α-Adrenergic Mechanisms in Myocardial Ischemia

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Dedicated to Prof. Dr. Franz Loogen on the occasion of his 70th birthday

α-Adrenoceptor-mediated effects of sympathetic activation on the heart and coronary circulation are reviewed with emphasis on the pathophysiology of myocardial ischemia. A classification of α-adrenoceptor subtypes is presented, and the effects of α-adrenoceptor activation on presynaptic sympathetic nerve terminals, cardiomyocytes, endothelium, platelets, and coronary smooth muscle cells are discussed. α-Adrenergic coronary vasoconstriction at rest and during situations of sympathetic activation such as exercise and excitement is analyzed for the segmental, transmural, and regional distribution of coronary blood flow. Evidence for a significant contribution of α-adrenergic coronary vasoconstriction to experimental and clinical myocardial ischemia is provided. Cardiomyocyte α-adrenoceptor activation may be involved in ischemic and reperfusion arrhythmias. The participation of presynaptic and postsynaptic α-adrenoceptors, as well as of α1- and α2-adrenoceptors, in experimental and clinical myocardial ischemia will require further investigation. (Circulation 1990;81:1-13)

During the sympathetic activation induced by exercise or excitement, the activity of cardiac sympathetic nerves, as well as the release of circulating catecholamines, is enhanced. The resultant activation of cardiac β-adrenoceptors by neuronal and humoral catecholamines mediates an increase in heart rate and myocardial inotropic state, thereby increasing myocardial oxygen demand. Increased oxygen demand is adequately matched by an augmented oxygen supply after metabolic dilation of the coronary vasculature under normal conditions. However, the direct effect of the sympathetic neurotransmitter norepinephrine on coronary vascular smooth muscle cells is vasoconstriction through activation of α1-adrenoceptors. Even when under normal conditions a substantial coronary dilator reserve is present, α-adrenergic constriction acts to limit metabolic coronary dilation by about 30%, such that myocardial oxygen extraction increases together with coronary blood flow during sympathetic activation to match oxygen supply to the increased myocardial oxygen demand.

Whether α-adrenergic coronary constriction is powerful enough to limit coronary blood flow also under ischemic conditions when endogenous coronary dilator reserve is exhausted is highly controversial. It is also controversial whether α-adrenergic coronary constriction, if effective during myocardial ischemia, exerts a beneficial or deleterious influence on the ischemic myocardium. These controversies arise from the use of different experimental animal preparations, from clinical observations on different types of angina, drugs, and procedures of sympathetic activation, and finally, to a major part, from the use of an ever-increasing number of α-adrenoceptor agonists and antagonists with significantly different pharmacologic properties.

The purpose of this review is to attempt a resolution of some of these controversies and provide evidence for multiple α-adrenergic mechanisms contributing to and aggravating myocardial ischemia and its complications.

α-Adrenoceptor Subtypes: Classification, Agonists, and Antagonists

α-Adrenoceptors are classified for their location as presynaptic or postsynaptic and for their pharmacologic properties as α1- or α2-adrenoceptors (Table 1). Traditionally, postsynaptic and α1-adrenoceptors have been regarded as identical, these receptors mediating the constriction of all kinds of vascular beds, including the coronary circulation. Conversely, presynaptic and α2-adrenoceptors have
been traditionally regarded as identical, these receptors mediating a feedback inhibition of neuronal norepinephrine release from sympathetic nerve terminals. However, this classification is too simplistic because recent studies indicate the presence of both \(\alpha_1\) and \(\alpha_2\)-adrenoceptors at presynaptic sympathetic nerve terminals as well as at postsynaptic sites of different target cells.

The endogenous catecholamines norepinephrine and epinephrine act on both \(\alpha_1\)- and \(\alpha_2\)-adrenoceptors. Methoxamine and phenylephrine are selective agonists for \(\alpha_1\)-adrenoceptors.\(^8\) However, phenylephrine simultaneously activates \(\beta\)-adrenoceptors and can therefore be used as a selective \(\alpha_1\)-adrenoceptor agonist only in the presence of \(\beta\)-blockade.\(^8\) BHT 920, BHT 933 (azepexole), and UK-14,304 are selective agonists for \(\alpha_2\)-adrenoceptors.\(^8\) Clonidine, which has occasionally been used as an \(\alpha_2\)-adrenoceptor agonist, has a lesser selectivity for \(\alpha_2\)-adrenoceptors and is only a partial agonist at presynaptic \(\alpha_2\)-adrenoceptors.\(^8\) Phentolamine is a nonselective \(\alpha\)-adrenoceptor antagonist. Prazosin is a highly selective \(\alpha_1\)-adrenoceptor antagonist. Yohimbine, rauwolscine, and particularly idazoxan are selective \(\alpha_2\)-adrenoceptor antagonists.\(^9,10\)

