Vasoconstriction of Canine Coronary Collateral Vessels With Vasopressin Limits Blood Flow to Collateral-Dependent Myocardium During Exercise

Blair W. Foreman, Xue-Zheng Dai, and Robert J. Bache

This study was performed to test the hypothesis that active constriction of coronary collateral vessels can worsen hypoperfusion of collateral-dependent myocardium during exercise. Studies were performed in seven adult mongrel dogs in which intermittent followed by permanent occlusion of the left circumflex coronary artery produced an area of collateral-dependent myocardium without gross evidence of infarct. Myocardial blood flow was determined with microspheres while measurement of aortic and distal coronary pressures allowed calculation of collateral and small vessel resistance at rest and during treadmill exercise. The ability of collateral vessel constriction to limit blood flow was assessed by infusion of vasopressin during exercise. During control conditions, blood flow in the collateral zone underwent a subnormal increase during exercise in comparison with the normal zone (1.74±0.27 versus 2.50±0.40 ml/min/g, respectively, p<0.05). Infusion of vasopressin in a dose that caused no change in normal zone flow (0.01 μg/kg/min i.v.) produced a 30±5% further decrease in flow to the collateral zone (p<0.01). This decrease in collateral zone flow resulted from a 48±14% increase in transcollateral resistance in response to vasopressin infusion (p<0.01), as well as a 40±9% increase in small vessel resistance in the collateral zone (p<0.01). These data demonstrate that active constriction of both collateral vessels and coronary resistance vessels can contribute to hypoperfusion of collateral-dependent myocardium during exercise. (Circulation Research 1991;69:657–664)

In response to gradual coronary artery occlusion, native collateral vessels may enlarge sufficiently to allow total arterial occlusion without producing infarction of the dependent myocardium.1,2 Although these collateral vessels can supply adequate arterial inflow to meet myocardial needs during resting conditions, they represent a significant locus of vascular resistance that can limit the ability to augment flow and thereby impair contractile performance during periods of increased cardiac activity.3–5 In addition to the fixed limitation of blood flow, which is determined by the state of maturation of the collateral vessels, functional changes within the collateral system might also influence the degree of flow limitation. Mature coronary collateral vessels have structural characteristics similar to small arteries, including a well-developed muscular media.1 Both in vitro studies using isolated vessel segments and open-chest canine studies have shown that these vessels are capable of vasomotor activity in response to pharmacological agonists.6,7 This suggests that collateral vessel vasomotion may have potential for mediating blood flow into the dependent myocardium during physiological conditions. Consequently, this study was carried out to test the hypothesis that vasoconstriction of coronary collateral vessels can worsen hypoperfusion of the dependent myocardium during exercise. To test this hypothesis, the vasoconstrictor arginine vasopressin was infused into dogs in which an area of myocardium had been rendered collateral-dependent without producing myocardial infarction. Vasopressin was chosen since it is known to cause vasoconstriction of moderately well-developed coronary collateral vessels6,7 but does not cause constriction of muscular arteries, which could also influence blood flow to the collateral-dependent region.6,8

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**Materials and Methods**

**Surgical Procedure**

Eleven dogs of either sex weighing 22–29 kg were premedicated with fentanyl (0.4 mg i.m.) and droperidol (20 mg i.m.), anesthetized with sodium pentobarbital (30–35 mg/kg i.v.), intubated, and ventilated with a respirator (Harvard Apparatus, South Natick, Mass.) with room air supplemented with oxygen. Under sterile conditions, a left thoracotomy was performed in the fifth intercostal space. A heparin-saline-filled polyvinyl chloride catheter (3.0 mm o.d.) was inserted into the internal thoracic artery and advanced into the ascending aorta. The pericardium was opened, and a high-fidelity micromanometer (model P5, Konigsberg Instrument Co., Pasadena, Calif.) was inserted into the left ventricle near the apical dimple. A heparin-filled catheter was also inserted into the left ventricle near the apical dimple for calibration of the micromanometer. The proximal left circumflex coronary artery was dissected free, and a Doppler flowmeter probe was fitted around the artery. A snare-type occluder and an inflatable hydraulic occluder were positioned on the artery distal to the flowmeter probe. In five dogs, a heparin-filled Silastic catheter (0.3 mm i.d.) was inserted into the circumflex artery distal to the hydraulic occluder by the method of Gwirtz.9 Finally, a polyvinyl chloride catheter was placed into the left atrium via the atrial appendage and secured with a purse-string suture. The pericardium was then loosely closed, the catheters and electrical leads were tunneled subcutaneously to exit in the interscapular area, and the chest was closed in layers. Catheters and electrical leads were protected by a nylon vest that the dogs had been trained to wear. Catheters were flushed with heparin-saline daily to maintain patency.

