Augmented \( \alpha \)-Adrenergic Constriction of Atherosclerotic Human Coronary Arteries

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**Background**—Although adrenergic activation plays a major role in the initiation of experimental myocardial ischemia, the significance of \( \alpha \)-adrenergic coronary constriction in humans has been questioned. The present study assessed the impact of selective \( \alpha \)-adrenergic receptor activation in patients with normal or atherosclerotic coronary arteries.

**Methods and Results**—In 39 patients, coronary blood flow (CBF, mL/min) was determined from combined angiography and Doppler measurements. In 8 patients with normal coronary arteries (group 1) and 9 with single coronary artery stenosis (group 2), doses of 1, 2.5, 5, and 10 mg IC of the \( \alpha_1 \)-agonist methoxamine (M) were injected. Identical doses of the \( \alpha_2 \)-agonist BHT933 (B) were injected in 8 patients with normal coronary arteries (group 3) and 8 with single stenosis (group 4). In 6 additional patients with single stenosis (group 5), aortocoronary sinus lactate differences were measured in response to M and B. CBF remained unchanged in group 1. In contrast, CBF was decreased dose-dependently in group 2, with a maximum at 10 mg M (39.0±9.4 versus 15.2±7.0). In groups 3 and 4, CBF was also decreased dose-dependently, with a maximum at 10 mg B (63.3±24.8 versus 49.1±27.9 and 41.5±19.0 versus 12.7±8.0, respectively). In group 5, there was more net lactate production with B than with M (−0.34±0.11 versus −0.04±0.09 mmol/L).

**Conclusions**—In normal coronary arteries, \( \alpha_1 \)-adrenergic activation does not reduce CBF, whereas \( \alpha_2 \)-adrenergic activation reduces CBF by microvascular constriction. Both \( \alpha_1 \) - and \( \alpha_2 \)-adrenergic epicardial and microvascular constriction are augmented by atherosclerosis and can induce myocardial ischemia. (Circulation. 1999;99:2090-2097.)

**Key Words:** coronary disease ■ angiography ■ ultrasonics

\( \alpha \)-Adrenergic coronary constriction limits increases in coronary blood flow (CBF) during sympathetic activation in normal coronary arteries\(^1\)–\(^3\) and initiates and aggravates myocardial ischemia distal to mechanical stenoses in healthy dogs.\(^4\)–\(^7\) These studies, however, were performed in the absence of atherosclerosis and the presence of a normal vasodilator capacity. Indeed, intact endothelial function attenuates \( \alpha \)-adrenergic coronary vasoconstriction.\(^8\) In contrast, removal of endothelium in canine iliac arteries augments \( \alpha_1 \)-adrenergic vasoconstriction.\(^9\) Also, hypercholesterolemia increases coronary vasoconstriction in response to norepinephrine.\(^10\) The relevance of \( \alpha \)-adrenergic coronary constriction in humans, particularly with atherosclerosis, remains unclear.

Previous studies investigated \( \alpha \)-adrenergic vasomotor tone in the human coronary circulation in vivo, but some have used only an antagonist approach.\(^11\),\(^12\) Not surprisingly, vasodilator responses to \( \alpha \)-antagonists were rather small, because \( \alpha \)-adrenergic vasomotor tone is minimal under resting conditions.\(^13\) Using quantitative coronary angiography and intracoronary Doppler measurements, Indolfi et al\(^14\) extended these results, because no \( \alpha_2 \)-adrenergic receptor–mediated vasomotor tone at rest in patients with angiographically normal coronary arteries was found.