The use of phenoxybenzamine in studies on \(\alpha\)-adrenergic mechanisms is problematic because it induces complete and irreversible blockade of \(\alpha_1\)-adrenoceptors but only incomplete blockade of \(\alpha_2\)-adrenoceptors.\(^11\)

A further subclassification of \(\alpha_{1A}\) and \(\alpha_{1B}\) adrenoceptors, as well as \(\alpha_{2A}\), \(\alpha_{2B}\), and \(\alpha_{2C}\) adrenoceptors, has been proposed on the basis of their different affinities in binding studies, their coupling to G-proteins, and their molecular characteristics.\(^12,13\) Also, a third subtype of \(\alpha\)-adrenoceptors has been proposed.\(^14\) However, at present these additional subclassifications are largely inferential and have little practical relevance to cardiovascular pharmacology.

### Targets for \(\alpha\)-Adrenoceptor Activation in the Heart

**Sympathetic Nerve Terminals**

The presence and functional role of presynaptic \(\alpha\)-adrenoceptors on cardiac sympathetic nerve terminals for sympathetic neurotransmission is well established. However, the augmentation of neuronal norepinephrine release\(^15,16\) and of myocardial\(^15,16\) and coronary vascular\(^17\) responses to sympathetic activation after nonselective \(\alpha\)-adrenoceptor blockade by phentolamine does not distinguish between presynaptic \(\alpha_1\)- and \(\alpha_2\)-adrenoceptors. Selective activation of presynaptic \(\alpha_2\)-adrenoceptors reduces neuronal norepinephrine release and the resulting tachycardia during cardiac sympathetic nerve stimulation.\(^8\) Their blockade enhances neuronal norepinephrine release during cardiac sympathetic nerve stimulation\(^18\) and exercise,\(^16\) resulting in markedly increased heart rate and contractility.\(^16,19\) Some studies also suggest the presence of \(\alpha_1\)-adrenoceptors on cardiac sympathetic nerve terminals of several species, also mediating a feedback inhibition of neuronal norepinephrine release during cardiac sympathetic nerve stimulation, similar to that mediated by \(\alpha_2\)-adrenoceptors.\(^19,20\)

However, the presence and functional importance of presynaptic \(\alpha_2\)-adrenoceptors for the hemodynamic responses to exercise in conscious dogs is controversial. Heyndrickx et al\(^16\) demonstrated that the arteriogenous norepinephrine gradient across the myocardium, as well as the increases in heart rate and left ventricular dP/dt during exercise, were potentiated by intravenous or intracoronary administration of the selective \(\alpha_2\)-antagonist yohimbine, whereas intravenous administration of the selective \(\alpha_1\)-antagonist prazosin caused no such potentiation. In contrast, in a recent study by Thaulow et al\(^19\) the exercise-induced increases in heart rate as well as in regional and global left ventricular contractility were augmented not only by intravenous infusion of the selective \(\alpha_2\)-antagonist idazoxan but also by intravenous infusion of the selective \(\alpha_1\)-antagonist prazosin when the prazosin-induced hypotension was prevented. The potentiation of exercise-induced increases in heart rate and contractility by either idazoxan or prazosin was eliminated by \(\beta\)-blockade, suggesting a functionally important role for both \(\alpha_1\)- and \(\alpha_2\)-adrenoceptors in the control of neuronal norepinephrine release.

### Table 1. Classification of \(\alpha\)-Adrenoceptor Subtypes in the Heart

<table>
<thead>
<tr>
<th>Site</th>
<th>Effects of activation</th>
<th>Selective agonists</th>
<th>Selective antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha_1)</td>
<td>Presynaptic</td>
<td>Feedback inhibition of norepinephrine release</td>
<td>Phenylephrine (also (\beta)-agonist)</td>
</tr>
<tr>
<td></td>
<td>Postsynaptic</td>
<td>Coronary vasoconstriction; Increase in myocardial inotropism (in some species)</td>
<td>Methoxamine</td>
</tr>
<tr>
<td>(\alpha_2)</td>
<td>Presynaptic</td>
<td>Feedback inhibition of norepinephrine release</td>
<td>(Clonidine)</td>
</tr>
<tr>
<td></td>
<td>Postsynaptic</td>
<td>Coronary vasoconstriction; Arrhythmias (?')</td>
<td>BHT 920, BHT 933, azepexole UK-14,304</td>
</tr>
</tbody>
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Norepinephrine is a nonselective agonist and phenotamine a nonselective antagonist at \(\alpha\)-adrenoceptors. Drugs in parentheses have lower selectivity and are preferably not used.
rime release during the sympathetic activation induced by exercise.