**Collateral Vessel Development**

Collateral vessel development was stimulated using a modification of the repetitive coronary occlusion technique of Franklin et al.10 Beginning 5–7 days after surgery, the dogs underwent 1–2-minute coronary occlusions every 5 minutes for 2–3 hours daily. Occlusions were performed by injecting saline into the hydraulic occluder while the flowmeter signal was monitored to ensure total occlusion. Distal coronary pressure was recorded before and during coronary artery occlusion to monitor collateral vessel development. When distal coronary pressure exceeded 35 mm Hg, the artery was occluded by tightening the snare occluder while left circumflex blood flow was monitored to ensure complete occlusion. Four of the 11 dogs did not survive the coronary occlusion procedure. In the remaining seven dogs, studies were performed 26±4 days after the beginning of the occlusion procedure, when the coronary artery had been totally occluded for a period of 1 week.

**Measurements of Myocardial Blood Flow**

Myocardial blood flow was measured with 15-µm diameter microspheres labeled with 113Sn, 57Co, or 46Sc (3M Co., St. Paul, Minn., and NEN Co., Boston). Microspheres were obtained as 1.0 mCi in 10 ml low molecular weight dextran. Three million microspheres were injected into the left atrium for each blood flow measurement. Microsphere measurements were calibrated with reference arterial blood samples obtained from the aortic catheter at a constant rate of 15 ml/min using a peristaltic pump. Reference blood sampling was begun at the time of microsphere injection and continued for 90 seconds.

**Experimental Protocol**

Aortic and peripheral coronary pressures were measured with Statham P23ID pressure transducers (Gould Instruments, Cleveland) at midchest level. Left ventricular pressure, including pressure recorded at high gain for measurement of end-diastolic pressure, and dP/dt were recorded from the intracavitary micromanometer. Data were recorded on an eight-channel direct-writing oscillograph (model 8800, Hewlett-Packard, Palo Alto, Calif.). After all recording instruments were connected, a 5-minute period of warmup exercise was performed while exercise intensity was gradually increased to 6.4 km/hr at a 15% grade. The dogs were then allowed to rest for 1 hour. Control resting hemodynamic measurements were performed with the dogs standing quietly on the treadmill; an injection of microspheres was administered for measurement of myocardial blood flow.

After completion of the resting measurements, exercise was begun at 6.4 km/hr at a 5% grade. Hemodynamic measurements were recorded continuously to ensure that steady-state conditions existed. Microsphere administration was performed 3 minutes after the onset of exercise. The dogs continued to exercise for 2 minutes after microsphere injection and were then allowed to rest for 1 hour.

An infusion of arginine vasopressin (0.01 µg/kg/min i.v.) was then begun. Three minutes after beginning arginine vasopressin, exercise was begun at a level that produced the same heart rate times the left ventricular systolic pressure product, which was observed during control exercise. Hemodynamic measurements and microsphere administration were performed after 3 minutes of exercise and continued for 2 minutes after microsphere injection.

**Determination of the Collateral-Dependent Zone**

Collateral-dependent myocardium was delineated using the shadow technique of Patterson and Kirk.11 The dogs were anesthetized with morphine sulfate (1–2 mg/kg i.m.) and α-chloralose (100 mg/kg i.v.), intubated, and ventilated with a respirator. A left thoracotomy was performed in the sixth intercostal space, and the left circumflex coronary artery was mobilized and cannulated at the site of the occlusion. A 26-gauge tube incorporated into the wall of the cannula allowed measurement of cannula tip pressure. During microsphere injection, the coronary cannula was perfused with nonradioactive blood from a reservoir pressurized.
to maintain cannula tip pressure 10 mm Hg above mean arterial pressure; radioactive microspheres were then administered into the left atrium. In this way, the area of collateral-dependent myocardium was perfused with nonradioactive blood while normal, non-collateral-dependent myocardium was perfused with blood containing microspheres.

