Ischemia-Induced Epicardial Vasoconstriction
A Potential Mechanism for Distant Myocardial Ischemia

Alan Chu, David E. Chambers, Chang-Chyi Lin, William D. Kuehl, and Frederick R. Cobb

This study evaluated the effects of transient coronary occlusion on the diameter of a nonischemic vessel or a nonischemic coronary segment proximal to the site of occlusion. Awake mongrel dogs chronically instrumented with dimension crystals, Doppler flow probes, and distal pneumatic occluders on the circumflex coronary arteries were subjected to transient 2-minute circumflex occlusions (n=9) under constant heart rate (120 beats/min). Left ventricular end-diastolic pressure increased by 60% (from 10±1 to 16±2 mm Hg), and dP/dt decreased by 8% (from 2,048±130 to 1,885±110 mm Hg/sec); systemic hemodynamics were unaltered. Epicardial coronary diameter proximal to the site of occlusion decreased by 4.37% (from 3.62±0.25 to 3.46±0.29 mm, p<0.05). Constriction began 15–20 seconds after the onset of ischemia and progressed to maximum in 1–2 minutes. Combined α- and β-receptor blockade (n=8) with phentolamine (2 mg/kg) and propranolol (1 mg/kg) or cyclooxygenase inhibition (n=5) with indomethacin (7.5 mg/kg) did not attenuate the ischemia-induced vasoconstriction response. Transient 2-minute occlusion of the left anterior descending coronary artery (n=6) also elicited significant epicardial vasoconstriction in the circumflex coronary artery in the first minute (from 3.88±0.31 to 3.81±0.31 mm, p<0.05); the constriction was attenuated subsequently by an increase (25.5%) in circumflex flow. When left anterior descending occlusion was repeated (n=6) with circumflex flow held constant, the ischemia-induced circumflex constriction was augmented; diameter decreased 3.7% (from 3.83±0.29 to 3.69±0.29 mm, p<0.05). This study demonstrates that myocardial ischemia induces constriction of proximal epicardial arteries in the same and distant coronary arteries. This ischemia-induced constriction is not mediated via adrenergic reflex or products of the cyclooxygenase pathway and is attenuated by flow-induced vasodilation. (Circulation Research 1990;66:1484–1490)

Vasospasm of epicardial coronary arteries may lead to transient myocardial ischemia or even myocardial infarction and ventricular fibrillation. Epicardial coronary vasomotor tone is influenced by multiple physiological mechanisms including the autonomic nervous system, prostaglandins and other metabolites of arachidonic acid, and platelet factors, as well as by blood flow and endothelium-mediated responses. The potential effects of these factors on epicardial coronary vasomotion have been previously reviewed by Young and Vatner. Experiments in isolated artery segments suggest that hypoxia or exposure to hypoxia/reperfusion before excision may alter vasomotor responses to certain influencing factors. In addition, myocardial ischemia in vivo may secondarily increase neurohumoral stimuli, which may subsequently influence the vasculature not directly exposed to ischemia.

To date, studies have not examined the effects of myocardial ischemia on epicardial coronary arteries that are not subjected to direct ischemia. Accordingly, this study was designed to examine in vivo the effects of transient myocardial ischemia on the diameter of distant coronary vessels not subjected to ischemia or a nonischemic coronary segment proximal to the site of occlusion. Studies were performed using chronically instrumented awake dogs to avoid the confounding effects of surgery and anesthesia.

Materials and Methods

Eleven mongrel dogs (30–35 kg), previously screened for the absence of anemia and infection, were subjected to left thoracotomy in the fourth intercostal space under general anesthesia with intravenous thiamylal sodium (60–80 mg/kg). Heparin-filled polyvinyl catheters were implanted in the aorta and left ventricle. A 5–10-mm segment of the left
circumflex coronary artery just distal to the atrial appendage was carefully dissected free. A pair of 7-MHz piezoelectric crystals (1.5×2.5 mm, 15–20 mg), insulated with Insl-X (Insl-X Products, Yonkers, New York) and attached to a Dacron backing, were sutured with 6-0 prolene (Ethicon, Somerville, New Jersey) to the adventitia on opposite surfaces of the dissected coronary segment. Proper alignment of the crystals was verified by on-line sonomicrometry (Sonomicrometer 120-2, Triton Technology, San Diego, California) and oscilloscope monitoring. A 10-MHz cuff-type pulse Doppler flow probe was placed distal to the crystals. A pneumatic oculder was implanted distal to the flow probe. All branches of the circumflex coronary artery between the crystals and the oculder were ligated. Another flow probe and pneumatic snare were similarly placed on a dissected segment of the left anterior descending coronary artery proximal to the first diagonal branch. A pair of epicardial pacing wires was sutured onto the right ventricular surface in all but two dogs. The catheters, wires, and tubings were tunneled to a subcutaneous pouch at the base of the neck.