Few studies have used an agonist approach to investigate the impact of \( \alpha \)-adrenergic coronary constriction in humans. Adrenergic activation induced by isometric exercise,\(^13\) supine exercise,\(^16\),\(^17\) or cold pressor test\(^18\)–\(^22\) induced myocardial ischemia, as demonstrated by ST-segment depression, myocardial dysfunction, or angina pectoris. In these studies, independent of the mode of adrenergic activation, angiographically normal segments dilated, whereas irregular and stenosed segments constricted. The \( \alpha \)-adrenergic activation in these studies was unspecific, however, and most of these studies neither elucidated the specific role of \( \alpha \)-adrenergic receptors in coronary vasoconstriction nor distinguished between epicardial and microcirculatory vasoconstriction. However, attenuation of coronary vasoconstriction and ischemia was observed with \( \alpha \)-blockade.\(^18\),\(^20\)

To date, only Indolfi et al\(^14\) used an \( \alpha_2 \)-agonist in humans and found a significant decrease in diameter and coronary flow in angiographically normal coronary arteries. Unexpectedly, the administration of the \( \alpha_2 \)-adrenergic receptor antagonist yohimbine also induced coronary vasoconstriction in
atherosclerotic but not in normal coronary arteries. This vasoconstriction was interpreted as the result of disinhibition of presynaptic norepinephrine release and subsequent α1-adrenergic vasoconstriction in the presence of β-blockade. However, such subsequent α1-adrenergic vasoconstriction was not tested by use of a selective antagonist.

To the best of our knowledge, no study has investigated the influence of both α1- and α2-agonists in human atherosclerotic coronary arteries in situ. Because adrenergic activation plays a major role in the induction and aggravation of myocardial ischemia in patients with coronary artery disease, the aim of the present study was to assess the impact of adrenergic activation by intracoronary injection of the α1-agonist methoxamine and the α2-agonist BHT933 and to compare vasomotor responses in normal and atherosclerotic epicardial and resistive vessels.

**Methods**

**Study Population**

Thirty-nine patients were assigned to 5 groups: 8 patients with normal coronary arteries (group 1) and 9 patients with single stenosis (group 2) received the α1-agonist methoxamine; 8 patients with normal coronary arteries (group 3) and 8 patients with single stenosis (group 4) received the β-blocker BHT933. Six additional patients with single stenosis received both methoxamine and BHT933 during the same investigational procedure (group 5). The demographic data are summarized in Table 1.

**Coronary Catheterization**

With the exception of aspirin 100 mg/d, all medication was stopped 24 hours before catheterization. Aortic pressure was measured with an 8F catheter. Coronary angiography was performed by...
the Judkins technique for routine evaluation of coronary arteries with a filmless HICOR System (Siemens). Only nonionic contrast medium was used to minimize hyperemic reactions. Coronary angiograms were reviewed by an observer blinded to the sequence of drug administration. Coronary artery stenoses were quantified offline by the CMS System (MEDIS).25 Luminal narrowing of ≥50% of lumen diameter was defined as significant stenosis.

Intracoronary Doppler flow measurements were performed with a 0.014-in Doppler wire (Cardiometrics). The Doppler wire was positioned in the middle segment of normal coronary arteries and in the poststenotic segment in patients with significant coronary stenosis (Doppler segment). Great care was taken to obtain an optimal stable signal throughout the protocol. All data were stored continuously on a videotape (Sony) for offline analysis. Intracoronary ultrasound investigations were performed after coronary angiograms with 30 MHz transducers (Boston Scientific and CVIS) as described previously.26

For measurements of coronary sinus lactate concentrations (in group 5), a left Amplatz-II guiding catheter was positioned within the coronary sinus ∼2 cm upstream from the ostium. Standard ECG limb leads were recorded throughout the procedure.

Study Protocol
Atropine 1 mg IV was given initially to prevent reflex bradycardia associated with increases of blood pressure. The respective α-agonists were diluted in 3 mL prewarmed saline and injected stepwise in increasing bolus doses (1, 2.5, 5, and 10 mg) through the guiding catheter. During baseline conditions and the respective maximum effect in the flow signal, a short angiographic scene was recorded. In 6 patients with single stenosis (group 5), arterial and coronary venous lactate concentrations during α1- and α2-stimulation were measured after only 5 and 10 mg of methoxamine or BHT933. Blood samples were analyzed for lactate concentrations with a standard blood-gas analyzer (Ciba-Corning).

Statistical Analysis
The results are expressed as mean±SD. Categorical data were compared by the Fisher exact test. Intragroup variations as well as comparisons between groups with regard to hemodynamic, angiographic, flow, and lactate data were performed by a 1-way or 2-way ANOVA for repeated measures, respectively.27 A value of $P<0.05$ was considered significant.