**Tissue Preparation**

At the conclusion of the shadow technique, 10 ml Evans blue dye was injected into the coronary artery cannula to stain the collateral-dependent area. The heart was then removed and fixed in 10% buffered formalin. After fixation, the right ventricle, atria, and great vessels were removed. The left ventricle was then sectioned into five transverse rings from base to apex. Each ring was sectioned radially into 12–15 sections; each section was further divided into epicardial and endocardial halves. The resultant specimens were weighed on an analytical balance and placed into vials for counting of radioactivity. Myocardial and blood reference specimens were counted in a gamma spectrometer (model 5912, Packard Instrument Co., Inc., Downers Grove, Ill.) with a multichannel analyzer at window settings corresponding to the peak energies of each radionuclide. The activity in each energy window was corrected for background activity and for overlapping counts between isotopes with a digital computer. Blood flow to each myocardial specimen ($Q_m$) was computed using the formula $Q_m = Q_s \cdot C_s/C_m$, where $Q_s$ is reference blood flow rate (ml/min), $C_s$ is counts per minute of the myocardial specimen, and $C_m$ is counts per minute of the reference blood specimen.

**Calculations**

Total collateral flow was determined as the sum of absolute blood flow to all myocardial samples in the collateral-dependent region as identified by the shadow technique. Transcollateral vessel resistance was calculated as the pressure drop from aortic pressure to the pressure at the catheter tip distal to the occlusion divided by total collateral zone blood flow. Small vessel resistance in the collateral-dependent region was calculated as (distal coronary artery pressure—left ventricular end-diastolic pressure)/total collateral zone flow. Total collateral system resistance was calculated as (mean aortic pressure—left ventricular end-diastolic pressure)/total collateral zone flow. Duplicate specimens from the anterior left ventricular wall were used to assess blood flow in normally perfused myocardium. Total vascular resistance in the normal zone was calculated as (aortic pressure—left ventricular end-diastolic pressure)/total normal zone blood flow. Resistance calculations were expressed as coronary resistance units (CRU, assessed in mm Hg/ml/min/100 g myocardium).

**Plasma Vasopressin Levels**

Plasma arginine vasopressin levels were determined in a separate group of five dogs surgically prepared as previously described but without a coronary occlusion. In these dogs, arginine vasopressin was also infused at a rate of 0.01 μg/kg/min i.v. for 6 minutes. Blood samples were withdrawn for determination of arginine vasopressin concentrations before beginning the infusion and at 6 minutes of infusion. Plasma arginine vasopressin was determined by using a modification of the radioimmunoassay technique described by Cowley et al., using rabbit arginine vasopressin antiserum and $^{125}$I-arginine vasopressin as the tracer antigen.

**Data Analysis**

Heart rate and all pressures were measured directly from the strip-chart recordings. Hemodynamic data were analyzed using analysis of variance for repeated measures. A value of $p<0.05$ was required for statistical significance. When a statistically significant result was found, individual comparisons were performed using Student's $t$ test for paired data and the Wilcoxon signed rank test. All data are expressed as mean±SEM.

**Results**

**Collateral Zone Determination**

Figure 1 shows myocardial blood flow in a representative left ventricular ring during resting conditions and during the shadow technique. Blood flow in the collateral zone during resting conditions was
22±7% less than in the normally perfused myocardium (p<0.05). Myocardial blood flow measurements obtained with the shadow technique demonstrated a sharp boundary between tissue perfused by nonradioactive blood through the left circumflex coronary cannula and the adjacent normally perfused myocardium. Total left ventricular mass ranged from 82.0 to 124.8 g (mean, 116.7±8.9 g). Collateral-dependent myocardium ranged from 12.2 to 56.5 g (mean, 25.5±5.6 g) and represented 21.7±4.4% of the left ventricle.

