Alpha-Adrenoceptor Blockade Prevents Exercise-Induced Vasoconstriction of Stenotic Coronary Arteries

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OBJECTIVES
The study aimed to evaluate the role of alpha-adrenergic mechanisms during dynamic exercise in both normal and stenotic coronary arteries.

BACKGROUND
Paradoxical vasoconstriction of stenotic coronary arteries has been reported during dynamic exercise and may be due to several factors such as alpha-adrenergic drive, a decreased release of nitric oxide, platelet aggregation with release of serotonin, or a passive collapse of the vessel wall.

METHODS
Twenty-six patients were studied at rest, during two levels of supine bicycle exercise and after 1.6 mg sublingual nitroglycerin. The alpha-blocker phentolamine was given to 16 patients before exercise, five of whom had also taken a beta-adrenergic-blocker the same morning. Ten patients served as controls. The cross-sectional areas of a normal and a stenotic coronary vessel were determined by biplane quantitative coronary arteriography.

RESULTS
In the normal vessel segments, coronary cross-sectional area did not change after phentolamine injection, but increased in all patient groups similarly during exercise. Although coronary vasoconstriction existed in stenotic vessel segments in control patients, phentolamine-treated patients showed exercise-induced vasodilation without difference in patients with and without chronic beta-blockade.

CONCLUSIONS
Exercise-induced vasoconstriction of stenotic coronary arteries is prevented by intracoronary administration of phentolamine. There was no difference in coronary vasomotion between patients receiving phentolamine alone and patients receiving phentolamine in addition to a beta-blocker. This finding suggests that exercise-induced vasoconstriction is mediated not only by endothelial dysfunction but also by alpha-adrenergic mechanisms. (J Am Coll Cardiol 1999;33:1499–505) © 1999 by the American College of Cardiology

Coronary vasomotor tone plays an important role in the pathophysiology of angina pectoris. An increase in vasomotor tone of stenotic arteries may result in a decrease in coronary blood flow and, thus, may precipitate myocardial ischemia. A reduction in exercise-induced angina pectoris and an increase in physical working capacity have been reported in patients with stable angina pectoris after intracoronary administration of phentolamine (1,2) or indoramine, a selective alpha1-adrenoceptor antagonist (3). Stenotic coronary arteries have shown paradoxical vasoconstriction during isometric (4) but also dynamic exercise (5). This exercise-induced narrowing of the stenotic arteries has been prevented by intracoronary administration of nitroglycerin (4) or diltiazem in doses that did not induce systemic vascular effects (6).

The exact mechanism that is responsible for the reported stenosis vasoconstriction is not clear but may involve several factors such as an enhanced sympathetic stimulation during exercise, endothelial dysfunction with reduced nitric oxide (NO) release or production, increased platelet aggregation with release of serotonin and thromboxane A2, or a passive collapse of the stenotic vessel segment within the stenosis due to the increase in flow velocity during exercise (Venturi effect).

Because changes in coronary vasomotor tone underlie neurogenic mechanisms, particular interest has focused on the link between myocardial ischemia and alpha-adrenergic tone during exercise. Thus, the purpose of the present study was to assess the influence of alpha-adrenergic mechanisms on coronary vasomotion in normal and stenotic coronary arteries during dynamic exercise.

METHODS
Study population. Twenty-six patients (mean age 54 ± 8 years) with coronary artery disease and stable angina pectoris were included in the present analysis. Biplane coronary arteriography was performed at rest and during two levels of exercise.
angiography was performed at rest, during supine bicycle exercise and after sublingual nitroglycerin. Patients who fulfilled the following baseline criteria were included in the study: 1) a history of stable, effort-related angina pectoris and 2) coronary artery stenosis clearly visible on angiography for quantitative evaluation. The first 10 of the studied patients did not receive any premedication prior to exercise and they served as controls (C). The remaining 16 patients obtained before exercise 2 mg intracoronary phentolamine, a nonselective alpha-blocker (P). Although 11 patients of this group did not have any vasoactive substances for at least 24 h before the study (P), five patients who were on chronic cardioselective beta-blockade (metoprolol or atenolol) had been instructed to take this medication also on the morning of the study (P⁺). Functional classification according to the New York Heart Association was 1.9 ± 0.6 in controls and 1.8 ± 0.9 in the phentolamine-treated patients (not significant [NS]). In the phentolamine-treated group, 4/11 patients had one-vessel disease, 4/11 patients had two-vessel disease, and 3/11 patients had three-vessel disease. Two patients who were pretreated with a beta-adrenergic-blocker and then received phentolamine during the study protocol were suffering from one-vessel disease, one had a two-vessel disease and two had a three-vessel disease. Of the control patients one-vessel disease was present in 4/10 patients, two-vessel disease was found in 3/10 patients, and three-vessel disease was present in 3/10 patients. Maximal stenosis severity for patients with phentolamine was <70% in three, 70% to 90% in four and >90% in three cases. For patients with alpha- and beta-blockade stenosis, severity amounted to 70% to 90% in 4 patients and <70% in 1 patient. One control patient had a <70% stenosis, seven had 70% to 90% stenoses, and 2 had >90% stenoses. Left ventricular ejection fraction averaged 61 ± 8% in controls and 64 ± 6% in phentolamine-treated patients (NS).