Cardiomyocytes

α-Adrenoceptors are present on the surface of cardiomyocytes from different mammalian species, including humans. In all but one study, the myocardial α-adrenoceptors were characterized as α₁-adrenoceptors. Activation of myocardial α₁-adrenoceptors by the selective α₁-agonists phenylephrine and methoxamine mediates a positive inotropic effect. In contrast to the β-adrenoceptor-mediated positive inotropic effect that is associated with shortened duration of contraction, the α₁-adrenoceptor-mediated positive inotropic effect is associated with a prolongation of contraction. During activation by norepinephrine or epinephrine, the α₁-adrenoceptor-mediated inotropic effect is of only minor functional importance as compared with that mediated by β-adrenoceptors. However, under certain circumstances of impaired β-adrenoceptor-mediated inotropic responses such as hypothyroidism, chronic propranolol treatment, or cardiac failure, myocardial α₁-adrenoceptor activation may serve as an inotropic reserve mechanism. The mechanism coupling myocardial α₁-adrenoceptor activation to the positive inotropic effect is not completely understood. α₁-Adrenoceptor activation induces the hydrolysis of phosphoinositides, although this effect may be only moderate. The cardiomyocyte α₁-adrenoceptor in isolated rat ventricular myocytes appears to be coupled to a GTP-binding protein. Cardiomyocyte α₁-adrenoceptor activation results in decreased intracellular (cyclic) cAMP content by stimulation of cAMP-phosphodiesterase. While cAMP thus appears not to be involved in the positive inotropic effect, myocardial α₁-adrenoceptor activation also causes an increase in intracellular calcium concentration. This increase in intracellular calcium concentration may not only mediate the positive inotropic effect but also significantly contribute to the α₁-adrenoceptor-mediated ventricular arrhythmias during ischemia and reperfusion.

However, it needs to be cautioned that the functional importance of cardiomyocyte α₁-adrenoceptor-mediated mechanical and electrophysiologic effects is largely species dependent. Significant responses to α₁-adrenoceptor activation have been demonstrated in rodents and cats. In dogs, the number of α₁-adrenoceptors, their importance in ischemic and reperfusion arrhythmias, and the α₁-adrenoceptor-mediated inotropic effect appear minimal. In a single study on isolated perfused rat hearts, there was an even greater importance of myocardial α₁- than α₁-adrenoceptors in reperfusion arrhythmias.

In cats, but not in rats, the number of α₁-adrenoceptors is increased during 30-minute ischemia. This increase in α₁-adrenoceptor density may be the underlying mechanism for the enhanced sensitiveness to α₁-adrenoceptor-mediated arrhythmias during ischemia and reperfusion in cats. In human ventricular myocardium, only a small portion of total adrenergic receptors is characterized as α₁-adrenoceptors that can mediate a positive inotropic effect.

Platelets

Human platelets carry α-adrenoceptors that have been characterized as α₂-adrenoceptors in radioligand-binding studies. Some but not all calcium antagonists compete for these binding sites. The activation of α₂-adrenoceptors mediates the aggregation of human platelets in response to norepinephrine and epinephrine. However, human platelets appear to also carry α₁-adrenoceptors at which phenylephrine acts as a partial agonist. Platelets may play a significant role both in the development of coronary atherosclerosis and in the precipitation of myocardial ischemia. The activation of platelets by catecholamines may be a contributing factor for enhanced platelet aggregation in patients with coronary artery disease during sympathetic activation such as exercise.

Endothelium

Endothelial cells of large canine and porcine coronary arteries carry α₂-adrenoceptors. Their activation by norepinephrine causes release of an endothelium-derived relaxant factor, which in turn attenuates norepinephrine-induced vasoconstriction mediated by vascular α₁-adrenoceptors. In rabbit carotid arteries, the endothelium attenuates the vasoconstriction induced by sympathetic nerve activation, metabolizes norepinephrine, physically limits norepinephrine overflow into the vessel lumen, and finally inhibits the release of norepinephrine from sympathetic nerve terminals. Shear stress at the endothelial surface of isolated rabbit carotid arteries activates the endothelial cells and causes them to attenuate adrenergic vasoconstriction. A shear stress-dependent, endothelium-mediated dilation has also been demonstrated in epicardial coronary arteries of conscious dogs at increased coronary blood flow and may act to modulate coronary vasomotion when metabolic dilation and α-adrenergic constriction compete during sympathetic activation. Conversely, loss of endothelial function in atherosclerotic coronary arteries may predispose such vessels to enhanced α-adrenergic coronary vasoconstriction.