**Hemodynamics**

Hemodynamic measurements at rest and during exercise are shown in Table 1. Heart rate at rest was 117±7 beats/min and increased significantly during exercise. Heart rates during exercise with vasopressin infusion tended to be less than heart rates during control exercise, but this did not achieve statistical significance. Mean aortic pressure was 101±3 mm Hg during resting conditions. Aortic pressure increased significantly during control exercise. Aortic pressure tended to increase further during exercise with vasopressin, but this did not achieve statistical significance. Left ventricular systolic pressure was 123±4 mm Hg at rest and increased during control exercise and during vasopressin infusion. The heart rate times left ventricular systolic pressure product increased significantly during exercise and was not different between control exercise and exercise with vasopressin. Left ventricular end-diastolic pressure was 10±2 mm Hg at rest and did not change during control exercise. However, during exercise with vasopressin infusion, left ventricular end-diastolic pressure increased significantly compared with rest and with control exercise (p<0.05). Left ventricular dP/dt was 2,700±218 mm Hg/sec at rest and underwent a 93±17% increase during control exercise (p<0.01).

Vasopressin infusion did not significantly alter exercising left ventricular dP/dt.

**Myocardial Blood Flow**

Blood flow to normally perfused and collateral-dependent myocardium is shown in Table 2 and Figure 2. During control conditions, blood flow in the normal zone was 1.51±0.22 ml/min/g, and flow to the subendocardial myocardium (ENDO) was significantly greater than flow to the subepicardial myocardium (EPI) (ENDO/EPI flow ratio=1.29±0.04). Control exercise resulted in an 82±15% increase in normal zone flow with a modest decrease in the ENDOP/EPI ratio (1.13±0.06, p<0.05 versus rest). Infusion of vasopressin did not alter mean flow or the transmural distribution of perfusion in the normal zone.

During resting conditions, blood flow in the collateral-dependent zone was 78±7% of normal zone flow (p<0.05 in comparison with the normal zone), and the ENDOP/EPI flow ratio was 1.03±0.10 (p<0.05 versus normal). Exercise resulted in a subnormal increase in blood flow in the collateral-dependent area (Figure 2). The increase in ENDOP flow in response to exercise (+0.53±0.21 ml/min/g) was less than the change in EPI flow (+0.74±0.12 ml/min/g), resulting in a decrease in the ENDOP/EPI flow ratio from 1.03±0.10 at rest to 0.86±0.15 during control exercise (p<0.05). Infusion of vasopressin caused a 30±5% decrease in mean tissue flow in comparison with control exercise (p<0.01). This decrease in flow in response to vasopressin was uniform across the left ventricular wall with no change in the ENDOP/EPI flow ratio.

**Collateral Resistance**

Mean aortic and distal coronary pressures, the pressure drop from aortic to coronary pressure, total

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**Table 1. Hemodynamic Data for Seven Chronically Instrumented Dogs**

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>LV dP/dt (mm Hg/sec)</th>
<th>RPP (mm Hg · beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>117±7</td>
<td>101±3</td>
<td>123±4</td>
<td>10±2</td>
<td>2,700±218</td>
<td>14,600±890</td>
</tr>
<tr>
<td>Control exercise</td>
<td>193±4*</td>
<td>110±5*</td>
<td>147±5*</td>
<td>11±5</td>
<td>5,200±547*</td>
<td>28,700±800*</td>
</tr>
<tr>
<td>Exercise+AVP</td>
<td>178±7*</td>
<td>120±5*</td>
<td>150±6*</td>
<td>18±3*†</td>
<td>4,900±1,070*</td>
<td>26,500±1,490*†</td>
</tr>
</tbody>
</table>

Values are mean±SEM. MAP, mean aortic pressure; LVSP, left ventricular (LV) systolic pressure; LVEDP, LV end-diastolic pressure; RPP, rate-pressure product; AVP, arginine vasopressin.

*p<0.05 vs. rest; †p<0.05 vs. control exercise.

**Table 2. Blood Flow and the Ratio of Subendocardial to Subepicardial Blood Flow in Normally Perfused and Collateral-Dependent Myocardium in Seven Chronically Instrumented Dogs**

<table>
<thead>
<tr>
<th></th>
<th>Normal zone (ml/min/g)</th>
<th>Collateral zone (ml/min/g)</th>
<th>ENDO/EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal zone</td>
</tr>
<tr>
<td>Rest</td>
<td>1.51±0.22</td>
<td>1.17±0.19*</td>
<td>1.29±0.04</td>
</tr>
<tr>
<td>Control exercise</td>
<td>2.50±0.40†</td>
<td>1.74±0.27*†</td>
<td>1.13±0.06†</td>
</tr>
<tr>
<td>Exercise+AVP</td>
<td>2.29±0.30†</td>
<td>1.22±0.14‡</td>
<td>1.20±0.03‡</td>
</tr>
</tbody>
</table>

Values are mean±SEM. ENDO/EPI, ratio of subendocardial to subepicardial blood flow.