Figure 1. Original angiographic recording with response to α-adrenergic activation. A, baseline conditions; B, after injection of 10 mg BHT; and C, after injection of 10 mg methoxamine.
TABLE 2. Heart Rate and Mean Aortic Pressure at Baseline and During $\alpha_1$- and $\alpha_2$-Adrenergic Activation

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>1.0 mg</th>
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<td>AOP$_{\text{mean}}$, mm Hg</td>
<td>HR, bpm</td>
<td>AOP$_{\text{mean}}$, mm Hg</td>
<td>HR, bpm</td>
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<td>$\alpha_1$</td>
<td></td>
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<tr>
<td>Group 1</td>
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<td>98±10</td>
<td>69±5</td>
<td>103±8*</td>
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</tr>
<tr>
<td>Group 2</td>
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<td>98±8</td>
<td>69±3</td>
<td>101±6*</td>
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<td>Group 3</td>
<td>67±5</td>
<td>95±3</td>
<td>67±5</td>
<td>96±4</td>
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<tr>
<td>Group 4</td>
<td>63±4</td>
<td>96±3</td>
<td>65±3</td>
<td>97±3</td>
<td>65±2</td>
</tr>
</tbody>
</table>

HR indicates heart rate; AOP, aortic pressure. *

$P<0.05$ vs baseline.

Results

Sex distribution, age, functional class according to the Canadian Cardiological Society, and medication were comparable between the patient groups (Table 1). Figure 1 shows an original angiogram demonstrating the response to $\alpha$-adrenergic activation.

Hemodynamic Data

Heart rate was comparable between groups at baseline and remained unchanged throughout the protocol (Table 2). Mean aortic pressure was also comparable between groups at baseline. Because the local coronary vasconstrictor effect occurred earlier (within 1 minute after the respective agonist injection) than peripheral vasconstriction in response to recirculating $\alpha$-agonists, arterial blood pressure was still unchanged when the local coronary vasconstrictor responses were measured. Table 2 reports the maximal increases in mean aortic pressure within the first 5 minutes after agonist infusion. In groups 1 and 2, 1 mg methoxamine increased aortic pressure significantly, and additional doses induced further increases. In groups 3 and 4, mean aortic pressure remained unchanged up to a dose of 2.5 mg BHT933, whereas doses of 5 and 10 mg increased aortic pressure significantly. Hemodynamic data in group 5 were not different from those in groups 2 and 4.

Coronary Angiographic Data

In group 1, cross-sectional area (CSA) remained unchanged during $\alpha_1$-adrenergic activation (Table 3). In group 2, CSA in the lesion segment was decreased (1.81±1.16 mm$^2$) with 5 mg methoxamine, reaching a trough value with 10 mg (1.01±0.75 mm$^2$, $P<0.05$). Percent area stenosis was increased (82±8%) with 5 mg methoxamine, reaching a maximum with 10 mg (89±8%, $P<0.05$). CSA in the Doppler segment was decreased with 2.5 mg methoxamine, reaching a trough value with 10 mg.

In group 3, CSA remained unchanged during $\alpha_2$-adrenergic activation. In group 4, CSA in the lesion segment was decreased (1.88±0.56 mm$^2$) with 2.5 mg BHT933, reaching a trough value with 10 mg (0.79±0.44 mm$^2$, $P<0.05$). Percent area stenosis was increased (79±4%) with 2.5 mg BHT933, reaching a maximum with 10 mg (89±4%, $P<0.05$). CSA in the Doppler segment was decreased with 2.5 mg BHT933, reaching a trough value with 10 mg.

In group 5, CSA in the Doppler segment was decreased (9.20±1.62 mm$^2$), reaching a trough value with 10 mg methoxamine (5.35±2.39 mm$^2$, $P<0.05$). Likewise, CSA was decreased from 9.05±1.53 mm$^2$ to a trough value of 4.80±2.31 mm$^2$ with 10 mg BHT933.

