**From Bench to Bedside**

**α-Adrenergic Coronary Vasoconstriction and Myocardial Ischemia in Humans**

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**Abstract**—The use of quantitative coronary angiography, combined with Doppler and PET, has recently been directed at the study of α-adrenergic coronary vasomotion in humans. Confirming prior animal experiments, there is no evidence of α-adrenergic coronary constrictor tone at rest. Again confirming prior experiments, responses to α-adrenoceptor activation are augmented in the presence of coronary endothelial dysfunction and atherosclerosis, involving both α₁- and α₂-adrenoceptors in epicardial conduit arteries and microvessels. Such augmented α-adrenergic coronary constriction is observed during exercise and coronary interventions, and it is powerful enough to induce myocardial ischemia and limit myocardial function. Recent studies indicate a genetic determination of α₂-adrenergic coronary constrictor tone. *(Circulation. 2000;101:689-694.)*

**Key Words:** coronary disease ■ ischemia ■ microcirculation ■ nervous system ■ receptors, adrenergic, alpha

**Under** normal circumstances, small coronary arteries and arterioles with a diameter of <300 µm are the principal determinants of coronary vascular resistance.¹ These vessels receive autonomic innervation, and their diameter is altered by activation of these nerves.² In animal experiments, there is little α-adrenergic coronary vasomotor tone at rest, and the increase in coronary blood flow during sympathetic activation is only somewhat blunted. When the coronary circulation, however, is impaired by hypercholesterolemia,³ endothelial dysfunction,⁴ exhaustion of autoregulation,⁵ or severe coronary stenosis,⁶,⁷ α-adrenergic vasoconstriction becomes unrestrained and powerful enough to reduce coronary blood flow and initiate myocardial ischemia.⁸ Both α₁- and α₂-adrenoceptors mediate coronary vasoconstriction, and there is a gradient with α₁-adrenoceptors more predominant in larger vessels and a reverse gradient with α₂-adrenoceptors more predominant in the microcirculation.⁹ Surprisingly, isolated coronary arterioles of a size that constricts in vivo to α₁-adrenoceptor activation are unresponsive in vitro,¹⁰ and cardiomyocytes on α₁-adrenergic activation release endothelin, which causes arteriolar constriction.¹¹

In the past, the study of α-adrenergic coronary vasoconstriction in humans has been limited by a lack of adequate techniques to quantify coronary blood flow and myocardial perfusion. In the last decade, quantitative coronary angiography has allowed quantification of the diameter of coronary arteries to ~0.5 mm. Study of the human coronary microcirculation is indirect¹² and relies on parameters such as coronary flow velocity, measured invasively with Doppler flow probes, or myocardial blood flow, quantified noninvasively with PET.¹³ Recently, these techniques have become widely available and directed toward the study of α-adrenergic coronary vasoconstriction in humans. Moreover, selective α₁- and α₂-agonists and -antagonists are now available for clinical use. The agonist approach is used to study the endogenous α-adrenergic coronary vasoconstriction at rest or during sympathetic activation. Different maneuvers to elicit sympathetic activation, eg, exercise, cold pressor test, mental stress, or sympathoexcitatory reflexes, may differ in their recruitment of α-adrenergic coronary vasoconstriction and in the concomitant activation of other mechanisms. The agonist approach is used to study the effect of selective α-adrenoceptor agonists on coronary blood flow, myocardial perfusion, and contractile function during different physiological and pathophysiological conditions. Also, a genetic determination of α-adrenergic coronary constrictor responses can now be analyzed in humans; a polymorphism in the genes encoding for a G-protein subunit explains part of the interindividual variation in α-adrenergic coronary vasoconstriction.¹³α

**α-Adrenergic Coronary Constrictor Tone in Subjects With Normal Coronary Angiograms**

Ideally, resting α-adrenergic constrictor tone is investigated (1) with intracoronary administration of an α-antagonist, (2) with β-blockade to avoid direct and indirect (metabolic) β-adrenergic dilation in response to augmented norepineph-
rime release after presynaptic α-blockade, and (3) under true resting conditions in the absence of changes in systemic hemodynamics. A few studies only come close to such rigid requirements.

