Role of $\alpha_2$-Adrenoceptors in Normal and Atherosclerotic Human Coronary Circulation

Ciro Indolfi, MD; Federico Piscione, MD; Bruno Villari, MD; Enrico Russolillo, MD; Virgilio Rendina, MD; Paolo Golino, MD; Mario Condorelli, MD; and Massimo Chiariello, MD

**Background.** Experimental studies on the effects of $\alpha_2$-adrenoceptors on regional coronary blood flow in normal and ischemic myocardium are highly controversial. A beneficial effect on regional ischemic myocardium has been demonstrated in different animal preparations with either $\alpha_2$-adrenoceptor blockade or stimulation. Animal studies also demonstrated that postsynaptic $\alpha_2$-adrenoceptors mediate vasoconstriction in coronary and femoral vascular beds. The aims of the study were 1) to investigate the effects of regional $\alpha_2$-adrenoceptor stimulation on regional coronary blood flow in subjects with angiographically normal coronary arteries, 2) to assess the effect of $\alpha_2$-adrenoceptor blockade on coronary circulation in control subjects, and 3) to examine the influence of atherosclerosis on coronary blood flow response to $\alpha_2$-adrenoceptor blockade.

**Methods and Results.** The effect of regional administration of BHT 933 (a selective $\alpha_2$-adrenoceptor agonist) was studied in eight subjects with angiographically normal coronary arteries. The coronary blood flow velocity was measured using a subselective intracoronary 3F Doppler catheter and coronary diameter by quantitative coronary angiography. BHT 933 induced a reduction in coronary artery diameter from 2.5±0.6 mm to 1.8±0.4 mm ($p<0.05$) as well as in coronary blood flow velocity (from 6.4±0.9 cm/sec to 4.6±1.9 cm/sec, $p<0.01$). In some subjects, ST segment abnormalities occurred. In patients with angiographically normal coronary arteries ($n=6$), the regional infusion of a selective $\alpha_2$-adrenoceptor blocking agent after $\beta$-blockade did not change coronary diameter or coronary blood flow velocity. In contrast, in patients with significant coronary stenoses ($n=6$), regional infusion of an $\alpha_2$-adrenoceptor blocking agent reduced regional coronary artery diameter (from 2.3±0.5 mm to 2.1±0.6 mm, $p<0.01$) as well as coronary blood flow velocity (from 5.8±0.8 cm/sec to 3.7±0.6 cm/sec, $p<0.05$); in addition, $\alpha_2$-adrenoceptor blockade significantly increased coronary sinus plasma norepinephrine levels (from 300±144 pg/ml to 429±207 pg/ml, $p<0.01$).

**Conclusions.** The selective in vivo stimulation of $\alpha_2$-adrenoceptors produces a reduction in coronary blood flow and diameter in humans with angiographically normal coronary arteries. $\alpha_2$-Adrenergic blockade does not change coronary blood flow in subjects with angiographically normal coronary arteries (suggesting no resting $\alpha_2$-adrenergic vasoconstrictor tone), whereas in patients with coronary artery stenosis, regional coronary blood flow decreases after $\alpha_2$-receptor blockade. Finally, our data also suggest that $\alpha_2$-adrenoceptors participate in the modulation of sympathetic neuronal norepinephrine release in the human heart. (Circulation 1992;86:1116–1124)

**Key Words.** $\cdot$ blood flow, coronary $\cdot$ coronary diameter $\cdot$ $\alpha_2$-adrenoceptors $\cdot$ norepinephrine

The coronary circulation in ischemic myocardium is mainly regulated by metabolic vasodilatation, extracellular compression, and sympathetic vasoconstriction.1–5 Experimental studies on the effects of $\alpha_2$-adrenoceptors on regional coronary blood flow in normal and ischemic myocardium are highly controversial.6,7 Heusch and Deussen8 demonstrated that sympathetic nerve stimulation increases coronary vascular resistances distal to severe stenoses because of $\alpha_2$-adrenoceptor activation and thereby causes myocardial ischemia. In conscious, chronically instrumented dogs with coronary artery stenosis, intracoronary $\alpha_2$-adrenoceptor blockade during exercise increased subendocar-