Cardiac catheterization. The study protocol was approved by the local ethics committee, and written informed consent was obtained from all patients. Vasoactive substances were withheld for at least 24 h before catheterization except in the five patients who received chronically a cardioselective beta-blocker. The catheter was inserted through the right femoral artery and was kept in place during supine bicycle exercise. Biplane left coronary angiography was performed at the end of the diagnostic coronary angiography. For the purpose of the present study protocol, the left coronary artery was selected to have a normal and a stenotic vessel segment for quantitative analysis. The study drug was, therefore, infused over the guiding catheter into the left coronary artery. Eight milliliters of a nonionic contrast material (Jepamiro 370) was injected into the left coronary artery at a flow rate of 4 ml/s using an electrogram–triggered power-injector.

First, biplane coronary angiography was carried out at rest with the patients’ legs elevated and attached to the bicycle ergometer. Angiography was performed on a Bicor Siemens system (Siemens Algis AG, Zurich) using cinefilm at a rate of 25 frames/s. Further biplane coronary angiograms were performed after administration of 2 mg intracoronary phentolamine (Infusion time: 5 min; 0.4 mg/min). Two levels of supine bicycle exercise were performed for 2 min in each patient. Biplane coronary angiography was repeated immediately after each exercise level while the patient was asked to hold his breath. Finally, coronary angiography was carried out 5 min following administration of 1.6 mg sublingual nitroglycerin. Aortic and pulmonary artery pressures were recorded continuously during exercise and were measured for subsequent analysis immediately before each angiogram. No adverse event occurred during the study, and there were no complications with regard to this study protocol.

Quantitative coronary angiography. Quantitative angiography was carried out with a semiautomatic computer system (7–9). The system is based on a 35-mm film projector (Tagarno 35 CX, Horsens, Denmark), a slow scan CCD-camera for image digitation and a computer workstation (Apollo DN 3000, Wangen, Switzerland) for image storing and processing. Contour detection was carried out with the use of a geometric-densitometric edge detection algorithm (8,10,11). The method for quantitative evaluation of coronary angiography has been described in detail elsewhere (5,7,10,11).

Both a normal and a stenotic vessel segment were chosen for quantitative analysis. In each patient at least one stenotic vessel was selected for analysis on the basis of clear visualization without overlapping vessels. The normal vessel segment was selected from a disease-free vessel when possible, otherwise an uninvolved prestenotic vessel segment was chosen at least four catheter-widths from the center of the stenosis, which was not used for quantitative evaluation (Fig. 1).

Statistical analysis. Statistical comparisons of hemodynamic and angiographic data among as well as between the patients were carried out by a two-way analysis of variance (ANOVA) for repeated measurements. If this test was significant, the Scheffé procedure was applied to determine the intra- and intergroup statistical differences. A p-value of less than 0.05 was considered to indicate statistical signifi-
RESULTS

Clinical findings. Patients in the two groups did not differ with respect to age, gender and functional classification according to the New York Heart Association or baseline hemodynamic values. Left ventricular ejection fraction was slightly lower in patients on chronic beta-blockade (P(α + β)) when compared with those without beta-blockers. Baseline hemodynamic data are summarized in Table 1. Physical working capacity was similar in the two groups (C: 109 ± 25 W, P: 100 ± 21 W; NS). Angina pectoris during supine bicycle exercise was present in four out of ten patients (40%) in C and 5 out of 16 patients in P (31%). Heart rate did not change after intracoronary phentolamine injection and increased to a similar extent in the two groups during exercise. Patients on chronic beta-blockade had a significantly lower rate-pressure product than did controls or P(α) (14.3 ± 2.7 vs. 20.8 ± 3.8 and 18.7 ± 3.8 mm Hg/min x 10^3, respectively; p < 0.05) (Fig. 2). Mean aortic and mean pulmonary artery pressures remained unchanged after intracoronary administration of phentolamine (C: 117 ± 18%, P: 117 ± 18%; NS) as well as after administration of sublingual nitroglycerin (C: 132 ± 15%; P: 132 ± 21%; NS).

