Coronary Vasodilator Reserve in Ischemic Myocardium of the Exercising Dog

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Background. Previous work has reported that coronary vasodilator reserve may persist in myocardium rendered ischemic by hypoperfusion. This study investigated the presence and extent of residual coronary vasomotor tone in myocardial regions made acutely ischemic by a flow-limiting coronary stenosis during exercise.

Methods and Results. Studies were done in chronically instrumented dogs undergoing treadmill exercise in the presence of a coronary stenosis that decreased distal left circumflex coronary artery perfusion pressure to approximately 40 mm Hg. Measurements of myocardial blood flow were made with radioactive microspheres during exercise (6.5 km/hr, 6% grade) and during intracoronary infusion of the potent coronary vasodilator adenosine (40 μg/kg/min). Distal coronary perfusion pressure was held equal before and during intracoronary adenosine infusion (43±5 versus 42±5 mm Hg) by adjusting the hydraulic coronary occluder. During exercise in the presence of a coronary stenosis, myocardial blood flow (milliliter per minute per gram) was significantly reduced in all layers of the ischemic posterior region compared with the nonischemic anterior region. During intracoronary adenosine infusion, with no change in coronary perfusion pressure, myocardial blood flow was significantly increased compared with preadenosine flows for both the subendocardial layer flow (1.03±0.74 versus 0.66±0.50; p<0.05) and mean transmural flow (1.54±0.59 versus 1.16±0.36; p<0.05). In the presence of a coronary stenosis, regional myocardial segment shortening in the ischemic region during exercise fell significantly to 49±8% of shortening in the absence of a coronary stenosis but improved modestly during adenosine infusion (65±7 versus 49±8%; p<0.05).

Conclusions. These results indicate that adenosine-responsive coronary vasodilator reserve persists during exercise-induced myocardial ischemia and suggest that residual microvascular vasoconstrictor tone may affect the extent of myocardial hypoperfusion occurring consequent to a flow-limiting coronary stenosis. (Circulation 1992;85:313–322)

Autoregulatory adjustments in vasomotor tone maintain coronary blood flow nearly constant over a range of perfusion pressures at similar levels of myocardial metabolic requirements. Thus, when perfusion pressure is reduced, coronary vasodilation occurs to maintain constant coronary flow. The concept of autoregulation implies that coronary blood flow is maintained in the face of decreasing perfusion pressure until vasodilator reserve is exhausted and that further decrements in perfusion pressure result in hypoperfusion of the myocardium.1,2 Wall stress (and therefore myocardial oxygen requirements) and extravascular compressive forces are greatest in the innermost layers of the left ventricular wall. The need for greater blood flow to the subendocardial myocardium requires a transmural gradient in coronary vascular resistance, with lower resistance in the subendocardial than subepicardial layers. As perfusion pressure falls, coronary vasodilator reserve has been reported to be exhausted first in the subendocardial regions. For this reason, when tissue ischemia supervenes, vasodilator reserve could still exist in the more superficial layers of myocardium3,4 at a time when reduced subendocardial perfusion would indicate a loss of vasodilator reserve.

Several investigators have presented evidence for pharmacologically recruitable residual transmural and subendocardial vasodilator reserve during signif-
significant coronary hypoperfusion due to low perfusion pressure.5-9 The current study was conducted to examine whether adenosine-recruitable coronary vasodilator reserve is present in myocardium made ischemic by exercise in the presence of a coronary artery stenosis and the extent of this recruitable blood flow reserve.