*p<0.05 vs. normal zone; †p<0.05 vs. rest; ‡p<0.05 vs. control exercise.
collateral zone blood flow, and transcullar resistance for five dogs with intracoronary catheters are shown in Table 3. Exercise resulted in a significant increase in mean aortic pressure, with a tendency toward a greater increase during vasopressin infusion, although this did not achieve statistical significance. Distal coronary pressure tended to be less during exercise than during resting conditions, but this difference was not significant. Exercise resulted in a significant increase in the aortic to coronary artery pressure drop from 27±8 mm Hg at rest to 48±6 mm Hg during control exercise (p<0.05), with a further significant increase to 53±7 mm Hg during exercise with vasopressin infusion (p<0.05). In comparison with the resting measurement, total blood flow into the collateral-dependent zone increased 64±8% during control exercise (p<0.05), while vasopressin infusion prevented collateral zone blood flow from increasing during exercise.

Transcullar resistance and small vessel resistance in the collateral-dependent region were computed to determine their relative effects on collateral zone blood flow (Table 3 and Figure 3). Transcullar resistance (from the aorta to the recipient coronary artery) did not change significantly from rest to control exercise. Infusion of vasopressin caused a 48±14% increase in collateral vessel resistance compared with control exercise (p<0.05) (Table 3). In comparison with rest, small vessel resistance in the collateral-dependent region decreased 53±7% during control exercise (p<0.01). Vasopressin infusion resulted in a 40±9% increase in small vessel resistance during exercise (p<0.02) (Figure 3). Thus, constriction of both the collateral vessels and the resistance vessels in the collateral-dependent region contributed to the reduction in myocardial blood flow during vasopressin infusion.

**Normal Zone Resistance**
During resting conditions, total coronary vascular resistance in the normal zone was not significantly different from small vessel resistance in the collateral zone. With exercise, normal zone resistance decreased and was similar to small vessel resistance in the collateral zone. Normal zone vascular resistance tended to increase during vasopressin infusion, but this did not achieve statistical significance (Figure 3).

**Plasma Vasopressin Levels**
The mean plasma vasopressin level during control conditions was 2.08±0.64 pg/ml (range, 1.4–2.9 pg/ml).

<p>| Table 3. Mean Aortic and Coronary Pressure, Aorta to Coronary Artery Pressure Drop, Total Collateral Zone Flow, and Transcullar Resistance for Five Chronically Instrumented Dogs |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Mean aortic pressure (mm Hg)</th>
<th>Distal coronary pressure (mm Hg)</th>
<th>Aorta-coronary pressure drop (mm Hg)</th>
<th>Total collateral zone flow (ml/min)</th>
<th>Transcullar resistance (mm Hg/min/ml/100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>102±4</td>
<td>75±10</td>
<td>27±8</td>
<td>37±14</td>
</tr>
<tr>
<td>Control exercise</td>
<td>112±6*</td>
<td>64±10</td>
<td>48±6*</td>
<td>52±22*</td>
</tr>
<tr>
<td>Exercise+AVP</td>
<td>121±7*</td>
<td>68±11</td>
<td>53±7*†</td>
<td>35±12†</td>
</tr>
</tbody>
</table>

Values are mean±SEM. AVP, arginine vasopressin. *p<0.05 vs. rest; †p<0.05 vs. control exercise.
ml). After 6 minutes of vasopressin infusion, the mean plasma level had increased to 98.2±34.3 pg/ml (range, 52.6–147.0 pg/ml). The mean change from baseline to 6 minutes of infusion was 94.3±8.7 pg/ml (range, 51.2–144.1 pg/ml).