Using quantitative coronary angiography and intracoronary Doppler, Hodgson et al.14 studied patients with angiographically normal coronary arteries and cardiac transplant recipients. With β-blockade, intracoronary infusion of the nonselective α-antagonist phentolamine induced minimal changes in epicardial diameter and coronary resistance in both normally innervated and denervated patients, indicating negligible resting α-adrenergic tone.14 Similarly, neither epicardial diameter nor coronary blood flow velocity was altered by intracoronary phentolamine in another study in cardiac transplant recipients.15 Although the subjects in the above studies had normal coronary angiograms, they had clinical indication of coronary catheterization, ie, chest pain. More recently, myocardial perfusion was measured with PET and 15O-labeled water in normal volunteers without signs, symptoms, or risk factors of coronary artery disease, and no difference in myocardial perfusion was found.16 Thus, there is no significant α-adrenergic coronary constrictor tone at rest, confirming prior experiments.17

The response of angiographically normal coronary arteries to sympathetic activation by the cold pressor test,15,18–22 mental stress,23,24 or exercise15,18,25,26 is vasodilation of both epicardial coronary arteries15,18,21–27 and microvessels.15,18,21–24,27 In contrast to animal studies,28 there is no evidence that vasodilation is limited by α-adrenergic coronary vasoconstriction and consequently enhanced by α-blockade in healthy humans.15,26

The limitation of coronary reserve by α-adrenergic coronary vasoconstriction is controversial. Using quantitative coronary angiography and Doppler in patients with normal coronary angiogram and in cardiac transplant recipients, Hodgson et al.14 found that coronary reserve, as recruited by intracoronary papaverine, was not increased by intracoronary α-blockade with and without additional β-blockade. In contrast, in normal volunteers, oral treatment with doxazosin increased the dipyridamole-recruited coronary reserve as assessed with PET,16 consistent with findings in conscious dogs.29 Part of the increase in coronary reserve with doxazosin could be attributed to increased circulating catecholamines in response to dipyridamole.30

Using the selective α2-antagonist yohimbine in the presence of β-blockade, Indolfi et al.31 found no changes in epicardial diameter and coronary blood flow velocity in patients with atypical chest pain but angiographically normal coronary arteries. Baumgart et al.,32 using intracoronary infusion of the selective α1-agonist methoxamine at increasing doses, observed no vasoconstriction of normal epicardial coronary arteries (as confirmed by intravascular ultrasound) or resistive vessels. Although it did not affect epicardial coronary artery diameter, intracoronary infusion of the selective α2-agonist BHT 933 induced a dose-dependent microvascular constriction.

Thus, there appears to be no α-adrenergic coronary constrictor tone at rest but possibly a limitation of coronary reserve. The constrictor response of the normal coronary circulation during sympathetic activation is mediated by α2-adrenoceptors and mainly affects the microcirculation.

Enhanced α-Adrenergic Vasoconstriction in Patients With Endothelial Dysfunction and Risk Factors

Intact endothelium opposes α-adrenergic vasoconstriction, and both shear stress and activation of endothelial α2-adrenoceptors contribute to the inhibition of α-adrenergic vasoconstriction in the experimental setting.4,33

Apparently, early stages of endothelial dysfunction and atherosclerosis already impair coronary dilator and predispose to constrictor responses. Exercise-induced dilation of angiographically normal epicardial vessels is largely attenuated in the presence of hypercholesterolemia34 or hypertension,35 and flow-mediated epicardial dilation is blunted in smokers.36 Nabel et al.31 first used quantitative coronary angiography and Doppler to compare changes in epicardial diameter and coronary blood flow in angiographically normal vessels with those in vessels with mild and more advanced atherosclerosis during the cold pressor test. They found a progressive reversal from vasodilation to vasoconstriction during the cold pressor test in both epicardial and resistive vessels with increasing severity of atherosclerosis. Zeiher et al.37 confirmed the loss of dilation of atherosclerotic epicardial and resistive vessels during the cold pressor test and found that the vasomotor response closely correlated with that to intracoronary acetylcholine. Patients with endothelial dysfunction in one protocol tended to experience exercise-induced ischemia during another protocol, as judged by thallium scintigraphy and anginal symptoms.37 With intracoronary infusion of the selective α1-agonist phenylephrine, a more pronounced coronary constriction was documented in mildly atherosclerotic epicardial segments that also constricted to acetylcholine, demonstrating the opposing influences of α-adrenergic coronary constriction and endothelium-mediated coronary vasodilation.38

Whether heart failure predisposes to enhanced α-adrenergic coronary vasoconstriction is not clear. However, neither α1- nor α2-adrenoceptors in the peripheral circulation are downregulated in patients with heart failure.39 Clearly, impairment of endothelial function and integrity even in early stages predisposes the human coronary circulation to enhanced α-adrenergic vasoconstriction during sympathetic activation.