The catheters and wires were exteriorized under local lidocaine anesthesia after 10–14 days of recovery. On a day before subjecting the dogs to the actual study protocol, acetylcholine (4 μg) was given via the left ventricular catheter to test the integrity of endothelium-dependent responses, and nitroglycerin (0.4 mg) was given to each dog to ensure a responsive vasculature. The lack of dilation in response to acetylcholine or dilations less than 3% in response to nitroglycerin were deemed inadequate, and these dogs (n=2) were excluded from the subsequent studies.

The dogs were studied while lying awake and loosely restrained. The laboratory was dimly illuminated and kept quiet. Aortic pressure, left ventricular end-diastolic pressure, dP/dt, external coronary diameter, and coronary flow were recorded continuously throughout the study. The catheters and pressure gauges (Statham P23Db, Gould, Cleveland, Ohio) were optimally damped with a corrector device (Norton Health Care Products, Akron, Ohio).

The circumflex coronary artery was occluded in all dogs (n=9) for 2 minutes, and the hemodynamic and coronary diameter changes were recorded. In seven dogs, right ventricular pacing (120 beats/min) was initiated 5 minutes before each coronary occlusion and maintained throughout each occlusion. To evaluate the contribution of the adrenergic nervous system to the vasoactive changes in response to ischemia, the circumflex coronary occlusion was then repeated 1 hour later in the presence of β-receptor blockade with propranolol (1 mg/kg)23 (n=8). After another 1-hour recovery period, the circumflex occlusion was performed in the same eight dogs in the presence of α- and β-receptor blockade with phentolamine (2 mg/kg)23 and propranolol (1 mg/kg). Adequate blockade was verified by appropriate challenges with α- and β-agonists. In all dogs, the 2-minute occlusions were repeated either on the same day and/or on different days to ensure reproducibility of the vasoactive responses. A maximum of four occlusions was performed in each dog on a given day (1-hour interval between occlusions) to avoid possible development of collateral vessels.

To assess the role of metabolites of the cyclooxygenase pathway on the coronary vasoactive changes during ischemia, the responses to a 2-minute circumflex coronary occlusion were measured (n=5) on a different day before and after cyclooxygenase inhibition with indomethacin (7.5 mg/kg18 given 30 minutes before occlusion). Ninety minutes was allowed between occlusions.

Finally, to assess the potential effects of changes in blood flow on the epicardial coronary vasomotor responses to ischemia, the left anterior descending coronary artery was occluded (n=6) for 2 minutes while the circumflex flow was allowed to increase and the circumflex coronary diameter was recorded. One hour later, a comparable left anterior descending occlusion was repeated in the same dogs, and the circumflex flow was maintained at the preischemic level by partial inflation of the circumflex pneumatic oculder below the crystal site.

Vasoactive changes were expressed as percent change from baseline dimensions. Statistical analyses were performed using Student’s paired t test.

Results

Response to Myocardial Ischemia

Figure 1A is a representative recording of the responses to a 2-minute circumflex occlusion. There was no significant change in aortic pressure. The left ventricular dP/dt was minimally depressed. The left ventricular end-diastolic pressure was significantly increased in all dogs. Heart rate was not significantly different since the heart was paced at 120 beats/min in most dogs. It should be emphasized that the coronary constriction was not a result of direct hypoxia or ischemia to the vessel or a change in pressure at the site of the crystals since the occlusion occurred distal to the dimension crystals. Coronary vasoconstriction did not occur immediately after the onset of coronary occlusions but, rather, began approximately 15–20 seconds after the onset of myocardial ischemia and gradually progressed to a maximum in 1–2 minutes. In several dogs, the constriction was progressive throughout the 2-minute period. Upon reperfusion, the coronary diameter rapidly increased to beyond the resting level in response to the reactive hyperemic blood flow. The hemodynamic and coronary responses in the entire group of dogs are summarized in Table 1.