Methods

Adult mongrel dogs of either sex weighing 23–30 kg were premedicated with fentanyl (0.4 mg i.m.) and droperidol (20 mg i.m.), anesthetized with sodium pentobarbital (30 mg/kg i.v.), and intubated and ventilated with a mechanical respirator with supplemental oxygen. Under sterile conditions, a left fifth interspace thoracotomy was made and a heparin-filled polyvinyl chloride catheter (3.0 mm o.d.) was advanced through the left internal thoracic artery into the ascending aorta. The pericardium was then opened and the heart was suspended in a pericardial cradle. Heparin-filled polyvinyl chloride catheters were placed into the left atrium through the atrial appendage and into the left ventricle through the apical dimple area and secured with purse-string sutures. A solid-state micromanometer (Konigsberg P5) was also inserted into the left ventricle through the apical dimple region and secured with a purse-string suture. Pairs of 5-MHz miniature piezoelectric crystals for measurement of myocardial segment shortening were implanted 1–2 cm apart into the inner third of the anterior and posterior left ventricle wall in the region of the left anterior descending and circumflex coronary artery perfusion beds. A segment of the proximal left circumflex coronary artery was dissected free and an appropriate size 10 MHz Doppler ultrasonic flow probe was fitted around the artery. A hydraulic occluder constructed of 2.7 mm o.d. polyvinyl tubing was then placed around the artery immediately distal to the flow probe. A heparin-filled catheter constructed of a 5-cm length of silastic tubing (internal diameter, 0.3 mm) bonded to a larger silastic tubing (internal diameter, 1.6 mm) was introduced into the left circumflex coronary artery just distal to the hydraulic occluder after the method of Gwirtz.10 The pericardium was then loosely closed, an indwelling chest tube was placed, and all catheters and leads were brought out between the ribs and tunneled subcutaneously to be externalized at the back of the neck. The chest was then closed and the pneumothorax was evacuated. Catheters and leads were protected by a nylon vest that the animals were trained to wear. The intracoronary catheter was flushed daily with heparin and all other fluid-filled catheters were flushed every second day with heparinized saline. Animals were allowed 10–14 days to recover from surgery.

Hemodynamic Measurements

Aortic pressure and coronary perfusion pressure were measured using Gould P23XL pressure transducers. Left ventricular pressure was obtained from the micromanometer-tipped catheter, which was calibrated to the fluid-filled left ventricular catheter. Left ventricular dP/dt was obtained by differentiation of the left ventricular pressure signal. All pressures and segment shortening data were recorded on a Model Hewlett-Packard 8800 direct-writing, eight-channel oscillograph.

Regional Myocardial Function Measurements

Segment length measurements were obtained by activating the implanted piezoelectric crystals with an ultrasonic dimension system (model 120, Triton, San Diego, Calif.) synchronized with the flow meter. Crystal separation for each channel was sampled at 1 kHz and converted to an analog voltage. The minimum resolution using 5-MHz crystals was approximately 0.07 mm. End-diastolic segment length was measured just before the onset of the upstroke of the left ventricular pressure tracing, and end-systolic segment length was taken at 20 msec before peak negative left ventricular dP/dt. Percent segment shortening was defined as \(\left[\frac{\text{end diastolic segment length} - \text{end systolic segment length}}{\text{end diastolic segment length}}\right] \times 100\). Beats from at least one or more full respiratory cycles (a minimum of eight to 10 beats) were averaged for each determination of regional function.

Myocardial Blood Flow Measurements

Distribution of blood flow across the wall of the left ventricle was estimated with tracer microspheres 15 μm in diameter labeled with one of the following radionuclides: 125I, 95Nb, 51Cr, 85Sr, 113Sn, or 46Sc. Microspheres were agitated in an ultrasonic mixer for 15 minutes before injection. Approximately \(3 \times 10^6\) microspheres were injected as a rapid bolus into the left atrial catheter and immediately flushed with 5 ml of normal saline for each measurement. A reference arterial blood specimen was withdrawn via an aortic catheter at a rate of 15 ml/min beginning 15 seconds before the injection and continuing for 120 seconds. Radioactivity in myocardial and blood reference specimens was determined using a Model 5912 Packard gamma spectrometer with multichannel analyzer at window settings appropriate for the combination of radioisotopes used during the study. The activity in each energy window, background activity, and sample weight was entered into a digital computer programmed to correct the counts recorded in each window for contaminant activity contributed by the associated isotopes, for background activity, and to compute the correct counts per minute per gram of myocardium (stripping technique). Knowing the rate of withdrawal of the reference sample (Qt), the radioactivity in the reference sample (Cr), and that complete mixing of the microspheres in the left ventricle and aortic root resulted in a uniform ratio of blood flow to radioactivity in the myocardium, myocardial radioactivity (Cm) was used to compute myocardial blood flow (Qm) as follows: \(Q_m = \frac{Q_t \times C_m}{C_r}\). Blood flows were expressed as milliliter per minute per gram of myocardium.
Study Protocol