Coronary Vascular Smooth Muscle

As compared with cutaneous and skeletal muscle vasculature, there are only minor α-adrenergic constrictor effects in canine coronary vessels during norepinephrine infusion and sympathetic nerve stimulation. During supramaximal cardiac sympathetic nerve stimulation in the presence of β-blockade, the increase in coronary resistance amounts to only 20–30% in anesthetized dogs. Both
postsynaptic α₁- and α₂-adrenoceptors are present on coronary vascular smooth muscle cells of various species. However, data on the quantitative contribution of vascular α₁- and α₂-adrenoceptors to the constriction of large epicardial, small resistive, and coronary collateral vessels are somewhat controversial. Although this review focuses on α-adrenergic mechanisms, it should be emphasized that neuropeptide Y is coreleased with norepinephrine from cardiac sympathetic nerve terminals, induces coronary vasoconstriction, and may facilitate α-adrenergic coronary vasoconstriction.

Epicardial coronary arteries. α-Adrenergic vasomotion of epicardial coronary arteries is probably of minor physiologic importance because epicardial coronary resistance contributes only about 5% to total coronary resistance in a setting without a coronary stenosis. Furthermore, the increase in epicardial coronary resistance during cardiac sympathetic nerve stimulation in the presence of β-blockade is even less pronounced than that of total coronary resistance. Conversely, the decrease in epicardial coronary diameter during cardiac sympathetic nerve stimulation in the presence of β-blockade is less than 5% of the resting diameter.

In isolated epicardial canine coronary arteries, adrenergic vasoconstriction appears to be mediated exclusively by α₁-adrenoceptors, whereas in isolated epicardial human and monkey coronary arteries, both α₁- and α₂-adrenoceptors are involved in norepinephrine-induced constriction. In epicardial coronary arteries of anesthetized β-blocked dogs, there is a vasoconstrictor response to the intracoronary infusion of the selective α₁-agonist methoxamine and a prazosin-sensitive constriction during cardiac sympathetic nerve stimulation, whereas intracoronary infusion of the selective α₂-agonist BHT 920 induces no epicardial coronary constriction. In conscious calves with β-blockade, however, equivalent reductions in epicardial coronary diameter by about 5% are induced by intracoronary infusion of either the selective α₁-agonist phenylephrine or the selective α₂-agonist BHT 920. These responses are abolished by the selective α₁-antagonist prazosin or the selective α₂-antagonist rauwolscine, respectively. Calcium antagonists inhibit the α-adrenoceptor-mediated constriction of epicardial coronary arteries both in vitro and in situ.

Coronary resistive vessels. With intravital microscopic analysis of the coronary microcirculation in cats, a nonuniform constrictor response to α-adrenoceptor activation by increasing doses of exogenous norepinephrine and frequencies of cardiac sympathetic nerve stimulation in the presence of β-blockade was demonstrated. A significant constriction of arterial and larger arteriolar segments with a resting diameter of more than 100 μm as well as a dilation of arterioles with a resting diameter of less than 100 μm occurred during α-adrenoceptor activation in the presence of β-blockade (Figure 1). These recent findings indicate a different coronary vascular site for metabolic dilation and α-adrenergic constriction and a redistribution of coronary vascular resistance toward larger coronary vessels during α-adrenoceptor activation. The simultaneous constriction and dilation of various coronary vascular segments may explain the weak net constrictor effect of α-adrenoceptor activation in the coronary circulation (see above) as compared with skeletal muscle in which α-adrenergic vasoconstriction occurs in a broad range of resistance vessels of different caliber.

Holz et al were the first to demonstrate that in anesthetized dogs the norepinephrine-induced increase in coronary resistance was significantly more attenuated by the selective α₂-antagonist rauwolscine than by the selective α₁-antagonist prazosin. The predominance of α₂-adrenoceptors in mediating coronary vasoconstriction in response to intracoronary α-adrenoceptor agonists and cardiac sympathetic nerve stimulation was later confirmed in anesthetized canine preparations. However, in conscious dogs the increase in end-diastolic resistance in response to intravenous norepinephrine appeared to be mediated by both α₁- and α₂-adrenoceptors because it was attenuated by the α₁-antagonist prazosin and the α₂-antagonist rauwolscine to almost the same extent. Whereas intravenous administration of norepinephrine also increases coronary perfusion pressure and ventricular afterload and causes reflex sympathetic withdrawal, regional intracoronary infusion of norepinephrine in conscious, chronically instrumented dogs revealed again a strong predominance of α₂-adrenoceptors in mediating the increase in end-diastolic coronary resistance, which was abolished by the selective α₂-antagonists rauwolscine and idazoxan. α₂-Adrenoceptor–mediated coronary constriction in anesthetized dogs can functionally be antagonized by the calcium antagonist nifedipine.

The presence of α₁- and α₂-adrenoceptors has also been shown in the coronary circulation of isolated guinea pig hearts. However, their distribution and functional importance in mediating constrictor responses to neuronal and humoral norepinephrine was not evaluated. In isoflurane-anesthetized pigs, α-adrenoceptor–mediated coronary constriction is even more sparse than in dogs, with virtually no responses to intracoronary infusion of the α₁-agonists phenylephrine and methoxamine and only weak and variable coronary constrictor responses to the α₂-agonist BHT 933. Both α₁- and α₂-adrenoceptor–mediated constrictions were also demonstrated in human forearm vessels in situ. However, the presence of α₁- and α₂-adrenoceptors, as well as their distribution and functional importance in the human coronary circulation, remain to be established.