Adrenergic Blockade

Table 1 illustrates the hemodynamic and coronary changes during the circumflex coronary occlusion in the presence of β-adrenergic blockade alone and in the presence of combined α- and β-adrenergic blockade, respectively. β-Adrenergic blockade did not
significantly alter aortic pressure, end-diastolic pressure, or coronary blood flow but did reduce dP/dt and resting coronary diameter. Coronary occlusion in the presence of β-adrenergic blockade induced a similar increase in end-diastolic pressure when compared with control. The degree of coronary vasoconstriction was, however, significantly enhanced despite a reduced resting coronary diameter. The addition of α-adrenergic blockade further decreased resting aortic pressure and dP/dt but did not further alter resting end-diastolic pressure, resting coronary diameter, or resting coronary blood flow. Although coronary occlusion in the presence of both α- and β-adrenergic blockade resulted in a reduced coronary

![Figure 1. Representative recordings showing the effects of a 2-minute circumflex coronary occlusion (panel A), a 2-minute left anterior descending coronary artery (LAD) occlusion (panel B), and a 2-minute LAD occlusion with circumflex flow held constant by partial inflation of a pneumatic snare on the distal circumflex artery (panel C). In each case, circumflex coronary diameter and circumflex flow are displayed. LV, left ventricular.](http://circres.ahajournals.org/lookup/suppl/doi:10.1161/01.RES.66.6.1486/-/DC1/FIG1A.jpg)

### TABLE 1. Hemodynamic Responses to a 2-Minute Circumflex Coronary Artery Occlusion at Rest and After Adrenergic Blockade

<table>
<thead>
<tr>
<th></th>
<th>AoP (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>LVEDP (mm Hg)</th>
<th>LV dP/dt (mm Hg/sec)</th>
<th>CD</th>
<th>CBF (KHz)</th>
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<td>Post</td>
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<td>Control circumflex occlusion (n=9)</td>
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<tr>
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<td>7</td>
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<td>2</td>
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<td>&lt;0.05</td>
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<tr>
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<td>105</td>
<td>111</td>
<td>11</td>
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</tr>
<tr>
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<td>6</td>
<td>1</td>
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<tr>
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<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.05</td>
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<tr>
<td>Circumflex occlusion after α- and β-adrenergic blockade (n=8)</td>
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<tr>
<td>Mean</td>
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<td>93†</td>
<td>109</td>
<td>113</td>
<td>9</td>
<td>13†</td>
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<tr>
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<tr>
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<td></td>
<td>&lt;0.05</td>
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</tbody>
</table>

Results are tabulated for measurements made before occlusion (Pre) and just before release (Post) of the occlusion. AoP, aortic pressure; LVEDP, left ventricular end-diastolic pressure; LV, left ventricular; CD, circumflex coronary diameter; CBF, circumflex coronary blood flow; Δ%, percent change in CD.

*P<0.05 when compared with control circumflex occlusion.

†P<0.05 when compared with circumflex occlusion after β-adrenergic blockade alone.
Constriction when compared with β-adrenergic blockade alone, resting coronary diameter, coronary blood flow, and the ischemia-induced vasoconstriction were not significantly different when compared with control conditions before adrenergic blockade. The effects of adrenergic blockade on the ischemia-induced vasoconstriction are further illustrated in Figure 2.

**Cyclooxygenase Inhibition**

Cyclooxygenase inhibition with indomethacin did not significantly change hemodynamic parameters. Coronary flow and proximal coronary diameter at rest were also not significantly altered after cyclooxygenase inhibition. Coronary occlusion in the presence of cyclooxygenase inhibition resulted in comparable increases in end-diastolic pressure and coronary vasoconstriction responses (Table 2, Figure 3).

### Response in Nonoccluded Vessel: Flow Effects

Figure 1B illustrates the response to occlusion of the left anterior descending coronary artery. The circumflex coronary flow monitored during the coronary occlusion increased during the 2-minute ischemic period (mean, 25.5%). Despite the increase in blood flow, proximal circumflex coronary constriction again was observed, indicating that the constriction was not due to flow changes. Figure 1C illustrates the response to occlusion of the left anterior descending coronary artery in the same dog when circumflex flow was held constant by partial inflation of the pneumatic snare distal to the crystal site. When compared with the free flow conditions in Figure 1B, flow restriction further enhanced the coronary constriction, indicating that the ischemia-induced coronary constriction was partially attenuated by the increased flow. The hemodynamic and coronary effects of this entire group of dogs are summarized in Table 3 and Figure 4. Circumflex coronary constriction was seen in

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**Figure 2.** Bar graph showing effects of adrenergic blockade on ischemia-induced coronary vasoconstriction (n=8). Changes in proximal circumflex coronary diameter during a 2-minute circumflex occlusion are expressed as percent change from resting diameter±SEM. β-Adrenergic blockade was achieved by propranolol (1 mg/kg); α-adrenergic blockade was achieved by phentolamine (2 mg/kg). *p<0.05.