Animals were only studied after coronary reactive hyperemic responses (determined with the flow probe) had returned to normal after surgery. Dogs underwent moderate exercise on a motor-driven treadmill at approximately 6.5 km/hr with a 6% grade adjusted to obtain a heart rate in the range of 200–210. After hemodynamic and regional myocardial function measurements had stabilized during exercise in the absence of a stenosis, an acute coronary stenosis was produced by inflating the hydraulic occluder with a syringe attached to a micrometer device. This device, consisting of a metal frame that securely fixes the syringe in place, a piston that applies pressure to the hub of the syringe plunger, and a hand-operated gear with a very large gear ratio that controls the piston’s movement, allowed precise adjustment of the occluder. The occluder was adjusted until the coronary perfusion pressure distal to the stenosis was stable at approximately 40 mm Hg. After 2 minutes of exercise with the coronary stenosis, an injection of microspheres into the left atrium was made to measure myocardial blood flow during control stenosis conditions.

Two minutes after this initial microsphere injection (after completion of the reference blood collection), an infusion of adenosine at a rate of 40 μg/kg/min was begun into the left circumflex coronary catheter while the stenosis was maintained. Adenosine (Sigma) was dissolved in sterile normal saline and diluted so that the appropriate dose would be delivered in a volume of 1.25 ml/min. Adenosine dose–response curves were carried out at rest and without a stenosis in animals before exercise. In most animals, maximal coronary flow rates were obtained with 4–5 μg/kg/min of intracoronary adenosine, and all animals were maximally vasodilated at ≤10 μg/kg/min. The larger adenosine dose of 40 μg/kg/min was chosen to ensure maximal coronary vasodilation during exercise and yet not affect systemic hemodynamics. After adenosine had been infused for 2 minutes, the hydraulic occluder was adjusted as necessary to return mean coronary perfusion pressure to the same value achieved during the control stenosis state. This was accomplished by serial small decrements of hydraulic occluder pressure with the micrometer device until coronary perfusion pressure rose to equal the perfusion pressure present during control stenosis conditions. During hydraulic occluder adjustments, the adenosine infusion was briefly interrupted to allow measurement of coronary artery pressure. However, attempts were made to limit interruptions of the adenosine infusion to about 5 seconds during the adjustment phase. Tracings were reviewed in all animals in the study; the time from resumption of pressure monitoring to achieving a stable coronary perfusion pressure, where judgments about adjusting the occluder could be made, were determined on three or more separate occasions in each animal. The time required for the pressure tracing to return to a stable level was 2.4±1 seconds (mean±1 SD). Thus, these brief interruptions were able to establish whether changes in stenosis severity needed to be made, small adjustments made, and infusion re instituted. Subsequent assessments of coronary perfusion pressure were made with a further brief interruption in the adenosine infusion. Once similar pressures were achieved, observations were made to verify stable pressures. Thus, several adjustment steps were necessary to obtain stable, matched perfusion pressures during adenosine infusion. Only when coronary perfusion pressure was stabilized equal to control stenosis pressure was another injection of microspheres made into the left atrium. Coronary perfusion pressure was measured for approximately 10 seconds immediately before and during the initial 5 seconds after microsphere injection and again 10–20 seconds later. With this protocol, coronary perfusion pressure during adenosine infusion could be reliably matched with coronary perfusion pressure during control stenosis conditions. Only animals in which stable, matched coronary perfusion pressures were obtained (≤2 mm Hg difference in mean coronary perfusion pressure between control and adenosine conditions during microsphere measurements) were considered successful studies. After reference blood sample collection was finished, the stenosis was released and exercise was terminated. Thirty to 60 minutes after exercise, an intracoronary infusion of adenosine at a dose of 40 μg/kg/min was made at rest without coronary stenosis. A third microsphere injection was then performed to define the myocardium in the perfusion bed of the intracoronary catheter, as indicated by the higher flow rates in this area.

