, although its specific role in the regulation of coronary flow especially under pathophysiological conditions, has not been clarified conclusively.

5.3 Prostanoids and endothelial control of coronary vasomotor tone
The prostaglandin-thromboxane system probably does not play a major role in the regulation of myocardial perfusion under physiological conditions. These prostanoids are derivatives of arachidonic acid and are produced by endothelial cells in a reaction regulated by cyclo-oxygenase, which can be blocked by substances such as indomethacin, acetylsalicylic acid (aspirin), and other non-steroidal anti-inflammatory agents.

Prostacyclin (PGI₂), or prostaglandin I₂, is the major breakdown product of cyclo-oxygenase and the major vasodilatory prostaglandin. It is mainly synthesized in endothelial cells and platelets and it exerts its vasodilatory and anti-aggregatory function by receptor-mediated activation of adenylate cyclase. In the vascular smooth muscle cell, the subsequent increase in cAMP causes relaxation. In platelets, the increase in cAMP inhibits adhesion, aggregation and the release of proaggregatory and vasoconstrictor compounds such as serotonin and thromboxane. The synthesis of PGI₂ can be enhanced by a variety of endogenous substances (ATP, bradykinin, histamine, catecholamines), and exogenous drugs (nifedipine, diltiazem, ACE-inhibitors, nitrovasodilators, dipyridamole).

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Thromboxane in turn, is mainly formed in platelets and only to a small extent in the vasculature, where it induces platelet aggregation and vasoconstriction, respectively. This is achieved by increasing the cytosolic concentration of calcium, via formation of inositol-1,4,5-triphosphate and a protein kinase C mediated mechanism, and a decrease in cAMP. However, the constrictor effect of thromboxane may partially be offset by the simultaneous release of prostacyclin by functionally intact endothelium.

Although both prostacyclin and thromboxane have the potential to influence coronary flow, they do not appear to play an important role in the process of coronary flow regulation, at least not under physiological conditions. Coronary vasomotor tone of functionally intact vessels was not substantially changed by blockade of prostanoid formation. Thus, in dogs, no change in coronary blood flow was found after indomethacin or selective thromboxane receptor blockade [118,119]. The flow-response to an increase in myocardial oxygen consumption induced by exercise was also preserved after indomethacin [118,119]. Thus, prostanoids are probably not involved in the process of metabolic coronary flow regulation.

In contrast, in patients with coronary artery disease, coronary vascular resistance and myocardial oxygen extraction increased substantially after intravenous administration of indomethacin [120,121]. This suggests that the contribution of prostacyclin to the vasodilator state of the vasculature becomes more pronounced in coronary artery disease. This is in line with the observation that prostacyclin-biosynthesis is increased in patients with coronary artery disease [122]. In conscious L-NMMA-treated dogs, it was shown that the cyclo-oxygenase pathway was involved in the coronary reactive hyperemia and in the residual relaxation to bradykinin, whereas in control dogs the cyclo-oxygenase pathway was not involved [123].

Thus it is conceivable that in pathological conditions in which certain vasodilator mechanisms are not longer functional, other vasodilator mechanisms, e.g. prostacyclin, may compensate for the reduced vasodilator potential.

5.4 Endothelins and endothelial control of coronary vasomotor tone

Endothelins (ET) are peptide hormones with a large array of potent biological actions, acting as modulators of vasomotor tone, cell proliferation and hormone production. To date, three members of the family have been described, ET-1, ET-2 and ET-3. ET-1 is exclusively produced in the endothelial cells, whereas a variety of other tissues produce ET-2 and ET-3. The synthesis and secretion of ET-1 can be activated within minutes. Initially ‘big endothelin’ is formed, from which ET-1 originates after extracellular proteolitic cleavage by endothelin converting enzyme. The synthesis and release of ET-1 can be elicited by various physico-chemical stimuli, including shear stress and hypoxia. In addition, the process can be initiated in a receptor-mediated manner by a variety of growth factors and vascular proteins, including thrombin, angiotensin II, interleukin-1, and insulin.

The release of ET-1 is for 75% directed towards the vascular smooth muscle (abluminal) side of the cells, where it can bind to specific receptors and cause vasoconstriction. The circulating endothelin levels are generally small, in the picomolar range, although levels are increased up to approximately fivefold under
Figure 2.9: Endothelin is mainly released abluminally to interact with \( \text{ET}_A \) and \( \text{ET}_B \) receptors on vascular smooth muscle. Activation of \( \text{ET}_B \) receptors on the endothelium causes vasodilation. PGI\(_2\), prostacyclin; ECE, endothelin converting enzyme. (From Lüscher et al. [124])

conditions of circulatory distress (e.g. shock, ischemia, shear stress). Plasma ET-1 is cleared for 80-90% by the lungs during first passage. For these reasons, ET is regarded more as a paracrine than as an endocrine hormone.

**Endothelin receptors.** The biological effects of endothelins are mediated by three different receptors, \( \text{ET}_A \), \( \text{ET}_B \), and \( \text{ET}_C \), linked to a G (guanine nucleotide binding) protein. \( \text{ET}_A \) receptors have a high affinity to ET-1 and ET-2 and are expressed abundantly on vascular smooth muscle cells and cardiac myocytes. They mediate the vasoconstrictor action of ET-1.

\( \text{ET}_B \) receptors have a similar affinity for all three endogenous endothelins and are expressed predominantly on endothelial cells and to a much lesser extent on vascular smooth muscle cells. The \( \text{ET}_B \) receptors on the endothelium mediate the release of relaxing factors, such as nitric oxide and prostacyclin. However, several reports demonstrated that \( \text{ET}_B \) receptors on some vascular smooth muscle cells also contribute to ET-induced vasoconstriction (figure 2.9) [124,125].