**Figure 3.** Bar graph showing effects of cyclooxygenase inhibition on ischemia-induced coronary vasoconstriction (n=5). Changes in proximal circumflex coronary diameter during a 2-minute circumflex occlusion are expressed as percent change from resting diameter±SEM. Cyclooxygenase inhibition was achieved by indomethacin (7.5 mg/kg given 30 minutes before coronary occlusion).

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**TABLE 2. Hemodynamic Responses to a 2-Minute Circumflex Coronary Artery Occlusion Before and After Cyclooxygenase Inhibition**

<table>
<thead>
<tr>
<th></th>
<th>AoP (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>LVEDP (mm Hg)</th>
<th>LV dP/dt (mm Hg/sec)</th>
<th>CD (mm)</th>
<th>CBF (KHz)</th>
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<td></td>
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<td>Pre Post</td>
<td>Pre Post</td>
<td>Pre Post</td>
<td>Pre Post</td>
<td>Pre Post</td>
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<td>Control occlusion (n=5)</td>
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<td></td>
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<td>10 8</td>
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<td>127 174</td>
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</tr>
<tr>
<td>p</td>
<td>NS NS</td>
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<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Circumflex occlusion after cyclooxygenase inhibition (n=5)</td>
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</tr>
<tr>
<td>Mean</td>
<td>104 103</td>
<td>110 116</td>
<td>18</td>
<td>1,830 1,830</td>
<td>3.40</td>
<td>-3.83</td>
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<tr>
<td>±SEM</td>
<td>6 6</td>
<td>10 4</td>
<td>2 2</td>
<td>139 135</td>
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</tr>
<tr>
<td>p</td>
<td>NS NS</td>
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<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Results are tabulated for measurements made before occlusion (Pre) and just before release (Post) of the occlusion. AoP, aortic pressure; LVEDP, left ventricular end-diastolic pressure; LV, left ventricular; CD, circumflex coronary diameter; CBF, circumflex coronary blood flow; Δ%, percent change in CD.
TABLE 3. Hemodynamic Responses to a 2-Minute Left Anterior Descending Coronary Artery Occlusion

<table>
<thead>
<tr>
<th>AoP (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>LVEDP (mm Hg)</th>
<th>LV dp/dt (mm Hg/sec)</th>
<th>CD</th>
<th>CBF (KHz)</th>
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<tr>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
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<td>Pre</td>
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<tr>
<td>Control LAD occlusion (n=6)</td>
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<tr>
<td>Mean</td>
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<td>11</td>
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<td>p</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

LAD occlusion with circumflex blood flow constant (n=6)

| Mean        | 111                    | 112         | 109                 | 118 | 10        | 2,113 | 1,450  | 3.83 | -3.70† | 2.00 | 2.06† |
| ±SEM        | 4                      | 3           | 11                  | 2   | 1         | 155   | 119    | 0.29 | 0.84   | 0.18 | 0.05  |
| p           | NS                     | NS          | <0.05               | <0.05 | <0.05 |       | NS     |      |         |      |       |

Results are tabulated for measurements made before occlusion (Pre) and just before release (Post) of the occlusion. AoP, aortic pressure; LVEDP, left ventricular end-diastolic pressure; LV, left ventricular; CD, circumflex coronary artery diameter; CBF, circumflex coronary artery flow; Δ%, percent change in CD; LAD, left anterior descending coronary artery.

*Coronary diameter at 1 minute after occlusion was significantly reduced by 1.86±0.49% when compared with control.

†p<0.05 when compared with control LAD occlusion.

all dogs during the first minute after left anterior descending occlusion (−1.86±0.49%, p<0.05). In some dogs, blood flow increased significantly in the circumflex coronary artery (25.5±4.6%, p<0.05) during left anterior descending occlusion, and the circumflex diameter (measured just before release) was not different from control (Table 3). However, when blood flow in the circumflex coronary artery was prevented from increasing, the vasoconstriction effect was unmasked (Table 3); diameter decreased by 3.70±0.84%. Thus, the increase in flow caused a delayed vasodilation that attenuated the vasoconstriction effect induced by distant myocardial ischemia.