Coronary cross-sectional area (CSA). Percent changes in coronary CSA of the normal and stenotic vessels are illustrated in Figure 3. The size of the normal vessel remained unchanged after administration of intracoronary phentolamine (105 ± 7.8%), but increased during exercise (C: 113 ± 11%; P: 117 ± 18%; NS) as well as after administration of sublingual nitroglycerin (C: 123 ± 15%; P: 132 ± 21%; NS). There was no difference in patients with or without chronic beta-blockade after phentolamine administration (P(α); 104 ± 11%, P(α + β); 107 ± 10%; NS). During exercise, CSA increased in both groups (P(α); 117 ± 11% and P(α + β); 118 ± 28%; NS) and the CSA was maximally dilated after sublingual nitroglycerin (P(α); 136 ± 20% and P(α + β); 125 ± 22%; NS).

Coronary CSA of the stenotic vessel remained unchanged after intracoronary administration of phentolamine (104 ± 8%). While phentolamine-treated patients showed exercise-induced vasodilation (113 ± 8%), there was coronary vasodilatation during exercise in controls (85 ± 23%; p < 0.001). Vasodilatation of the stenotic vessel segment was similar after sublingual nitroglycerin in both groups (C:}

![Figure 1. Quantitative coronary angiography of the left anterior descending coronary artery in a patient with moderate lesion in Aldridge projection. Automatic evaluation of the stenotic segment was performed by computer analysis. The proximal and distal reference segments are marked with two lines. The minimal luminal diameter was 2.6 mm at Rest, 2.7 mm after intracoronary phentolamine (Reg), 2.6 mm during the first (Ex 1) and 2.6 mm during the second (Ex 2) exercise level, and amounted to 3.0 mm after sublingual nitroglycerin (NTG).](image)

![Figure 2. Rate-pressure product (RPP) and mean pulmonary artery pressure (mPAP) at rest (R), after intracoronary administration of phentolamine (Drug), during two levels of supine bicycle exercise (Ex1; Ex2), and after sublingual nitroglycerin administration (NTG). Note the significant rise of both parameters during exercise. However, patients on chronic beta-blockade reached a lower rate-pressure product than did the two other groups. Open circles = alpha-blockers; solid circles = alpha- plus beta-blockers; solid triangles = control group. NTG = nitroglycerin. *p < 0.05 versus alpha- plus beta-blockers.](image)
116 ± 19%; P: 119 ± 14%; NS), but was less in the stenotic than in the normal vessel segment (p < 0.05). There was no difference in the behavior of the stenotic vessel segments in patients with and those without chronic beta-blockade after phentolamine administration (P(a): 102 ± 7%, P(a + b): 109 ± 5%) as well as during exercise (P(a): 112 ± 8% and P(a + b): 113 ± 10%) and after nitroglycerin administration (P(a): 119 ± 15% and P(a + b): 119 ± 10%) (all NS). For absolute values, see Table 3. The main findings are also illustrated in Figure 3.

**DISCUSSION**

Alpha-adrenergic vasomotion in normal coronary arteries. Alpha-receptor dependent vasomotion of the normal coronary arteries is of minor physiologic importance, because resistance of the epicardial coronary arteries contributes only 5% to total coronary resistance (19). In the presence of beta-adrenergic blockade, the increase in epi-

![Figure 3](image_url)

**Figure 3.** Responses of normal and stenotic coronary arteries to dynamic exercise after intracoronary phentolamine administration in patients without (a; upper panel) and with chronic beta-blockade (a + b; lower panel). For comparison purposes, data are shown also for controls (C). Coronary cross-sectional area (CSA) is expressed in percent of resting luminal area. Normal vessel size remained unchanged after phentolamine administration and increased during exercise both before and after administration of phentolamine or nitroglycerin. The CSA of the stenotic vessel segments also remained unchanged after phentolamine administration. However, in phentolamine-treated patients with or without chronic beta-blockade, paradoxical stenosis vasoconstriction was prevented during exercise. Coronary vasoconstriction was reversible after nitroglycerin administration.