ial blood flow and attenuated regional left ventricular dysfunction.9 In contrast, Nathan and Feigl10 observed a beneficial effect of adrenergic coronary vasoconstriction induced by nonselective $\alpha_2$-adrenoceptor activation on transmural flow distribution during coronary hyperfusion. In addition, in anesthetized dogs, Kitakaze et al.11 demonstrated that a selective $\alpha_2$-adrenoceptor stimulation can attenuate myocardial ischemia mainly because of enhancement of vasodilatory effects of adenosine released from the ischemic myocardium. It has also been demonstrated in conscious calves with $\beta$-blockade that equivalent reductions in epicardial coronary diameter can be induced by either the selective $\alpha_1$-receptor antagonist phenylephrine or the selective $\alpha_2$-agonist BHT 920.12 These responses are abolished by a selective $\alpha_1$-receptor antagonist or a selective $\alpha_2$-receptor antagonist.13 A recent experimental study also demonstrated that postsynaptic $\alpha_2$-adrenoceptors mediate vasoconstriction in coronary and femoral vascular beds.14 How-

From the Division of Cardiology, Department of Medicine, University Federico II, Napoli, Italy.
Address for correspondence: Ciro Indolfi, MD, Cattedra di Cardiologia, Università degli Studi di Napoli, Via Pansini, 5, Napoli, Italy.
Received July 22, 1991; revision accepted June 24, 1992.
ever, there are no data to date on the effects of α₂-adrenoceptors on the human coronary circulation in vivo, and our hypothesis was that also the human coronary arteries should be innervated with different α-adrenoceptor subtypes.

Therefore, the aims of the present study were 1) to investigate the effects of regional α₂-adrenoceptor stimulation on regional coronary blood flow in subjects with angiographically normal coronary arteries, 2) to assess the effect of α₂-adrenoceptor blockade on coronary circulation and norepinephrine release in control subjects, and 3) to examine the influence of atherosclerosis on coronary blood flow response to the α₂-adrenoceptor blockade.

Methods

Study Population

Twenty-three subjects were included in the study. They were referred to our institution for evaluation of chest pain and had clinical indication for coronary angiography. The study was approved by the Institutional Review Board of the University of Naples, and written informed consent was obtained from all patients before the study. No complications were encountered during this protocol. No patients had unstable angina, angina at rest, previous or acute myocardial infarction, diabetes mellitus, hypertrophic cardiomyopathy, systemic hypertension, or congestive heart failure.

All subjects underwent right- and left-sided heart catheterization in the morning, in the supine position, after an overnight fast. No drugs were allowed in the week preceding the study. Diagnostic coronary angiography was performed by a standard percutaneous femoral approach using the Judkins technique. A 5F bipolar pacing catheter was placed in the right ventricular apex and set in a demand mode.

Study Protocol: α₂-Adrenoceptor Stimulation

Table 1. Individual Clinical Characteristics of Patients With Coronary Artery Disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>Stenosis (%)</th>
<th>Vessel</th>
<th>LV function (angiography)</th>
<th>Exercise stress test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>Cx</td>
<td>Normal</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>LAD</td>
<td>Normal</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>LAD</td>
<td>Normal</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>LAD</td>
<td>Normal</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>Cx</td>
<td>Normal</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>Cx</td>
<td>Normal</td>
<td>+</td>
</tr>
</tbody>
</table>

LV, regional left ventricular; Cx, circumflex coronary artery; LAD, left anterior descending coronary artery; +, positive exercise stress test.

Rowing with ST abnormalities occurred. In two patients, we were unable to obtain a stable blood flow velocity signal.

Study Protocol: α₂-Adrenoceptor Blockade

Group 2: Patients with angiographically normal coronary arteries. Six patients (one man and five women ranging in age from 41 to 65 years; mean, 47±7 years) with entirely smooth, angiographically normal-appearing coronary arteries and negative exercise stress test were studied. In all subjects, β-blockade (propranolol 0.15 mg/kg i.v. bolus) was administered before the infusion of the α₂-adrenoceptor blockade in order to avoid any possible indirect myocardial or direct vascular effects of β-adrenoceptor stimulation on coronary velocity and diameter due to increased norepinephrine release. Serial intracoronary infusions of yohimbine (a selective α₂-adrenoceptor blocking agent) were administered through the Doppler catheter in the following sequence: control (saline, 0.9%) and graded concentration of yohimbine 0.2 μg/kg/min, 1 μg/kg/min, and 2 μg/kg/min, each dose over 4 minutes (at the flow rate under 1.5 ml/min).