Intracoronary Doppler Data

Average peak velocity (APV) remained unchanged during $\alpha_1$-adrenergic activation in group 1. In contrast, APV was decreased in group 2 (18.4±1.2 cm/s) with 2.5 mg methoxamine, reaching a trough value with 10 mg (8.4±1.2 cm/s, $P<0.05$). APV was decreased in group 3 (19.0±1.9 cm/s) with 5 mg BHT933, reaching a trough value with 10 mg (14.6±1.9 cm/s, $P<0.05$). Likewise, APV was decreased in group 4 (17.8±1.9 cm/s) with 2.5 mg BHT933, reaching a trough value with 10 mg (7.6±1.9 cm/s, $P<0.05$). In group 5, APV was decreased (13.2±2.0 cm/s), reaching a trough value with 10 mg methoxamine (10.5±3.6 cm/s, $P<0.05$). Likewise, APV was decreased from 13.8±2.8 cm/s to a trough value of 9.9±3.8 cm/s ($P<0.05$) with 10 mg BHT933.

TABLE 3. CSA of the Doppler Segment at Baseline and During $\alpha_1$- and $\alpha_2$-Adrenergic Activation

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>1.0 mg</th>
<th>2.5 mg</th>
<th>5.0 mg</th>
<th>10.0 mg</th>
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<tbody>
<tr>
<td>$\alpha_1$</td>
<td></td>
<td></td>
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<tr>
<td>Group 1</td>
<td>11.26±4.26</td>
<td>11.28±4.22</td>
<td>11.21±4.22</td>
<td>11.44±4.43</td>
<td>11.23±4.29</td>
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<tr>
<td>Group 2</td>
<td>7.05±1.17†</td>
<td>6.65±1.34†</td>
<td>6.32±1.29*†</td>
<td>5.92±1.21*†</td>
<td>5.88±1.21*†</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>11.45±2.98</td>
<td>11.65±2.85</td>
<td>11.37±3.03</td>
<td>11.35±3.28</td>
<td>11.45±3.13</td>
</tr>
<tr>
<td>Group 4</td>
<td>7.73±2.76†</td>
<td>7.24±2.08†</td>
<td>6.33±1.58*†</td>
<td>5.39±1.63*†</td>
<td>4.44±1.70*†</td>
</tr>
</tbody>
</table>

* $P<0.05$ vs baseline; † $P<0.05$ vs group 1 or group 3, respectively.
Calculated CBF

CBF, as calculated from CSA and APV, remained unchanged during \( \alpha_1 \)-adrenergic activation in group 1. In contrast, CBF was decreased in group 2 with 2.5 mg methoxamine, reaching a trough value with 10 mg. CBF was significantly lower at 5 mg and 10 mg methoxamine in group 2 than in group 1 (Figures 2 and 3).

CBF was decreased in group 3 with 2.5 mg BHT933, reaching a trough value with 10 mg (Figure 4). Likewise, CBF was decreased in group 4 with 2.5 mg BHT933, reaching a trough value with 10 mg. CBF was significantly lower at 5 mg and 10 mg BHT933 in group 4 than in group 3 (Figure 5).

In group 5, CBF was also decreased (36.5 ± 9.4 mL/min), reaching a trough value with 10 mg methoxamine (15.7 ± 5.5 mL/min, \( P < 0.05 \)) and BHT933 (13.1 ± 4.8 mL/min, \( P < 0.05 \)).

Aortic and Coronary Sinus Lactate

In group 5, net lactate consumption at baseline was reversed to net lactate production, reaching a trough value with 10 mg methoxamine and BHT933, respectively. Lactate production was significantly higher with BHT933 than with methoxamine (Figure 6).

Clinical Signs of Ischemia and ECG Changes

None of the patients with \( \alpha_1 \)-adrenergic stimulation in groups 1, 2, and 5 and with \( \alpha_2 \)-adrenergic stimulation in group 3 experienced clinical signs of ischemia. In contrast, 3 patients in group 4 and 2 patients in group 5 complained about retrosternal pressure, interpreted as angina pectoris, during the highest dose of BHT933. In addition, in 2 of these patients in group 4 and in the 2 patients in group 5, ST-segment depression was noted. Intracoronary verapamil reversed symptoms and ECG changes immediately (Figure 7).