Discussion

This study presents the first documentation that active vasoconstriction of coronary collateral vessels can aggravate hypoperfusion of the dependent myocardium during physiological conditions in the intact animal. During control conditions, exercise resulted in a subnormal increase in myocardial blood flow in the collateral-dependent region. However, this limitation of blood flow was not fixed, as demonstrated by worsening hypoperfusion in the collateral-dependent region during infusion of vasopressin. Impairment of collateral flow occurred with a dose of vasopressin that did not significantly alter systemic hemodynamics and did not decrease blood flow in the normally perfused myocardium. This finding demonstrates that collateral vessel constriction can contribute to the limitation of blood flow in the dependent myocardium during exercise.

Collateral Resistance at Rest

Computed values for collateral vascular resistance have not previously been reported in the intact awake animal. In open-chest canine preparations with moderately well-developed coronary collateral vessels, collateral resistance was reported to be 0.22 mm Hg·ml/min/100 g13 and 0.24±0.02 mm Hg·ml/min/100 g.6 These values are similar to the present results in which transcollateral resistance in awake animals was 0.25±0.10 mm Hg·ml/min/100 g during resting conditions. Calculations of vascular resistance from single measurements of flow and pressure do not take into account the pressure–flow characteristics of the vascular system. Eng and Kirk14 demonstrated that flow across coronary collateral vessels may be modified by a vascular waterfall mechanism. These investigators emphasized the distal bed of the collateral-dependent region to prevent antegrade flow into the myocardium when coronary cannula pressure was raised, thus allowing evaluation of the pressure–flow characteristics of the collateral vessels. Measurements of retrograde flow during increasing cannula pressure demonstrated a back-pressure–independent region extending from 0 to ~20 mm Hg. This finding is compatible with the concept that, at a pressure <20 mm Hg, flow is determined by a vascular waterfall operating within the collateral vessels. In the present study, distal pressures in the collateral-dependent artery were always above this value, so that the collateral vessel waterfall should not have influenced the results.

Blood flow in the collateral-dependent region was significantly less than in normally perfused myocardium during resting conditions. This was not due to exhaustion of vasodilator reserve, since flow in this region was able to increase in response to exercise. Although no gross evidence of infarct was found in the collateral zone, it is possible that increased fibrosis in this region could have contributed to the decreased resting blood flow. Canty and Klocke15 also observed decreased resting blood flow rates in collateral-dependent myocardium of dogs early after an ameroid constrictor had caused total arterial occlusion. The decreased blood flow in that study did not result from loss of viable myocardium, since later measurements demonstrated that blood flow and systolic function did eventually return to normal. The investigators suggested that the early decrease in blood flow may have been associated with a downward adjustment in myocardial work (and thus oxygen demands) in the collateralized region.15,16

Collateral Resistance During Exercise

Exercise results in flow-mediated vasodilation of the epicardial coronary arteries.17,18 Since developed collateral vessels are histologically similar to small arteries, these vessels might also be expected to dilate during exercise.1 However, computed collateral resistance did not decrease during exercise. Several factors might account for failure of collateral resistance to decrease during exercise. First, vasodilation might not have been detected. The increased blood flow in the normal zone during exercise would increase the pressure drop from the aorta to the origin of the collateral vessels.19 This would increase the calculated transcollateral resistance and tend to conceal vasodilation of the collateral vessels. However, the moderate exercise intensity used in this study caused only a 66% increase in normal zone flow. Since the epicardial artery segment contributes only a small fraction to total transcollateral resistance, it is unlikely that substantial collateral vasodilation could have been concealed by this moderate increase in normal zone flow. Second, collateral vessels may be maximally dilated at rest and unable to dilate further. This possibility is supported by the finding that transcollateral resistance values in the present study were similar to those previously reported in open-chest, maximally vasodilated canine preparations.6,13 Third, vasodilation in response to increased flow may be impaired because of altered endothelium-dependent relaxing factor production or sensitivity.20 Finally, it is possible that production of endothelium-dependent constricting factors or increased sensitivity to humoral factors such as angiotensin could oppose collateral vessel dilation during exercise.6,13