Group 3: Patients with coronary artery stenosis. We included six patients, five men and one woman ranging in age from 38 to 57 years (mean, 49±7 years) with chronic, stable, effort-induced angina and positive results on exercise testing, with a stenosis in at least one coronary artery. For ethical reasons, severe stenoses (>80% reduction in diameter) were avoided. The individual clinical characteristics of the patients of this group are reported in Table 1. β-blockade was first performed, as described above. Because the first part of the protocol performed in subjects with angiographically normal coronary arteries showed no change in coronary blood flow at any dose of yohimbine, only the higher dose of this drug (2 μg/kg min over 4 minutes) was administered, keeping the flow rate under 1.5 ml/min in patients with coronary atherosclerosis to test the effect of α₂-adrenoceptor blockade in this group of patients (group 3). In one patient, a stable coronary blood flow velocity signal was not obtained.

Coronary Blood Flow Velocity Studies

After the completion of the diagnostic catheterization, an additional 5,000 units of heparin was administered followed by 500 mg i.v. of acetylsalicylic acid/bisulfate. An 8F Judkins guiding catheter (USCI, Bard, Inc.) was introduced into the right or left main coronary artery. A 20-MHz pulsed Doppler crystal mounted on a 3F catheter (Nyros, NuMed, Hopkinton, N.Y.) was positioned distal to the segment of the coronary artery
to be studied. The Doppler catheter was placed in the center of the vessel (and not moved during the entire study) with a 0.014-in. guide wire (ACS, Advanced Catheter System, Temecula, Calif.) extending from the tip of the catheter in order to obtain a stable flow velocity signal with minimal noise. The Doppler catheter was connected to a velocimeter (Triton Technology, Mod. 100, San Diego, Calif.). This technique for measuring subselectively flow velocity was recently described and found reliable and safe in patients with coronary atherosclerotic lesions and in subjects with normal coronary arteries. In patients with coronary artery disease, the Doppler catheter was placed in a coronary artery with its tip just proximal to the stenosis. Care was taken to position the Doppler catheter in a coronary segment without collateral branches. The Doppler flow velocity catheter position was optimized in the coronary artery, and the output was connected to a multichannel oscillographic recorder (Siemens Mingograf 804, Erlangen, FRG) to display phasic and mean velocity waveforms (in centimeters per second), as previously described in our laboratory. At the end of each infusion, coronary blood flow velocity, ECG tracing, and arterial pressure were recorded, and coronary angiography was performed. Continuous phasic and mean coronary blood flow velocity were measured during saline infusion (control) and during continuous drug pump infusion. Arterial pressure (obtained via the side port of the arterial sheath) and ECG were continuously recorded.

Estimates of Changes in Coronary Blood Flow

Estimates of coronary blood flow (Q) were made from measurements of mean coronary blood flow velocity (V) and vessel cross-sectional area (CSA) according to the equation previously described by Nabel: Q = V \times CSA.

Quantitative Coronary Angiography

Coronary angiography was performed at the end of each infusion using an injection of 8–9 ml of nonionic contrast medium (Omnipaque 350, Winthrop-Breon Laboratories, New York, N.Y.). Cineangiograms were recorded using a Siemens radiographic system at a rate of 50 frames per second. The projection that allowed the best visualization of the coronary artery under evaluation was chosen from among the diagnostic angiograms and was used consistently throughout the study for quantitative analysis. End-diastolic cine frames were blindly videodigitized and stored in the image analysis system (Mipron, Kontron Electronics, Eching, FRG) in a 512x512 matrix with eight-bit gray scale, with the 12-cm field of view, resulting in a pixel density of 7.3 pixels/mm² (References 16 and 18). Automatic vessel segment contour detection was performed by a geometric edge differentiation technique using a method previously described. In brief, after interactive determination of a centerline within the vessel to ensure the reproducibility of the measurements, 1-cm segments of the coronary artery were selected, starting from the tip of the Doppler catheter. In the segment to be measured, the computer automatically generates a number of scan lines perpendicular to the centerline. The first and second derivative function of densograms along each scan line are then computed, and the contour point is defined as 70% of the distance between the extrema of the first and second derivatives. With the use of the detected contour points, the computer then automatically generates a refined centerline of the vessel segment, and the edge detection algorithm is repeated. Each individual scan line is smoothed by a second-order polynomial fit, and smoothing of the contour is obtained by averaging three neighboring scan lines. The diameter of the guiding catheter in the field of view was used to convert the imaging data from pixels to millimeters.