The combined stimulation of both \( \text{ET}_A \) and \( \text{ET}_B \) receptors with exogenous endothelin infused at supraphysiological concentrations, causes a transient coronary
dilator response, attributable to ET$_B$ receptor-mediated release of nitric oxide and prostacyclin, followed by a severe and long lasting coronary constrictor response that can be blocked by specific, rather selective antagonists of ET$_A$ receptors. This ability of endothelins to produce severe coronary constriction has been suggested to be associated with the induction of coronary spasm [126]. However, any conclusive evidence for a role of endothelin as the cause for coronary spasm is still missing.

Endothelins interact with a variety of hormones and other vasoactive substances, mediating some of their vascular effects. Of these interactions, the relation between ET-1 and angiotensin II appears one of the most important. Angiotensin II stimulates the production of ET-1 and ET-1 can stimulate the conversion of angiotensin I to angiotensin II. Inhibition of either angiotensin II-induced ET-1 production or inhibition of ET-1 itself can therefore prevent the cardiac hypertrophic effects of angiotensin II [127].

The interaction of endothelin with the vasodilators nitric oxide and prostacyclin may also be clinically relevant. Nitric oxide and prostacyclin inhibit the production of ET-1, through a common cGMP-mediated mechanism [128,129]. Therefore, it cannot be excluded that the vasodilator action of these substances is mediated in part by inhibition of the production and action of endothelin.

**Endothelins and coronary flow control.** It has been suggested that ET-1 and ET$_A$ receptors contribute to the basal coronary vasomotor tone of human arteries, since infusion of BQ-123, a selective ET$_A$ receptor antagonist, in the brachial artery resulted in progressive vasodilation and a long lasting increase in forearm blood flow [130]. However, in the in vivo coronary circulation, ET$_A$ receptor antagonists only dilated large epicardial conductance arteries, whereas coronary flow remained unchanged [131]. Importantly, these observations were similar before and after blockade of nitric oxide, ruling out a putative functional interaction between endothelin and nitric oxide [131]. Furthermore, ET$_B$ receptor blockade had no influence on baseline caliber of either large epicardial arteries or coronary flow. These observations demonstrate that ET$_A$-receptor activation, but not ET$_B$ receptor activation contributes to the basal coronary vasomotor tone of large epicardial vessels, whereas coronary flow regulating resistance vessels are not affected [131].

In contrast, endothelin’s role in pathophysiological processes is probably much more pronounced. In this context it should be noted that the vasoconstrictor effect of endothelins is increased in atherosclerotic vessels, probably because the opposing vasodilator effect of nitric oxide in these vessels is lost. In addition, plasma endothelin concentrations are markedly increased during myocardial ischemia and following myocardial infarction. In dogs and rats, blockade of endothelin receptors reduced the extent of experimentally induced myocardial infarction by 40% [132,133], suggesting a role for endothelins in the extent of myocardial damage. In addition, the vasoconstrictor action of endothelins could contribute to the extent of myocardial reperfusion injury [134]. Finally, endothelins are probably involved in the pathogenesis of congestive heart failure. In patients with moderate to severe congestive heart failure, plasma ET-1 levels are elevated twofold to fourfold, and closely correlate with the severity of the disorder. ET antagonists in turn,
demonstrated significant beneficial effects in conditions of congestive heart failure, pulmonary hypertension, and essential hypertension [135].

6. Summary

Coronary blood flow is primarily regulated by metabolic factors and both metabolic coronary vasodilation as well as autoregulation can be explained on the basis of this control process. In this process, changes in tissue levels of oxygen tension, other metabolic substrates, or metabolites probably modulate coronary vasomotor tone continuously, in order to maintain the balance between myocardial oxygen supply and demand. The precise mediators and mechanisms linking metabolic activity to coronary vascular resistance however remain to be clarified.

There are indications that ATP dependent potassium channels play an important role in the control of coronary flow, since both metabolic vasodilation and coronary autoregulation were impaired after blockade of these channels. In addition these channels are sensitive to oxygen and metabolites (e.g. ADP, lactate), which makes these structures a likely candidate to be involved in the (metabolic) control of coronary flow.

Under physiological conditions, adenosine does not contribute to coronary flow control. However, under conditions of hypoperfusion, the release of this substance is greatly increased and some studies suggested that adenosine may constitute a compensatory mechanism that may increase coronary flow when other mechanisms fail to maintain the balance between myocardial oxygen supply and demand.

The endothelium releases several vasoactive relaxing and constricting factors, including nitric oxide, bradykinin, prostacyclin and endothelin, that may influence coronary flow control. Although nitric oxide is probably not directly involved in the initial metabolic adjustment of vascular tone in coronary arterioles, it contributes importantly to the (flow-induced) vasodilation of large coronary arteries. In the presence of endothelial dysfunction, as in coronary artery disease, the absence of nitric oxide mediated vasodilation may thus result in reduced coronary vasomotor responses.

Finally, it has been shown that the neurohumoral contribution to coronary flow control is probably limited in the normal coronary circulation. However, in the presence of coronary atherosclerosis and endothelial dysfunction, $\alpha$-adrenergic constriction may predominate leading to inappropriate vasoconstriction.

Thus, many different substances may heterogeneously influence coronary vasomotor tone. The important overall result, is a complex and well regulated system in which coronary blood flow and ultimately oxygen delivery is adequately controlled to maintain myocardial function under a variety of physiological conditions.

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