Collaterals. The vasomotor response of coronary collateral vessels to α-adrenoceptor activation has so far only been studied in dogs. Collateral vasoconstriction in response to the α₁-agonist phenylephrine was suggested to occur based on an acute study in fibrillating dog hearts during cardiopulmonary bypass. However, in this study phenylephrine was infused.
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Bilateral Stellate Stimulation

FIGURE 1. Plots of percent changes in coronary vascular diameter (%ΔD) during bilateral stellate stimulation versus resting diameter (Di) of coronary vessels. Vessels with diameter larger than 100 μm constrict, whereas vessels with diameter smaller than 100 μm dilate during sympathetic activation in presence of β-blockade. From Reference 58 by permission from the American Heart Association.

systemically and the effects of phenylephrine on coronary perfusion pressure, the extravascular component of coronary resistance, and coronary vasomotor tone in the nonischemic and ischemic myocardium could not be adequately separated from its effects on the collateral circulation. In another study,68 no α-adrenoceptor–mediated constriction of mature collaterals, as well as of native coronary vessels in response to intracorony norepinephrine was reported. However, a marked constriction in response to intracoronary infusion of the selective α2-agonist BHT 920 was observed. It remains unclear why in this study the selective α2-agonist BHT 920 induced a constrictor response that was not observed in response to norepinephrine, which acts on coronary vascular α1 and α2-adrenoceptors.

The absence of any constrictor response to α1 as well as α2-adrenoceptor activation was reported from carefully controlled experiments on the native immature69 and mature70,71 canine collateral circulation in situ, and the lack of responsiveness to α-adrenoceptor activation was confirmed after isolation of the collateral vessels in vitro.70

Because of the apparent lack of α-adrenergic vasoconstriction in the collateral vessels themselves, collateral blood flow during sympathetic activation is determined by the driving pressure gradient across the collaterals. This driving pressure gradient is reduced during sympathetic activation by a simultaneous metabolic vasodilation in the terminal vascular bed of the nonischemic donor side and an α-adrenoceptor–mediated vasoconstriction in the terminal vascular bed of the ischemic recipient side.72

Regional and transmural distribution of α-adrenergic coronary constriction. During electrical stimulation of different cardiac sympathetic nerves in anesthetized,
β-blocked dogs, there are marked regional variations in the coronary constrictor response in different regions of the left and right ventricle. Electrical stimulation of the left ventrolateral cardiac sympathetic nerve induced a more pronounced vasoconstrictor response in the subepicardial layers of the posterolateral myocardium than in the subendocardial layers, resulting in an improved ratio of subendocardial to subepicardial blood flow. However, it should be emphasized that this improved subendocardial to subepicardial blood flow ratio was still associated with some decrease in subendocardial blood flow. The coronary constrictor response to intracoronary α1-adrenoceptor activation with phentolamine and α2-adrenoceptor activation with BHT 933 is transmurally homogeneous, with no transmural redistribution of blood flow occurring in nonischemic myocardium.

α-Adrenergic coronary constrictor tone at rest. Significant α-adrenergic coronary constrictor tone at rest has been suggested by several studies in anesthetized and conscious dogs. A further reduction in coronary vasomotor tone resulted from nonselective α-adrenoceptor blockade by phenolamine in conscious dogs with β-blockade and maximal pharmacologic coronary dilation by adenosine. Reduction of α-adrenergic coronary constrictor tone at rest resulting in a preferential improvement in subendocardial blood flow was reported in anesthetized, vagotomized dogs after surgical left stellactomy and in conscious dogs after chemical regional myocardial sympathectomy by 6-hydroxydopamine. Obviously it is critical for all these studies to confirm true resting basal conditions. Such a true resting state certainly does not exist in chloralose-anesthetized dogs, and heart rate or maximum dP/dt were relatively high in the two studies with conscious dogs. Furthermore, nonselective coronary vasodilation secondary to toxic damage by 6-hydroxydopamine cannot be excluded. In contrast to the previously mentioned studies, Chilian et al reported in well-controlled experiments were unable to demonstrate any α-adrenergic coronary constrictor tone in conscious dogs under true resting conditions in a myocardial region sympathectomized by perivascular incisions and topical application of phenol.

In humans there appears to be some evidence for resting α-adrenergic coronary constrictor tone, because normally innervated patients are characterized by a higher resting coronary resistance and a higher coronary arteriovenous oxygen difference than cardiac transplanted patients, this difference being abolished by nonselective α-blockade with phenolamine. However, the conclusions of this study are largely based on the use of coronary sinus thermodilution, which may not be suitable to detect small changes in coronary blood flow. Additional studies using more reliable techniques are needed to resolve the issue of α-adrenergic coronary constrictor tone at rest in humans.