Phantom Validation of Quantitative Angiography

The accuracy and precision of quantitative angiographic measurements were determined from the analysis of cine films of 11 Plexiglas blocks with precision-drilled models of coronary arteries filled with contrast medium. The reproducibility of the measured minimal stenosis diameter (repeated analysis of the cineangiograms by one analyst) revealed a coefficient of variation of 2.3 ± 1.8%.18

Drugs

Propranolol (Inderal, 5-m1 vials, 5 mg) was purchased from ICI-Pharma (Milan, Italy). Yohimbine chloride was obtained from the Apotheek Academisch Ziekenhuis, Leiden, The Netherlands. BHT 933 was prepared by dissolving BHT 933 (azepexol hydrochloride, Boehringer Ingelheim, KG) in saline 0.9%. The solution was then filtered through a sterilizing filter (0.22 μm) and periodically checked for sterility and the presence of pyrogens.

Coronary Sinus and Aortic Norepinephrine Measurements

Because we observed a different coronary effect of α1-adrenoceptor blockade in patients with coronary atherosclerosis, we decided to measure coronary sinus plasma concentration of norepinephrine as a guide to changes in norepinephrine release. Because no systemic effects and no differences in aortic norepinephrine plasma levels of intracoronary infusion of yohimbine up to 2 μg/kg/min were observed, changes in norepinephrine concentration in the coronary sinus would be expected to reflect changes in release rate or reuptake rate in the synaptic cleft in response to the regional drug infusion.

Blood samples for plasma norepinephrine assay were obtained from a 7F Sidewinder II catheter (Cordis, Roden, The Netherlands) positioned in the coronary sinus via a right femoral approach during the control period and during the last minute of yohimbine infusion (2 μg/kg/min). In three additional patients with normal coronary arteries after β-blockade (propranolol 0.15 mg/kg i.v.), coronary sinus and aortic norepinephrine levels were measured in the control state (saline) and after intracoronary yohimbine infusion (2 μg/kg/min).

Plasma catecholamines were measured using reverse-phase, high-performance liquid chromatography with electrochemical detection after purification and concentration by extraction with alumina according to Anton and Sayre. Further details of this technique have been extensively described in our laboratory previously. The accuracy and reproducibility of plasma catecholamine measurements were further determined in 12 additional
patients undergoing routine cardiac catheterization. Blood samples for plasma norepinephrine assay were obtained 15 minutes apart from a 6F pigtail positioned in the ascending aorta and from a 7F Sidewinder II catheter (Cordis, Rodyen, The Netherlands) positioned in the coronary sinus via the right femoral approach. Aortic and heart rate were continuously monitored and recorded by a computer-aided system for cardiac catheterization (Siecor, Siemens). Pressure waveform analysis was performed within a user-definable analysis window over 8 consecutive beats.

Statistical Analysis

Results are expressed as mean±SD. Statistical analysis was by ANOVA for repeated measures using a SYSTAT program. When a significant overall effect was detected, Tukey’s test was applied to compare single mean values. Significant differences were assumed to be present at a value of p<0.05. A paired t test was used for analysis of data in patients with coronary artery stenosis (group 3).