Enhanced α-Adrenergic Vasoconstriction in Patients With Established Coronary Artery Disease

Recent studies using quantitative coronary angiography and Doppler confirm prior studies using coronary sinus thermodilution or xenon-133 clearance that found an increase in coronary resistance in patients with coronary artery disease during the cold pressor test.19,20,40 which was prevented by intravenous phentolamine19 or intravenous trimazosin, a selective α1-antagonist.40 Mental stress also induces dilation of normal and constriction of atherosclerotic epicardial and resistive vessels.23,24 Finally, smoking increases coronary
resistance in patients with coronary artery disease, and this effect is counteracted by intravenous phentolamine. 41

Most of the above studies that observed constrictor responses either did not report on signs and symptoms of ischemia or reported angina in only a minority of patients with coronary artery disease. 19, 20, 24 Also, in most of these studies in which the cold pressor test or mental stress was used to induce sympathetic activation, there was no evidence of the α-adrenergic nature of the observed vasoconstriction, but intracoronary phentolamine induced a greater decrease in coronary resistance than placebo during mental stress. 23 In patients with coronary artery disease, intracoronary infusion of the selective α2-antagonist yohimbine with concomitant β-blockade increased coronary sinus norepinephrine levels and reduced both epicardial diameter and coronary blood flow velocity, possibly because of enhanced α1-adrenoceptor activation. 31 An increase in coronary vascular resistance index in response to intravenous norepinephrine was found in patients with coronary artery disease. 42 Baumgart et al. 32 using intracoronary infusion of the selective α1-agonist methoxamine at increasing doses in patients with coronary artery disease, reported constriction of both epicardial and resistive coronary vessels. Intracoronary infusion of the selective α2-agonist BHT 933 did not induce constriction of normal but did induce constriction of atherosclerotic epicardial segments (the Figure). The decrease in coronary blood flow by BHT 933 in normal vessels was enhanced in the presence of atherosclerosis and was sufficient to induce net myocardial lactate production and ECG signs of ischemia, 32 supporting prior studies in anesthetized 6 and conscious dogs. 7 In summary, coronary atherosclerosis unmasks α1-adrenergic coronary constriction and augments α2-adrenergic coronary constriction, which can precipitate myocardial ischemia.

**Exercise-Induced Stenosis Constriction**

In the early 1980s, the concept of dynamic coronary stenosis was introduced, 43, 44 which proposed that a stenotic coronary segment with an eccentric plaque and an adjacent wall region retaining vasomotor function might undergo active critical narrowing during sympathetic activation. With respect to more recent findings on the predisposition of vessels with endothelial dysfunction and atherosclerosis to undergo α-adrenergic coronary vasoconstriction, stenosis constriction can be viewed as an extreme variant of this process. Isometric exercise (handgrip) decreased the angiographically determined minimal luminal area and induced angina in some patients, 45 an effect that was also elicited by combined propranolol and epinephrine, 44 supporting the α-adrenergic nature of the observed stenosis constriction.

Stenosis constriction is also induced by dynamic exercise (supine bicycle) in patients with coronary artery disease and associated with angina in 2 of 3 patients studied. 25 The vasomotor nature of stenosis constriction during exercise is evidenced by its reversal with nitroglycerin, 25, 45 but its α-adrenergic nature became evident only recently. In patients with coronary artery disease, intracoronary phentolamine,
without and with β-blockade, had no effect on epicardial cross-sectional area at rest but reversed the exercise-induced vasoconstriction of the stenotic segment into vasodilation.26

α-Adrenergic Coronary Vasoconstriction During Interventions

A series of recent studies has related epicardial coronary vasoconstriction that has been reported early after PTCA46,47 to α-adrenergic activation.48–52 Gregorini et al48 observed a constrictor response not only of the culprit segment and a distal segment of the vessel that underwent PTCA but also of the nonmanipulated control vessel. This vasoconstriction was abolished by intracoronary (at the coronary ostium) phentolamine. With β-blockade, phentolamine still reversed constriction of the proximal segments of the culprit and control vessels but not of the respective distal segments. The selective α2-antagonist yohimbine also attenuated the observed epicardial vasoconstriction, although only partially at the stenosis level.48 Phentolamine with and without β-blockade and yohimbine also reversed the decrease in coronary blood flow, but only phentolamine without β-blockade caused a significant increase in coronary blood flow in the culprit vessel. Using a somewhat different protocol, Indolfi et al49 compared epicardial vasomotion in control patients undergoing PTCA to that in patients pretreated with intracoronary (subselectively at the stenosis) phentolamine; phentolamine prevented constriction distal to the site of PTCA but not in the control segment. These findings were interpreted as evidence of a cardio-cardiac sympathoexcitatory reflex initiated by coronary stretch and/or myocardial ischemia and resulting in α-adrenergic coronary vasoconstriction, as previously demonstrated in experiments.53,54 A significant vasoconstriction after successful PTCA was also found in the forearm circulation and was prevented by regional phentolamine. Because this α-adrenergic forearm vasoconstriction was not accompanied by increased heart rate or arterial pressure, it possibly originated from the same thoracic spinal reflex as the α-adrenergic coronary vasoconstriction and did not reflect a generalized adrenergic activation.55