Reflex regulation of α-adrenergic coronary constriction. An α-adrenoceptor-mediated increase in coronary resistance is part of the cardiac response to carotid baroreceptor reflex activation. Carotid chemoreceptor activation induces a biphasic coronary vasomotor response with an early dilation and a late constriction. In conscious dogs with intracarotid injection of nicotine, the dilator response has been suggested to involve the withdrawal of α-adrenergic coronary constrictor tone secondary to an increased depth of inspiration. However, an equivalent attenuation of this coronary dilator response by α-adrenoceptor blockade in normally innervated and cardiac-denervated conscious dogs excludes a significant role of cardiac sympathetic nerves in the coronary dilation during carotid chemoreceptor activation. In contrast to dogs, the pulmonary inflation reflex has almost no physiologic significance in the coronary circulation of conscious humans. With controlled ventilation, a significant α-adrenoceptor-mediated coronary constrictor response is apparent in conscious dogs during carotid chemoreceptor activation.

Several central nervous sites from which α-adrenergic coronary constriction can be elicited have been identified in anesthetized cats. However, a physiological or pathological role for these central nervous sites in regulating coronary blood flow remains to be established.

α-Adrenergic coronary constriction during exercise. In the absence of β-blockade, nonselective α-blockade by phenolamine, as well as selective α1-blockade by prazosin and selective α2-blockade by yohimbine or idazoxan, augments the decrease in coronary vascular resistance during exercise. However, as discussed previously, in the absence of β-blockade this effect of systemic or regional intracoronary α-blockade can be caused by presynaptic disinhibition of neuronal norepinephrine release, resulting in enhanced metabolic coronary vasodilation, as well as by the attenuation of α-adrenergic coronary vasoconstriction. Furthermore, systemic phenolamine and prazosin induce hypotension, resulting in an additional baroreflex-mediated sympathetic activation. The quantitative contribution of baroreflex mediated sympathetic activation, presynaptic disinhibition of norepinephrine release, and attenuation of α-adrenergic coronary vasoconstriction to the potentiation of exercise-induced coronary vasodilation by α-blockade are difficult to assess. Nevertheless, studies in conscious dogs with β-blockade demonstrate that α-adrenergic coronary vasoconstriction limits exercise-induced metabolic coronary dilation. Whereas Gwirtz et al even reported a limitation of exercise-induced increases in cardiac function by α-adrenergic coronary vasoconstriction, no augmentation of cardiac performance occurred in two other studies using treadmill exercise in β-blocked conscious dogs after systemic phenolamine or selective α1- or α2-blockade.

This apparent difference could be due to different exercise workloads, resulting in a different recruitment of coronary arteriovenous oxygen difference in matching oxygen supply to myocardial oxygen demand.
The contribution of α₁- and α₂-adrenoceptors to coronary vasoconstriction during exercise has not been assessed in a β-blocked preparation so far.

α-Adrenergic coronary constrictor tone during submaximal exercise is exerted predominantly by circulating catecholamines and not by local catecholamine release from cardiac sympathetic nerves because there was no difference in myocardial blood flow between an innervated and a sympathectomized region in exercising dogs during β- and combined α- and β-blockade. There was also no difference in the transmural distribution of myocardial blood flow between the innervated and the sympathectomized region, suggesting transmurally homogeneous α-adrenergic coronary vasoconstriction. In contrast, Huang and Feigl claimed a transmurally nonuniform α-adrenergic coronary vasoconstriction, which acts to maintain a homogeneous transmural blood flow distribution during exercise by preferential α-adrenergic vasoconstriction in the subepicardium. However, even apart from the problematic use of phenoxybenzamine in this study, only small differences in highly normalized and interpolated transmural blood flow ratios between an intact and a phenoxybenzamine-treated region were demonstrated. Because total blood flow was still higher in the phenoxybenzamine-treated region, a beneficial role of α-adrenergic coronary vasoconstriction for transmural myocardial perfusion during exercise seems not to be well substantiated.

α-Adrenergic Coronary Constriction in Experimental Myocardial Ischemia

In 1967, Bassenge et al were the first to observe a shift from metabolic coronary dilation to coronary constriction during intracoronary norepinephrine infusion when coronary perfusion pressure in anesthetized dogs was progressively reduced (Figure 2). This important dependence of norepinephrine-induced coronary vasoconstriction on the preexisting coronary vasomotor tone was not further pursued until 1981 when Buffington and Feigl demonstrated the persistence of α-adrenergic coronary vasoconstriction distal to a moderate stenosis during intracoronary norepinephrine infusion. This poststenotic α-adrenergic coronary vasoconstriction was powerful enough to limit oxygen supply up to the point of cardiac failure. However, net lactate production did not occur.