Table 2. Exercise Data

<table>
<thead>
<tr>
<th></th>
<th>Ex (Watt)</th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>MPAP (mm Hg)</th>
<th>RPP (10^3 mm Hg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Ex</td>
<td>B</td>
<td>Ex</td>
<td>B</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>α-Blocker</td>
<td>95 ± 21</td>
<td>67 ± 13</td>
<td>111 ± 15</td>
<td>102 ± 16</td>
<td>120 ± 13</td>
</tr>
<tr>
<td>α + β-Blocker</td>
<td>112 ± 18</td>
<td>59 ± 12</td>
<td>102 ± 10</td>
<td>92 ± 9</td>
<td>108 ± 13</td>
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<tr>
<td>C vs. α</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>C vs. α + β</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
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<tr>
<td>α vs. α + β</td>
<td>NS</td>
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</tr>
</tbody>
</table>

Ex = exercise; B = baseline; HR = heart rate; MAP = mean aortic pressure; MPAP = mean pulmonary artery pressure; RPP = rate pressure product; α = patients receiving phentolamine; α + β = patients on chronic beta-blockade receiving phentolamine before supine bicycle exercise testing; C = controls.
may be induced by isometric as well as dynamic exercise, blockade was observed (26). In an experimental model, post-stenotic coronary vasoconstriction that was prevented by intravenous phentolamine or the calcium-antagonist diltiazem, probably owing to the direct vasodilating properties of these two agents.

The precise mechanism responsible for exercise-induced vasoconstriction of stenotic vessel segments is not clear. Besides an activation of the alpha-adrenergic sympathetic nervous system, endothelial dysfunction with a decreased production and/or release of nitric oxide, increased platelet activation with release of serotonin and thromboxane A2, and a passive collapse of the normal vessel wall within the stenotic lesion (Venturi phenomenon) have been considered as potential mechanisms. In the present study, nonselective alpha-adrenoceptor blocker with intracoronary phentolamine was able to prevent vasoconstriction of the stenotic arteries during exercise. These findings suggest that alpha-adrenergic activation plays an important role in exercise-induced vasoconstriction of stenotic coronary segments although it may not explain all mechanisms such as why the stenotic vessel becomes reactive to circulating catecholamines but not the normal vessel. Preexisting endothelial dysfunction may render the stenotic vessel sensitive to circulating catecholamines; in other words, the functioning endothelium releases NO, which overruns the vasoconstrictor effects of the alpha-adrenergic system. Blockade of these vasoconstrictor effects prevents, therefore, exercise-induced vasoconstriction.

Previous data showed a decrease in exercise-induced ST-segment depression and a reduction in angina pectoris after intracoronary phentolamine administration (1). An increase in exercise capacity after oral administration of phentolamine (2) and indoramine (3), a selective alpha1-adrenoceptor blocker, has been reported in patients with stable angina pectoris. Phentolamine was also able to prevent coronary vasoconstriction during cold pressor testing (27) and during isometric exercise (4), which are associated with stimulation of the sympathetic nervous system (28).

In the absence of beta-blockade, alpha-blockade may result in a decrease in coronary vascular resistance during exercise due to presynaptic disinhibition of neuronal epinephrine release, which results in an increase in oxygen requirements. This may lead to metabolic vasodilation in addition to the attenuation of alpha-adrenergic coronary vasoconstriction. In the present study, chronic beta-blockade was present in 5 of 16 phentolamine-treated patients. Because coronary vasomotion in patients with and without beta-blockade did not differ among each other, the direct effect on arterial adrenoceptors appears to be more important than metabolic vasodilation.

Although the various effects of alpha-adrenergic blockade on post-stenotic coronary vasomotion have been previously evaluated in dogs (26,29–31), the present study documents for the first time a direct effect of alpha-adrenergic blockade on coronary stenosis vasomotion during exercise in humans.