Gregorini et al50 extended their studies to patients undergoing rotational atherectomy and PTCA; intracoronary infusion of the selective α1-antagonist urapidil after atherectomy or PTCA reversed the observed decrease in epicardial diameter, and pretreatment with urapidil prevented any decrease in diameter. Subsequently, they also studied the consequences of PTCA-induced reflex α-adrenergic coronary vasoconstriction on myocardial contractile function by transesophageal echocardiography.51,52 Intracoronary phentolamine and intravenous urapidil again reversed the decreases in the diameter of the distal poststenotic and control vessels and in coronary blood flow; they also reversed the observed decreases in systolic wall thickening in the previously ischemic and nonischemic myocardium.51 Finally, in patients with recent acute myocardial infarction and subsequent thrombolysis who then underwent PTCA and stent implantation, intracoronary phentolamine and intravenous urapidil reversed the observed α-adrenergic vasoconstriction and reduction in systolic wall thickening in both the infarct-related and non–infarct-related artery territories; the improvements seen with urapidil were slightly attenuated by concomitant β-blockade.52

In carefully controlled clinical trials, although in a small number of patients, no benefit from prazosin in terms of angina, nitroglycerin use, and ECG changes was found in patients with Prinzmetal’s variant angina,56,57 a finding that did not support an important role of α-adrenergic coronary constriction in this syndrome. A role of α1-adrenergic coronary vasoconstriction in syndrome X, ie, in patients with normal coronary angiogram but exercise-induced chest pain and ECG alterations, was previously hypothesized, because doxazosin increased the diprydiamole-recruited coronary reserve in some patients. However, in 7 of 10 patients, diprydiamole-induced chest pain persisted.58 In a subsequent double-blind randomized study, no difference in diprydiamole-recruited coronary reserve was found in patients with syndrome X treated with doxazosin versus placebo, and the flow reserve in syndrome X patients was comparable with that in normal volunteers.58a

Exercise duration is prolonged with oral phentolamine,59 and exercise-induced ST-segment depression and angina are reduced by intracoronary phentolamine60 in patients with chronic stable angina. Oral treatment with the selective α1-antagonist indoramin also improved exercise capacity and reduced ST-segment depression,61 although intracoronary indoramin was less effective than phentolamine in one study62 and oral indoramin did not reduce exercise-induced ST-segment depression in another study,63 suggesting a predominant role of α1-adrenergic poststenotic coronary vasoconstriction in exercise-induced ischemia, as previously demonstrated in dogs.6,7

To what extent epicardial and microvascular circulation were affected by α-blockade in these studies remains unclear. Larger, controlled trials looking at the effect of α-blockade in patients with chronic stable angina are lacking and are probably worthwhile only with agents that do not block presynaptic α2-adrenoceptors and thus do not increase noradrenaline release but are nevertheless effective at postsynaptic α2-adrenoceptors, which appear more important than α1-adrenoceptors in mediating α-adrenergic coronary vasoconstriction. Such requirements are well met by calcium antagonists that may counteract α-adrenergic coronary constriction in both the experimental64 and clinical setting.65

Perspective

Studies in the catheterization laboratory or using PET have established the existence of α-adrenergic coronary constriction in humans and confirmed prior experimental studies. Importantly, the role of α-adrenergic constriction during the cold pressor test, mental stress, and isometric and dynamic exercise, as well as coronary interventions, has been clearly demonstrated. The value of α-antagonism in daily ischemic scenarios is less clear.

Further progress in imaging technique (better spatial resolution in PET, echo contrast) will also permit study of α-adrenergic coronary constrictor influences on transmural blood flow distribution66 in humans. Further progress is also expected from recent studies demonstrating a genetic
determination of α-adrenergic coronary constriction. A polymorphism in the gene encoding for the Gβ3 subunit of G proteins that is associated with alternative splicing, enhanced signal transduction, and hypertension also induces pronounced supersensitivity to α₂-adrenergic coronary constriction.¹³ Future randomized, placebo-controlled studies should clarify the value of α₂-antagonists in the treatment of various forms of ischemic heart disease, such as chronic stable angina or morning angina.

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