Results

Effects of Regional α2-Adrenoceptor Stimulation in Patients With Normal Coronary Arteries (Group 1)

The responses of coronary vessels to intracoronary infusions of graded concentrations of BHT 933 are reported in Table 2. BHT 933 did not change heart rate (from 84±14 to 85±17 beats per minute), systolic aortic pressure (from 123±23 to 119±24 mm Hg), or diastolic aortic pressure. The infusion of BHT 933 was terminated at the dose of 0.1 μg/kg in one patient and at the dose of 1 μg/kg in three because of vessel narrowing and ST segment abnormalities. BHT 933 reduced coronary diameter from 2.5±0.6 mm to 1.8±0.4 mm (p<0.01) and coronary cross-sectional area from 4.8±2.9 cm² to 2.5±1.3 cm² (p<0.05) (Figure 1). Regional coronary blood flow velocity decreased from 6.4±0.9 cm/sec to 4.6±1.9 cm/sec (p<0.01) at the dose of 0.1 μg/kg (n=6). The calculated coronary blood flow was reduced at the third dose of BHT 933 by 49%. Only two patients had a reliable coronary blood flow velocity during the highest dose of BHT 933. Figure 2 shows an original recording of a patient with normal coronary arteries, illustrating hemodynamic and regional mean and phasic blood flow velocity during selective infusion of BHT 933.

In four patients, chest pain and ST abnormalities occurred after BHT infusion. In one of them, intracoronary administration of nitroglycerin (0.05 mg bolus) reversed the effects of BHT 933. In contrast, in three patients, nitroglycerin did not relieve symptoms or coronary vasoconstriction, but further intracoronary infusion of 0.2 mg of nifedipine (in two patients) or intravenous diltiazem (in one patient) produced a regression of coronary vasoconstriction and chest pain.

Effect of α2-Adrenoceptor Blockade in Subjects With Normal Coronary Arteries (Group 2)

The hemodynamic changes after yohimbine infusion after β-adrenergic blockade are summarized in Table 3. Coronary artery diameter and coronary blood flow velocity were unchanged at any doses of yohimbine (Table 3 and Figure 3). Estimated coronary blood flow (coronary blood flow velocity corrected for changes in cross-sectional area) showed no changes in response to yohimbine infusion. In addition, the intracoronary infu-

![Figure 1](http://circ.ahajournals.org/figures/I1119.png)

**Fig 1.** Individual data points of cross-sectional area (CSA) after graded intracoronary infusion of BHT 933 in patients with normal coronary arteries. A significant reduction in coronary cross-sectional area was found after α2-adrenoceptor stimulation. BHT 1, BHT 933 0.1 μg/kg; BHT 2, BHT 933 1 μg/kg; BHT 3, BHT 933 10 μg/kg.
sion of yohimbine did not change heart rate and aortic pressure (Table 3). No symptoms or ECG changes were observed in this group of patients.

**Effects of α2-Adrenergic Blockade in Patients With Coronary Artery Stenosis (Group 3)**

There was no significant change in heart rate or mean arterial blood pressure associated with the intracoronary infusion of saline or yohimbine (2 μg/kg/min) before the onset of myocardial ischemia.

In patients with coronary atherosclerosis, after β-blockade, the regional infusion of yohimbine induced a significant reduction in coronary diameter (from 2.4±0.8 mm to 2.1±0.6 mm, p<0.01) and in coronary blood flow velocity (from 5.8±0.8 cm/sec to 3.6±0.5 cm/sec, p<0.05) (48% reduction of calculated coronary blood flow). Figures 4 and 5 depict individual changes in coronary cross-sectional area and coronary blood flow velocity after yohimbine infusion. Four patients had a shift in the ST segment (elevation in two and depression in two) that was associated with angina. Coronary vasoconstriction and ST segment abnormalities and symptoms were abolished by intracoronary administration of nitroglycerin (0.05 mg bolus) and were associated in some patients with intravenous infusion of diltiazem.

Finally, no change in coronary artery diameter was observed in the control coronary segment (not manipulated by Doppler catheter) during infusion of saline or α2-adrenergic blocker.

**Coronary Sinus Norepinephrine Response**

Coronary sinus blood samples after yohimbine infusion were obtained in five patients with coronary atherosclerosis and in three subjects with angiographically normal coronary arteries. In 12 additional subjects, the reproducibility of repeated measures (15 minutes apart) of aortic and coronary sinus norepinephrine levels revealed a coefficient of variation of 8.3% and 13.5%, respectively.