Small Vessel Resistance

To take into account the contribution of extravascular compressive forces acting on the intramural coronary vessels, left ventricular end-diastolic pressure was subtracted from distal coronary pressure to obtain the effective driving pressure for computation of small vessel resistance.22 Small vessel resistance in the collateral-dependent zone at rest was not different from total vascular resistance in the normally perfused myocardium. However, in response to exer-
cise the resistance vessels failed to dilate maximally despite a subnormal increase in blood flow in the collateral-dependent region. Using dogs with chronic ameroïd occlusion of a proximal coronary artery, several investigators have reported that minimum coronary vascular resistance during maximum vasodilation with adenosine is 0.16–0.22 CRU. This is substantially lower than the value observed during exercise in the present study (0.37±0.08 CRU). Several factors could have contributed to failure of the resistance vessels to dilate more fully during control exercise in the present study. First, the response of small vessels in the collateral zone may be altered. Quillen et al demonstrated that chronic perfusion through collateral vessels selectively impairs receptor-mediated endothelium-dependent dilation in the microcirculation distal to the arterial occlusion. Second, metabolic demands of myocardium distal to an occlusion may be decreased. The metabolic stimulus for small vessel dilation would, therefore, be decreased. Finally, impaired vasodilation during exercise could be due to a circulating vasoconstrictor agent.

Response to Vasopressin

In the present study, an infusion rate of vasopressin was chosen to cause minimal effect on systemic hemodynamic variables. This dose of vasopressin did not significantly alter blood flow in the normally perfused myocardium but increased transcollateral resistance 48±14% and virtually abolished the increase in blood flow in response to exercise in the collateral-dependent myocardium. Vasopressin has previously been demonstrated to cause constriction of collateral vessels in isolated vascular ring preparations and in acute open-chest animals. During pharmacological coronary vasodilation with adenosine in isolated perfused canine hearts, Harrison et al showed that vasopressin infusion increased transcollateral resistance from 0.24±0.13 to 0.53±0.28 CRU (p <0.05), while blood flow to the collateral-dependent myocardium was reduced by half. The present study demonstrates that vasodilatation of collateral vessels by vasopressin can also impair perfusion of the collateral-dependent region in the intact animal during physiological conditions. Of interest was the finding that vasopressin also opposed vasodilation of the resistance vessels in the collateral-dependent region during exercise. In comparison with control exercise, small vessel resistance was increased 40±9% during vasopressin infusion (p<0.02 versus control exercise). In contrast, vasopressin did not cause a significant increase in vascular resistance in the normally perfused region. This difference in the response of vascular resistance between the normal and collateral zones may have resulted from altered endothelium-derived relaxing factor activity in the collateral zone, which normally opposes vasopressin-induced vasoconstriction.

Although this study was designed to test the general hypothesis that vasoconstriction of coronary collateral vessels can aggravate hypoperfusion of the dependent myocardium and vasopressin was merely used as a convenient agent with appropriate characteristics to test this hypothesis, it is of interest to speculate whether the levels of vasopressin achieved could occur during physiological or pathological situations. Circulating levels of vasopressin are known to increase in response to cigarette smoking, volume depletion, and hemorrhage. In normal human subjects, Waer et al found that average plasma vasopressin levels increased from 1.3 pg/ml during basal conditions to 12.7 pg/ml after smoking two cigarettes. However, the response was highly variable, with increases in vasopressin level in response to cigarette smoking ranging from 0.6 to 7.0 pg/ml. Two of five dogs in the present study had vasopressin levels (52.6 and 67.9 pg/ml) within the range observed by Waer et al during cigarette smoking. Acute blood loss of moderate degree may increase plasma vasopressin to levels comparable to those in the present study. Goetz et al reported that slow continuous hemorrhage in dogs resulted in progressive increases of plasma vasopressin levels; after removal of 20 ml/kg blood, the mean plasma vasopressin level increased to 113±24.1 pg/ml. Moderately severe hemorrhage with a blood loss of 30 ml/kg resulted in a further increase in vasopressin level to 296±54.4 pg/ml. These studies demonstrate that cigarette smoking may occasionally increase vasopressin levels to the range seen in the present study, whereas hemorrhage of moderate degree regularly produces such an increase.

Clinical Implications

Although blood flow to collateral-dependent regions may be adequate to meet myocardial demands during resting conditions, the resistance offered by the collateral vessels may prevent flow from increasing normally during exercise. This study demonstrates that collateral resistance during exercise is not fixed and supports the hypothesis that active vasoconstriction of collateral vessels can further limit blood flow to the dependent myocardium during exercise.

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References

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