Discussion

The major findings of the present study are that (1) \( \alpha_1 \)-adrenergic activation does not reduce CBF in normal human coronary vessels; (2) \( \alpha_2 \)-adrenergic activation reduces CBF exclusively by microvascular constriction in normal coronary vessels; (3) in human atherosclerotic coronary vessels, both \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic activation elicit vasoconstriction in both conduit and resistance vessels; and (4) the \( \alpha \)-adrenergic coronary vasoconstriction can induce myocardial ischemia.

\( \alpha_1 \)-Adrenergic Activation

The present study shows that \( \alpha_1 \)-adrenergic activation does not constrict normal human coronary vessels but does constrict arteries with significant coronary stenosis, sufficient to induce myocardial ischemia, as reflected by net lactate production.

The absence of significant \( \alpha_1 \)-adrenergic vasoconstriction in normal coronary arteries may be attributed to the low density of vascular \( \alpha_1 \)-adrenergic receptors in coronary com-

![Figure 2. Calculated CBF in patients with normal coronary arteries with \( \alpha_1 \)-adrenergic activation. *\( P < 0.05 \) vs baseline.](http://circ.ahajournals.org/)

![Figure 3. Calculated CBF in patients with coronary stenosis with \( \alpha_1 \)-adrenergic activation. *\( P < 0.05 \) vs baseline; \#\( P < 0.05 \) vs group 1.](http://circ.ahajournals.org/)

![Figure 4. Calculated CBF in patients with normal coronary arteries with \( \alpha_2 \)-adrenergic activation. *\( P < 0.05 \) vs baseline.](http://circ.ahajournals.org/)

![Figure 5. Calculated CBF in patients with coronary stenosis with \( \alpha_2 \)-adrenergic activation. *\( P < 0.05 \) vs baseline; \#\( P < 0.05 \) vs group 3.](http://circ.ahajournals.org/)
pared with peripheral arteries. Doses of methoxamine up to 2.5 mg did not cause any effect in the coronary circulation but did produce a significant rise in aortic pressure. Whether or not the density of vascular $\alpha_1$-adrenergic receptors increases with atherosclerosis remains speculation. Certainly, an intact functional endothelium counteracts adrenergic vasoconstriction.28,29 In contrast, when endothelial function is impaired with atherosclerosis, EDRF release is reduced 30,31 and $\alpha_1$-adrenergic vasoconstriction is enhanced.8,10 Also, activation of $\alpha_1$-adrenergic receptors in cardiomyocytes, which may be increased in myocardial ischemia,32 may release endothelin, which then contributes to microcirculatory vasoconstriction.33

The present data are consistent with earlier studies in which other approaches were used. Nonselective or selective $\alpha_1$-blockade resulted in no or only a slight decrease of coronary resistance in normal subjects under resting conditions.11,12,34 Resistance in normal coronary arteries was not affected by sympathetic activation during the cold pressor test, whereas an increase in resistance in patients with coronary stenosis was abolished by intravenous phentolamine18 and the $\alpha_1$-antagonist trimazosin.20 The impact of $\alpha_1$-adrenergic receptors might, however, be more prominent under conditions of maximal hyperemia. Indeed, oral treatment with an $\alpha_1$-antagonist increased dipyridamole-recruited coronary reserve in normal subjects.34 Also, epicardial vasoconstriction and the increase in coronary resistance elicited by balloon angioplasty were attenuated only by phentolamine, whereas yohimbine did not substantially improve coronary diameter or reduce coronary resistance. Thus, these effects were attributed mainly to $\alpha_1$-adrenergic activation.35

In contrast to our study, Vatner et al36 reported an increase in coronary resistance by 92% in conscious dogs after 10 minutes of intravenous methoxamine. In addition to the higher dose and the longer exposure time to methoxamine in that study, there may be species differences. We minimized the dose and the exposure time to methoxamine using an intracoronary bolus to ensure patient safety. Whereas there was no vasoconstriction in normal coronary arteries, the $\alpha_1$-adrenergic vasoconstriction was powerful enough to induce ischemia in patients with atherosclerosis.