The infusion of yohimbine increased coronary sinus plasma norepinephrine levels in coronary artery disease patients from 300±144 pg/ml to 429±207 pg/ml (p<0.01). Coronary sinus plasma norepinephrine levels also increased in subjects with angiographically normal coronary arteries after α2-adrenoceptor blockade (from

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**TABLE 3. Effects of Regional Intracoronary Infusion of Yohimbine After β-Blockade in Patients With Normal Coronary Arteries**

<table>
<thead>
<tr>
<th></th>
<th>Base</th>
<th>Y1</th>
<th>Y2</th>
<th>Y3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary blood flow</td>
<td>7.4±1.9</td>
<td>7.4±1.8</td>
<td>7.3±2.7</td>
<td>7.3±2.7</td>
</tr>
<tr>
<td>diameter (mm)</td>
<td>2.8±0.52</td>
<td>3.0±0.43</td>
<td>2.9±0.6</td>
<td>3.0±0.4</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>67±7</td>
<td>68±8</td>
<td>67±8</td>
<td>68±7</td>
</tr>
<tr>
<td>Systolic aortic pressure (mm Hg)</td>
<td>143±12</td>
<td>141±13</td>
<td>142±9</td>
<td>143±4</td>
</tr>
<tr>
<td>Diastolic aortic pressure (mm Hg)</td>
<td>77±4</td>
<td>76±8</td>
<td>77±9</td>
<td>75±8</td>
</tr>
<tr>
<td>Coronary sinus NE levels (pg/ml)</td>
<td>270±98</td>
<td>...</td>
<td>...</td>
<td>379±174</td>
</tr>
<tr>
<td>Aortic NE levels (pg/ml)</td>
<td>269±134</td>
<td>...</td>
<td>...</td>
<td>294±150</td>
</tr>
</tbody>
</table>

Base, saline infusion; Y1, yohimbine 0.2 μg/kg/min; Y2, yohimbine 1 μg/kg/min; Y3, yohimbine 2 μg/kg/min (each dose over 4 minutes); NE, norepinephrine. n=6 patients.
270±98 pg/ml to 379±174 pg/ml), whereas aortic plasma norepinephrine levels did not change (269±134 pg/ml versus 294±150 pg/ml). This finding is consistent with an augmented release of norepinephrine from cardiac sympathetic nerve terminals after α2-adrenoceptor blockade.

**Discussion**

The major findings of the present study indicate that 1) the selective in vivo stimulation of α2-adrenoceptors produces a reduction in regional coronary blood flow in subjects with angiographically normal coronary arteries, providing evidence that α2-adrenoceptors exist in the human coronary circulation, 2) resting sympathetic vasoconstrictor tone mediated by α2-adrenoceptors could not be demonstrated in the normal human coronary circulation, and 3) atherosclerosis influences the response of regional coronary blood flow to α2-adrenoceptor blockade.

**Effect of α2-Adrenoceptor Stimulation**

The existence and the pathophysiological role of α2-adrenoceptors in human coronary arteries in vivo are still unknown. In vitro studies have demonstrated that α2-adrenergic stimulation indirectly dilates normal animal coronary arteries through the release of endothelium-derived relaxing factor (EDRF). In addition, the presence of α2-adrenoceptors has been demonstrated on endothelial cells, suggesting that the activation of these receptors may promote the release of EDRF, which might counteract the contraction of smooth muscle cells. However, an α2-adrenoceptor-mediated release of EDRF has never been demonstrated in humans.

It has been demonstrated that in isolated canine coronary arteries, only α1-adrenoceptor stimulation produces vasoconstriction. However, several laboratories have demonstrated that both α2- and α2-adrenoceptors mediate coronary constriction. For instance, in conscious calves with β-blockade, intracoronary infusion of either the selective α1-receptor agonist phenylephrine or the selective α2-receptor agonist BHT 920 produced an equivalent reduction in epicardial coronary artery diameter.