**Discussion**

The present study demonstrated for the first time that the proximal coronary artery may undergo significant vasoconstriction in response to distant myocardial ischemia. The constriction was not due to a decrease in coronary blood flow or a change in perfusion pressure since vasoconstriction of the circumflex coronary artery occurred when the left anterior descending coronary artery was occluded and blood flow through the circumflex coronary artery increased. An additional important finding of this study is the demonstration that increases in coronary blood flow may significantly modify vasoconstriction stimuli in the coronary vasculature. Prevention of the flow increases in the circumflex coronary artery during left anterior descending occlusion resulted in significantly greater constriction of the circumflex coronary artery. The observation that phasic flow in the circumflex coronary artery increased during left anterior descending occlusion indicated dilation of the circumflex resistance vasculature and suggested that this ischemia-induced constriction occurred primarily in the conductance arteries.

The present study further demonstrated that the basic ischemia-induced coronary constriction was not mediated by adrenergic stimulation since combined α- and β-adrenergic blockade did not significantly attenuate the response. Selective β-adrenergic blockade did enhance the constriction, suggesting unmasking of an unopposed α-receptor-mediated vasoconstriction in response to ischemia. The unmasked vasoconstriction was abolished by α-adrenergic blockade. Relative to the ischemia-induced constriction, the unmasked α-receptor-mediated response was mild. Thus, although the present study demonstrated that the epicardial vasoconstriction response to ischemia could be modified by selective adrenergic blockade, the basic response was not significantly influenced by adrenergic stimulation.

It is unlikely that the ischemia-induced coronary constriction was due to release of metabolites of the cyclooxygenase pathway, such as thromboxane, since the response was not attenuated after cyclooxygenase inhibition with indomethacin.
The magnitude of vasoconstriction seen in the present study was large, with 3–8% external diameter reduction, representing an approximately 10–35% change in cross-sectional area. This degree of vasoconstriction was more potent than that caused by serotonin in denuded arteries in this model.9 Although this degree of epicardial coronary constriction would not likely alter perfusion in a vessel with normal luminal diameter, the vasoconstriction may be sufficient to reduce flow in vessels with compliant stenotic lesions secondary to atherosclerosis. Since atherosclerotic vessel segments have been shown to demonstrate abnormal endothelin-mediated responses,27,28 the normally flow-mediated dilation responses may no longer attenuate the ischemia-induced coronary constriction, leading to further reduction in luminal area. As demonstrated in the present study, this vasoconstriction response may not be confined to the occluded artery and may occur in distant vessels not subjected to occlusion. In the presence of severe myocardial ischemia, vasoconstriction in a distant coronary distribution may not only increase global ischemia but may also reduce collateral flow originating from these coronary arteries, leading to exacerbation of ischemia.

The mediator of this ischemia-induced constriction remains to be determined. The relatively rapid onset and recovery suggest a reflex mechanism. Although selective adrenergic blockade modified the response, the lack of significant attenuation in the presence of α- and β-receptor blockade makes it unlikely that the vasoconstriction response is mediated via adrenergic mechanisms. Other nonadrenergic neurotransmitter substances such as neuropeptide Y29 or serotoninergic mechanisms9–12 cannot be excluded as mediators of this ischemia-induced coronary constriction. Endothelin is a newly described, potent vasoconstrictor peptide synthesized by the endothelium. It has been shown to cause hypertension in the intact animal and vasoconstriction of in vitro vascular strip preparations.30 Effects of endothelin on the coronary arteries are still controversial.31,32 Since its vasoconstrictive effects are generally believed to be prolonged, the rapid reversal (<1 minute) of the constriction response upon reperfusion of the ischemic myocardium in the present study makes endothelin a less likely candidate. Other classes of endothelium-derived constricting factors have been described in in vitro vascular ring preparations subjected to stimuli such as hypoxia.21,22 Additional possible mediators include platelet activating factor33 and leukotrienes.34

The present study established the presence of an ischemia-induced vasoconstriction response. The data demonstrate that distant myocardial ischemia may induce a significant, generalized, nonadrenergically mediated vasoconstriction of the epicardial coronary arteries. This ischemia-induced constriction can be attenuated by flow-mediated vasodilation. In the setting of proximal stenosis due to atherosclerosis, an ischemia-induced epicardial vasoconstriction response may be a mechanism not only for potentiating ischemia in the vasculature experiencing ischemia but also for inducing vasoconstriction and ischemia in the distant regions.

Acknowledgments

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References


**KEY WORDS**
- myocardial ischemia
- epicardial coronary vasoconstriction
- distant ischemia
- adrenergic nervous system
- flow-mediated dilation
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