<table>
<thead>
<tr>
<th>Table 3. Coronary Cross-Sectional Area: Absolute Values</th>
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<tbody>
<tr>
<td>Rest (mm²)</td>
</tr>
<tr>
<td>Controls</td>
</tr>
<tr>
<td>α-Blocker</td>
</tr>
<tr>
<td>α + β-Blocker</td>
</tr>
<tr>
<td>Normal segment</td>
</tr>
<tr>
<td>Controls</td>
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<tr>
<td>α-Blocker</td>
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<tr>
<td>α + β-Blocker</td>
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</tbody>
</table>

α-Blocker indicates patients receiving phentolamine and α + β-Blocker patients on chronic beta-blockade receiving phentolamine before supine bicycle exercise testing.
The effects of alpha-adrenergic blockade were, however, small in the normal vessel segment (Fig. 3) but large in the stenotic segment. This may be explained by the fact that the adrenergic vascular effects become much more prominent when there is endothelial dysfunction with a reduced release or production of NO. Beta-blocker administration may have increased this response, which was, however, not the case in the present study. One might have expected an even larger effect owing to the blocking of the beta-mediated vasostricting effects, which did not become evident.

**Clinical implications.** Endothelial dysfunction is assumed to occur in most stenotic coronary arteries, resulting in a decreased flow to the post-stenotic regions, which may precipitate myocardial ischemia during exercise. The functional abnormalities of the endothelium and the enhanced alpha-adrenergic sympathetic nervous system are probably responsible for the occurrence of stenosis vasoconstriction during exercise. Interestingly, a positive feedback mechanism between myocardial ischemia and post-stenotic coronary vasoconstriction has been described by Heusch and co-workers (31). Exercise-induced vasoconstriction of the coronary arteries after balloon-induced endothelial denudation has been previously shown by Berdeaux and co-workers in dogs (32). Similarly, an inhibitory role of the endothelium against alpha-adrenergic nerve stimulation has been reported by Main et al. (33) in isolated coronary artery rings from dogs with heart failure.

Endothelial cells of large canine and porcine coronary arteries possess alpha2-adrenoceptors. Their activation by norepinephrine causes release of an endothelium-derived relaxant factor, which in turn attenuates norepinephrine-induced vasoconstriction mediated by alpha1-adrenergic coronary vasoconstriction. Conversely, loss of endothelial function in atherosclerotic coronary arteries may predispose to enhanced alpha-adrenergic coronary vasoconstriction (34–36).

Alpha-blocking agents in general have rarely been used in the treatment of coronary artery disease. Although these drugs elicit an important vasodilatory effect, the clinically limiting factors appear to be tachyphylaxis, an increase in cardiac output and interference in the feedback inhibition of norepinephrine release. Increased catecholamine release may blunt the action of postsynaptic alpha-blockers.

**Study limitations.** Systemic effects of phentolamine include arterial hypotension with baroreflex-mediated sympathetic activation and, thus, beta-adrenergic vasodilation (13). However, no significant hemodynamic changes were observed in the present study after intracoronary phentolamine injection, and, thus, it can be assumed that the abolition of coronary stenosis vasoconstriction during exercise is due to a direct effect on sympathetic alpha-adrenoceptors.

The exact subtype of alpha-adrenoceptors involved in paradoxical coronary stenosis vasoconstriction cannot be derived from our study, as no selective alpha-blocker was used. This issue was addressed in canine experiments as well as in humans, but the results are controversial. Gwirtz and colleagues (29) reported that post-stenotic vasoconstriction during sympathetic nerve activation is abolished by selective alpha2-antagonists, whereas Heusch and co-workers (26,30,31) found that it was mediated by alpha2-adrenoceptors. The existence of alpha2-adrenoceptors in human coronary arteries has been documented by Indolfi and co-workers (24). A reduction in exercise-induced ST-segment depression and an increase in exercise capacity were observed in patients with stable angina pectoris treated with the selective alpha2-antagonist indoramine (3), whereas exercise-induced ST-segment depression in a similar patient group was more attenuated by the nonselective alpha-antagonist phentolamine than the selective alpha2-antagonist indoramine, suggesting an important role for vascular alpha2-adrenoceptors in human coronary circulation (37).

**Conclusions.** Nonselective alpha-adrenoceptor blockade with intracoronary phentolamine is able to prevent exercise-induced vasoconstriction of stenotic coronary arteries during exercise. This observation suggests that alpha-adrenergic sympathetic nerve activation plays an important role in coronary stenosis vasoconstriction and may aggravate myocardial ischemia during exercise in patients with stable angina pectoris. These effects are probably unmasked as a consequence of endothelial dysfunction with a decreased production and reduced release of endogenous vasodilators from the stenotic vessel segments leading to enhanced coronary vasoconstriction during exercise.

**References**

8. Suter TM, Buechi M, Hess OM, Haemmerli-Saner C, Gaglione A, Krayenbuehl HP. Normalization of coronary vasoconstriction after percu-