The presence of α2-adrenoceptor-mediated vasoconstriction was also documented in peripheral human vessels. Our hypothesis was that different α-adrenoceptor subtypes should also be present in the human coronary circulation. In the present study, we demonstrated that α2-adrenoceptor stimulation reduces coronary artery blood flow in resting humans, and that this vasoconstriction is more pronounced in the microvasculature. However, previous studies in anesthetized dogs demonstrated that coronary vasoconstriction induced by nonselective α-adrenoceptor stimulation produced a beneficial effect on transmural flow distribution during hypoperfusion. Nathan and Feigl hypothesized an "antitransmural" steal whereby α-receptor-mediated vasoconstriction in the outer layer of the left ventricle helped to maintain the perfusion pressure for the inner layer. One of the mechanisms proposed is that either sympathetic α-receptor density or coronary innervation is greater in the outer layer of the left ventricle (epicardium) than that in the inner layers. Whether this vasoconstriction is beneficial or detrimental is still an unsolved issue.
Resting $\alpha_\text{2}$-Adrenergic Tone in Patients With Angiographically Normal Coronary Arteries

Although a significant resting sympathetic coronary vasoconstritor tone has been previously demonstrated in dogs, another experimental study does not support this finding. Our data demonstrate that the regional infusion of an $\alpha_2$-adrenoceptor blocking agent does not change resting coronary blood flow in normal coronary arteries after $\beta$-blockade, suggesting that a resting $\alpha_2$-adrenergic vasoconstriction does not exist in humans.

To avoid the effects of $\beta$-adrenergic stimulation on regional coronary blood flow, our study was performed in the presence of $\beta$-blockade. In $\beta$-blocked dogs, regional infusion of an $\alpha_2$-adrenoceptor blocker also did not produce any change in coronary blood flow. In contrast, in the last decade, several different laboratories have demonstrated that an $\alpha_1$-35-37 and $\alpha_2$-adrenergic5 coronary vasoconstriction limits the increase in coronary blood flow during exercise in dogs.

A recent study by Kubo et al38 showed that intraarterial infusion of yohimbine produced a dose-related increase in forearm blood flow and a decrease in forearm vascular resistance in normal subjects and in patients with congestive heart failure. Unfortunately, in the study of Kubo and associates, $\beta$-blockade was not induced, thus preventing the assessment of the pure effect of $\alpha_2$-adrenoceptor blockade on blood flow. In fact, it is well known that presynaptic $\alpha_2$-receptors may be active in inhibiting norepinephrine release into the synaptic cleft. Therefore, in the absence of $\beta$-blockade, selective $\alpha_2$-adrenoceptor blockade by yohimbine may increase regional blood flow due to presynaptic release of norepinephrine, resulting in vasodilation.

To our knowledge, this is the first in vivo study that documents the role of $\alpha_2$-adrenoceptors in human coronary arteries using selective regional infusion of an $\alpha_2$-receptor agonist (BHT 933) and a selective $\alpha_2$-receptor antagonist (yohimbine).

Paradoxical Effects of $\alpha_2$-Adrenoceptor Blockade in Patients With Coronary Atherosclerosis

In $\beta$-blocked patients with significant coronary stenosis, the intracoronary infusion of an $\alpha_2$-adrenoceptor blocking agent produced coronary vasoconstriction. We showed that the $\alpha_2$-adrenoceptors participate in the modulation of norepinephrine release in human coronary circulation. Our hypothesis is that the presynaptic release of norepinephrine observed after $\alpha_2$-adrenoceptor blockade in the presence of coronary atherosclerosis might stimulate the postsynaptic $\alpha_2$-adrenoceptors, which, in turn, in the presence of $\beta$-blockade, can produce vasoconstriction (Figure 6).

Further in vitro studies on atherosclerotic human coronary arteries using $\alpha_2$-adrenoceptor blockade should be performed to clarify the mechanism(s) by which this phenomenon occurs. In this regard, it should be pointed out that a new drug has been recently developed that causes selective blockade of postsynaptic $\alpha_2$-adrenoceptors.40 In a number of arteries from different species, the removal of the endothelium augments the contraction to $\alpha$-adrenergic agonists, and the vasoconstrictor response to norepinephrine is markedly potentiated by the absence of the endothelium.41 The first observation of enhanced $\alpha_1$-adrenergic responsiveness in chronically deendothelialized canine vessels was reported by Young and Vatner.42

After the removal of the endothelium, epinephrine infusion decreased artery diameter, which was increased in the presence of intact endothelium. The removal of the endothelium also enhanced the constriction observed with norepinephrine and phenylephrine.42