At termination of the study, the animals were given a lethal dose of pentobarbital and the hearts were removed and fixed in 10% buffered formalin. After fixation, the left ventricle was cut into four transverse rings from base to apex and each ring was divided circumferentially into seven regions. Each region was divided into four transmural layers of equal thickness from epicardium to endocardium, weighed on an analytical balance, and placed in counting vials. Myocardial and blood reference radioactivity and myocardial blood flow were then determined as previously described. Nonischemic region flows were determined as the mean of the anterior left ventricular region samples from at least two myocardial rings. Ischemic region myocardial flows were determined as the mean of posterior regions from at least two rings, with the regions being those from between the posterior ultrasonic crystal pair and within the region of highest myocardial flow during the adenosine-induced vasodilation in the absence of coronary stenosis. Bilateral kidney sampling was also made to compute renal blood flow to determine if left and right renal blood flow was similar, thus confirming adequate mixing of the microspheres.

Statistical comparisons for microsphere measurements of myocardial blood flow were made using
two-way analysis of variance (ANOVA). When significant differences were found by ANOVA, individual comparisons were made using Student's t test for paired data, with a modified Bonferroni correction for multiple simultaneous comparisons. Statistical comparisons of paired hemodynamic data were made using Student's t test for paired data, also with the modified Bonferroni correction for multiple simultaneous comparisons. Significance was defined as p<0.05. All values are reported as mean±SD.

**Results**

Ten animals were successfully studied, and the hemodynamic and myocardial blood flow data for these animals are reported. Regional myocardial segment shortening was available for nine of the 10 animals. Representative recorder tracings from two individual studies, representing two types of responses commonly observed in this study, are shown in Figures 1 and 2.

**Hemodynamic Measurements**

Hemodynamic data are summarized in Table 1. In comparison with control exercise with a coronary stenosis, mean aortic pressure, left ventricular systolic and diastolic pressure, left ventricular dP/dt, and coronary perfusion pressure were not different with intracoronary adenosine infusion during exercise with a coronary stenosis. Coronary perfusion pressure was 43±5 mm Hg during control stenosis conditions; this fell to 37±5.6 mm Hg after institution of the adenosine infusion but before adjustment of the hydraulic occluder and was 42±5 mm Hg with intracoronary adenosine infusion after adjustment of the hydraulic occluder. The range (and average) of coronary perfusion pressures dur-
FIGURE 2. Hemodynamic tracings from an individual dog at rest (panel A), during exercise (panel B), during coronary stenosis (panel C), during intracoronary adenosine infusion and stenosis (panel D), and during adenosine infusion after hydraulic occluder adjustment has returned coronary perfusion pressure (CPP) to equal that during control stenosis conditions (panel E). Note that with initiation of intracoronary adenosine infusion there is a fall in CPP accompanied by a fall in coronary blood flow velocity (CBF) despite no further adjustment of the hydraulic occluder at this time. This is probably due to worsening of the coronary stenosis due to passive collapse of the stenosis when the distending pressure decreases concomitant with the fall in distal CPP (panel D). (See “Discussion” for details.) After hydraulic occluder adjustment to return CPP equal to control stenosis conditions, CBF is greater than during control stenosis conditions. Transient interruption of flow signal in panel is due to a brief calibration check. AOP (mean), mean aortic pressure; LVP, left ventricular pressure; LV dP/dt, first derivative of LVP; anterior region segment length, anterior (nonischemic) region myocardial segment length; posterior region segment length, posterior (ischemic) region myocardial segment length.