During electrical cardiac sympathetic nerve stimulation in anesthetized dogs, metabolic coronary dilation was progressively reversed to α-adrenergic coronary constriction when coronary dilator reserve was progressively reduced by an increasing severity of coronary stenosis (Figure 2). Distal to a severe coronary stenosis, which exhausted poststenotic coronary dilator reserve, significant α-adrenergic coronary constriction was induced by cardiac sympathetic nerve stimulation, resulting in the precipitation of myocardial ischemia as evidenced by regional contractile dysfunction and net lactate production. The poststenotic coronary constriction and the resulting ischemia were prevented by phentolamine or selective α₂-blockade with rauwolscine in the absence and presence of β-blockade. Nifedipine also functionally antagonized the α₂-adrenoceptor-mediated poststenotic coronary constriction and prevented the resulting myocardial ischemia.
The presence of α-adrenergic constrictor tone during coronary hyperperfusion was confirmed in anesthetized open-chest dogs with a presumably high resting sympathetic tone. This α-adrenergic constriction was attenuated by the selective α1-antagonist prazosin and not by the selective α2-antagonist yohimbine. The different involvement of α1 or α2-adrenoceptors in coronary vasoconstriction during myocardial ischemia may be related to the different level of sympathetic activation in these studies.

In contrast to all previously discussed studies, which agree on a deleterious role of α-adrenergic coronary constriction during myocardial ischemia, Nathan and Feigl concluded from their data that α-adrenergic coronary constriction exerts a favorable effect on ischemic myocardium by preventing a transmural redistribution of blood flow away from the ischemic subendocardium. In anesthetized dogs, they observed during constant inflow coronary hyperperfusion an increase in interpolated subendocardial to subepicardial blood flow ratios in a control as compared with a phenoxybenzamine-treated region during intracoronary norepinephrine infusion. However, the use of constant inflow coronary hyperperfusion prevented the most significant beneficial effect of α-blockade in the studies described above, that is, an increase in total coronary blood flow. Absolute data for subendocardial blood flow or measures of regional contractile function and metabolism were not presented to substantiate the aggravation of ischemia in the phenoxybenzamine-treated region. Under ischemic circumstances, the complete α1 but incomplete α2-blockade by phenoxybenzamine is particularly problematic because α1-adrenergic coronary constriction is attenuated by ischemia, whereas α2-adrenergic coronary constriction is not. Thus, phenoxybenzamine may have removed α1-constrictor tone in the less-ischemic subepicardium and left α2-constrictor tone in the most-ischemic subendocardium unopposed, causing an artificial imbalance of transmural blood flow distribution rather than proving a protective role of physiologic α-adrenergic coronary constriction.

A transmurally nonuniform α2-adrenergic coronary vasoconstriction contributing to the severity of myocardial ischemia has indeed been demonstrated in conscious β-blocked dogs when during sympathetic activation by exercise ischemia was induced by an acute coronary stenosis (Figure 3). Intra-coronary infusion of the selective α2-antagonist idazoxan distal to the stenosis resulted in significant increases in ischemic subendocardial and midmyocardial blood flow, whereas subepicardial blood flow was unchanged (Figure 4). Whereas the transmural distribution of coronary vascular α1- and α2-adrenoceptors is uniform in nonischemic myocardium, the preferential α2-adrenergic coronary constriction in the most ischemic inner myocardial layers may be related to the attenuation of α1- but not α2-adrenergic coronary constriction by ischemia, potentially because of the different sensitivity of α1- and α2-adrenoceptors to acidosis. Recruitment of coronary dilator reserve presumably through attenuation of α2-adrenergic coronary constriction by the calcium antagonist nifedipine also improved subendocardial and midmyocardial blood flow and attenuated regional contractile dysfunction.
during exercise-induced ischemia in conscious dogs with a fixed chronic coronary artery stenosis.99

A true protective role of cardiac sympathetic nerves in an ischemic myocardial region through preferential subepicardial \( \alpha \)-adrenergic coronary constriction was demonstrated in conscious dogs during exercise-induced ischemia because subendocardial blood flow was higher in the innervated than in a phenol-denervated poststenotic region.100 However, this protective role of subepicardial \( \alpha \)-adrenergic coronary constriction was strictly limited to neuronally released norepinephrine, whereas as previously shown by the same authors,89 the coronary vasomotor effects in exercising dogs are essentially exerted by circulating catecholamines. Thus, systemic \( \alpha \)-blockade with phentolamine actually increased ischemic subendocardial blood flow in the innervated as well as in the denervated region.100 The failure to demonstrate any \( \alpha \)-adrenergic coronary constriction distal to a severe coronary stenosis with exhausted poststenotic dilator reserve in anesthetized open-chest dogs during cardiac sympathetic nerve stimulation101 was probably due to the use of pentobarbital anesthesia, which is known to inhibit \( \alpha \)-adrenergic coronary vasoconstriction selectively.46,102 The relatively weak poststenotic coronary vasoconstriction in pigs during intravenous norepinephrine infusion, which did not result in a reduction of regional myocardial blood flow,103 was probably related to the paucity of \( \alpha \)-adrenoceptors in the coronary circulation of the pig.65