A previous study demonstrated that atherosclerosis influences the vasomotor response of epicardial coronary artery to exercise in humans. Considerable experimental evidence from intact animals indicates that atherosclerosis is associated with enhanced vasoconstriction in response to catecholamines.44 In that study, an enhanced sensitivity to norepinephrine in the hind limbs of hypercholesterolemic monkeys occurred in vessels before atherosclerotic lesions appeared. Moreover, Chilian demonstrated recently that with autoregulatory adjustment blunted during hypoperfusion, coronary arterioles respond to $\alpha_1$- and $\alpha_2$-adrenergic activation.

Our study also demonstrated that $\alpha_2$-receptor blockade with yohimbine resulted in an increase in the coronary sinus norepinephrine concentration; this finding suggests for the first time that the presynaptic $\alpha_2$-receptor may be active in inhibiting norepinephrine release into the synaptic cleft in human coronary arteries.

Advantages and Limitations of the Study

In the present study, we used quantitative angiography to assess coronary diameter and a Doppler catheter to assess regional coronary blood flow velocity and to infuse drugs subselectively. This method has been previously validated in our laboratory and others to measure regional coronary blood flow velocity and coronary diameter during subselective infusion of drugs, although the stability of the signal is essential for the reliability of the data.

The intracoronary use of highly selective drugs allowed study of the regional effects of $\alpha_2$-adrenoceptor stimulation and blockade. However, we did not test the efficacy of the $\alpha_2$-adrenoceptor blockade against a specific $\alpha_2$-agonist in patients of group 2. In this regard, it should be pointed out that we used three doses of yohimbine: The third dose is the dose that completely blocks selectively $\alpha_2$-adrenoceptors in dogs, and the third dose of yohimbine increased norepinephrine concentration in the coronary sinus. In group 3, we measured only coronary sinus norepinephrine concentra-
tion. However, a subselective yohimbine infusion did not change aortic norepinephrine in control subjects. In patients with coronary stenoses, we did not test the integrity of the endothelium by using acetylcholine. However, it is very likely that in this group of patients, an endothelium dysfunction was present.

In the BHT 933 group, a selective antagonist of \( \alpha_2 \)-adrenoceptors was not used. In fact, we felt more comfortable using well-established drugs (i.e., nitroglycerin, nifedipine) to reverse the reduction of coronary blood flow (especially in critical situations in which patients experienced angina pectoris and ST segment changes) instead of using yohimbine (with unknown clinical results). We also believed it unethical to infuse BHT 933 in patients with significant coronary stenoses in which platelet aggregation might contribute to thrombus formation; moreover, in the presence of damaged endothelium, an even more marked vasoconstriction than observed in group 1 patients should be present after BHT 933 infusion.42-44 Finally, we cannot rule out microvascular dysfunction in patients with normal coronary arteries that might potentially affect the BHT 933 response.

Pathophysiological and Clinical Relevance of the Study

The demonstration that \( \alpha_2 \)-adrenoceptors exist on human coronary arteries and that their stimulation reduces coronary blood flow might have many pathophysiological and important clinical implications. First, our finding suggests that \( \alpha_2 \)-adrenoceptors participate in the modulation of sympathetic prejunctional neuronal norepinephrine release in human myocardium. Second, \( \alpha_2 \)-adrenergic blockade does not change coronary blood flow in subjects with angiographically normal coronary arteries, suggesting no resting \( \alpha_2 \)-adrenergic vasoconstrictor tone, whereas the atherosclerosis influences the coronary response to \( \alpha_2 \)-adrenoceptor blockade. Finally, the coronary vasoconstriction that occurs in patients with coronary artery disease during sympathetic stimulation (stress, cold) may also be due to an \( \alpha_2 \)-adrenoceptor stimulation.

Acknowledgments

We thank Salvatore Buonera, Giuseppe D’Alise, and Arthur Bruno for excellent technical assistance. In addition, we thank Giuseppe Lembo, MD, for helping in plasma catecholamine measurements. The BHT 933 was kindly supplied by Boehringer Ingelheim.

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Circulation. 1992;86:1116-1124
doi: 10.1161/01.CIR.86.4.1116

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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