$\alpha_2$-Adrenergic Activation

The role of $\alpha_2$-adrenergic receptors in the human coronary circulation in vivo appears somewhat controversial. In the present study, the $\alpha_2$-agonist BHT933 reduced coronary flow in vessels without and with significant stenosis. In contrast, Indolfi et al14 reported a vasoconstriction by both $\alpha_2$-adrenergic receptor stimulation in normal and $\alpha_2$-blockade in atherosclerotic coronary arteries. The latter result was interpreted as an increase in presynaptic norepinephrine release with a subsequent activation of postsynaptic $\alpha_1$-adrenergic receptors, although a selective antagonist was not tested. The present study supports these findings as to the existence of $\alpha_2$-adrenergic receptors in the human coronary circulation and extends them to more pronounced constriction of atherosclerotic coronary arteries, significant enough to induce angina pectoris, net lactate production, and ST-segment depression.

There was no change in epicardial diameter with $\alpha_2$-adrenergic activation in normal coronary arteries, again possibly because of the presence of an intact endothelium and

![Figure 6](http://circ.ahajournals.org/)

**Figure 6.** Aortocoronary sinus lactate difference in response to methoxamine and BHT933. *P<0.05 vs baseline; #P<0.05 vs methoxamine.

![Figure 7](http://circ.ahajournals.org/)

**Figure 7.** Original ECG tracing demonstrating ST-segment depression with BHT933 and reversal on intracoronary verapamil.
a low density of $\alpha_2$-adrenergic receptors in epicardial coronary arteries.\textsuperscript{37} Therefore, the observed reduction in coronary flow at unchanged blood pressure must reflect microvascular constriction. In contrast, Indolfi et al.\textsuperscript{14} found a significant reduction of epicardial CSA by $\approx 50\%$ in response to $\alpha_2$-adrenergic activation in normal coronary arteries. However, coronary arteries were defined as normal on the basis of angiography only. In our study, normal coronary arteries were defined with IVUS, because previous investigations revealed that only 52% of angiographically normal coronary arteries show no atherosclerotic plaque formation on IVUS.\textsuperscript{38} Therefore, it cannot be ruled out that those patients in the study by Indolfi et al. had early atherosclerotic alterations leading to augmented coronary constriction after $\alpha_2$-adrenergic activation, as has been demonstrated with impaired endothelial function.\textsuperscript{8,30} Of note, $\alpha_2$-adrenergic activation in the present study also reduced coronary flow in normal coronary arteries, whereas $\alpha_1$-adrenergic activation did not. Whether or not this finding relates to a different receptor density or agonist affinity along the coronary circulation is unclear at present. There is indeed a differential distribution of $\alpha_2$-adrenergic receptors in the canine coronary circulation, with $\alpha_2$-adrenergic receptors mediating epicardial vasoconstriction\textsuperscript{37,40} and $\alpha_2$-adrenergic receptors mediating predominantly microvascular constriction.\textsuperscript{8,37,40} With reference to these data, there appears to be a similar differential functional distribution of $\alpha_2$-adrenergic receptors in the human coronary circulation as well.

**Clinical Implications**

Detailed knowledge of the impact of $\alpha$-adrenergic activation on the human coronary circulation will help to further understand clinical and angiographic findings. Until now, therapy has focused on epicardial coronary arteries. With the development of sophisticated invasive tools, attention can also be directed toward the microcirculation as the main regulatory site of coronary flow. The present study demonstrates that atherosclerosis predisposes both epicardial and microcirculatory vessels to $\alpha$-adrenergic constriction. These findings support the concept that precipitation of ischemia during sympathetic activation is a consequence not only of increased oxygen demand but also of reduced blood supply.\textsuperscript{7} It has been proposed that $\alpha$-adrenergic epicardial constriction might be beneficial for transmural flow distribution under certain circumstances.\textsuperscript{3,41} Clearly, however, with atherosclerosis, $\alpha$-adrenergic vasoconstriction reduces coronary flow and induces ischemia. The present findings may also have relevance during interventional revascularization when cardiocardiac sympathetic reflexes are operative and capable of inducing microvascular constriction.\textsuperscript{35} The involvement of $\alpha_2$-adrenergic receptors may be a target for more specific drug therapy.

**Acknowledgment**

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