In conclusion, \( \alpha \)-adrenergic constrictor tone in ischemic myocardium can be demonstrated in appropriate experimental models. \( \alpha \)-Adrenergic coronary vasoconstriction acts to initiate or aggravate poststenotic myocardial ischemia. The involvement of \( \alpha_1 \)- and \( \alpha_2 \)-adrenoceptors is not yet clear.

\( \alpha \)-Adrenergic Coronary Constriction in Clinical Myocardial Ischemia

Spasm

There are several more or less anecdotal observations of \( \alpha \)-adrenoceptor involvement in coronary vasospasm,104–106 which may be precipitated by the combined administration of epinephrine and propranolol104 or the cold pressor test105 and can be prevented by phentolamine104 or prazosin.106 However, in carefully controlled clinical trials, an important role of \( \alpha \)-adrenergic coronary constriction for the precipitation of vasospasm in epicardial coronary arteries was ruled out.107–109

Dynamic Coronary Stenosis

In a stenotic coronary artery segment with an eccentric atherosclerosis and an adjacent arterial wall region retaining vasomotion, sympathetic activation by isometric exercise can induce critical narrowing,110,111 which then results in ischemic myocardial dysfunction and angina pectoris.110 This critical narrowing of an epicardial coronary segment with a preexisting eccentric atherosclerosis is presumably due to \( \alpha \)-adrenoceptor activation during isometric exercise and can be prevented by intracoronary nitroglycerin110 as well as by the calcium antagonist diltilazem in a dose that does not induce unspecific epicardial coronary dilation.111 A vasoconstriction of stenotic coronary arteries resulting in myocardial ischemia was also demonstrated with biplane quantitative coronary angiography during dynamic bicycle exercise in patients with chronic stable angina, and it was also prevented by intracoronary nitroglycerin.112

Cold Pressor Test

The cold pressor test is used as a provocative intervention to study the effects of reflex sympathetic activation in patients with coronary artery disease.

**FIGURE 4.** Effects of the selective \( \alpha_1 \)-antagonist idazoxan on regional myocardial blood flow in conscious dogs with severe coronary stenosis inflated during exercise. Idazoxan significantly improves blood flow to the most ischemic subendocardium and midmyocardium, whereas blood flow to the less ischemic subepicardium remains unchanged. From Reference 63 by permission of the American Heart Association.
Whereas intact coronary arterial segments dilate during the cold pressor test, there is a preferential vasodilation of atherosclerotic coronary arterial segments. A significant increase in coronary vascular resistance was induced by the cold pressor test in patients with coronary artery disease, resulting in the precipitation of angina pectoris in some of them. This increase in coronary vascular resistance during the cold pressor test appears to be mediated by activation of α-adrenoceptors because it is prevented by phentolamine. Nifedipine also prevents the increase in coronary vascular resistance as well as a net lactate production indicative of myocardial ischemia during the cold pressor test. However, caution should be used in interpreting these studies because they were performed either using angiography of epicardial coronary segments, which may contribute little to coronary resistance (see above), or using coronary sinus thermodilution techniques, which may be unreliable in the presence of flow heterogeneities caused by coronary artery disease. Additional studies on this subject are certainly needed.

**Effort Angina**

There is evidence for a significant role of α-adrenergic coronary vasoconstriction in exercise-induced myocardial ischemia in patients with stable angina pectoris. The exercise-induced ST-segment depression and angina pectoris in patients with chronic stable angina are reduced by intracoronary phentolamine (Figure 5), and exercise duration is prolonged by intravenous phentolamine. A reduction in exercise-induced ST-segment depression and an increase in exercise capacity were also achieved in patients with chronic stable angina treated with the selective α₁-antagonist indoramin. However, the role of α₂-adrenergic coronary constriction in human exercise-induced myocardial ischemia has not been investigated so far.

In conclusion, there is good evidence for a significant involvement of α-adrenergic coronary vasoconstriction in the initiation and aggravation of experimental and clinical myocardial ischemia, and α-adrenoceptor-mediated effects on cardiomyocytes or platelets may contribute to myocardial ischemia and its complications as well. The detailed participation of presynaptic and postsynaptic adrenoceptors, as well as that of α₁- and α₂-adrenoceptors, in clinical myocardial ischemia remains to be investigated.

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