Regional Myocardial Function

Regional myocardial systolic segment shortening results are shown in Table 1. Ischemic region myocardial segment shortening was significantly decreased during exercise with stenosis compared with exercise without stenosis (6.7±3.1 versus 14.0±3.1%; p<0.01). Although segment shortening during adenosine infusion during exercise with stenosis was also significantly decreased compared with exercise in the

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>AoM (mm Hg)</th>
<th>CPP (mm Hg)</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>+dP/dt (mm Hg/sec)</th>
<th>Pos SS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>124±25</td>
<td>106±19</td>
<td>98±22</td>
<td>131±24</td>
<td>7±3.6</td>
<td>2,325±736</td>
<td>11.4±3.3</td>
</tr>
<tr>
<td>Exercise</td>
<td>209±22</td>
<td>114±19</td>
<td>94±22</td>
<td>149±22</td>
<td>11.5±9.5</td>
<td>3,350±1,990</td>
<td>14.0±3.1</td>
</tr>
<tr>
<td>Exercise+stenosis</td>
<td>214±31</td>
<td>110±19</td>
<td>43±5</td>
<td>139±19</td>
<td>20.3±10.7*</td>
<td>3,600±1,420</td>
<td>6.7±3.1*</td>
</tr>
<tr>
<td>Exercise+stenosis+adenosine</td>
<td>216±28</td>
<td>109±19</td>
<td>42±5.4</td>
<td>138±19</td>
<td>16.5±9.8</td>
<td>3,658±1,107</td>
<td>8.5±3.1*†</td>
</tr>
</tbody>
</table>

AoM, mean aortic pressure; CPP, distal circumflex perfusion pressure; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end diastolic pressure; +dP/dt, left ventricular dP/dt; Pos SS, posterior (ischemic) region segment shortening.

Values are mean±SD; n=10.

*p<0.05 compared with exercise.
†p<0.05 compared with exercise with stenosis.
absence of a coronary stenosis (8.5±3.1 versus 14.0±3.1%; p<0.01), it was slightly greater than segment shortening during control exercise with stenosis (8.5±3.1 versus 6.7±3.1%; p<0.05).

Regional Myocardial Blood Flow

Myocardial blood flows measured with microspheres and the ratio of subendocardial layer to subepicardial layer flow for the ischemic posterior region and the nonischemic anterior region are shown in Table 3 and Figures 3 and 4. During exercise in the presence of a stenosis anterior (nonischemic) region, subepicardial blood flow was 2.40±0.92 ml/min/g, subendocardial layer flow was 3.30±1.14 ml/min/g, mean transmural flow was 3.07±1.17 ml/min/g, and ratio of subendocardial to subepicardial layer flow was 1.39±0.15. Infusion of adenosine into the left circumflex coronary artery did not alter the anterior (nonischemic) region flow. In the posterior region, coronary stenosis resulted in decreases of blood flow in all myocardial layers and reversal of the normal blood flow distribution so that subendocardial layer blood flow was lowest (20% of nonischemic region subendocardial flow). Subepicardial layer flow was 1.66±0.39 ml/min/g, subendocardial flow was 0.66±0.50, mean transmural flow was 1.16±0.36, and subendocardial to subepicardial layer flow ratio was significantly decreased at 0.41±0.30.

Intracoronary adenosine infusion in the presence of a coronary stenosis resulted in increased myocardial blood. This increase was statistically significant for the inner and midlayers of myocardium and for mean transmural flow. Although flow increased 22% in the subepicardial layer, 56% in the subendocardial layer, and 33% for mean transmural flows, the absolute magnitude of the increase in flow was similar in all layers of myocardium. The ratio of subendocardial to subepicardial blood flow did not change significantly (0.41±0.30 versus 0.49±0.26; p=0.07, control versus adenosine).

### Table 2. Coronary Perfusion Pressures During Blood Flow Measurements

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>CTRL-ADEN</th>
<th>CTRL-ADEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44-46 (45)</td>
<td>42-46 (44)</td>
</tr>
<tr>
<td>2</td>
<td>37-40 (38)</td>
<td>35-36 (36)</td>
</tr>
<tr>
<td>3</td>
<td>46-50 (49)</td>
<td>46-47 (47)</td>
</tr>
<tr>
<td>4</td>
<td>44-45 (45)</td>
<td>45-47 (47)</td>
</tr>
<tr>
<td>5</td>
<td>43-45 (44)</td>
<td>42-45 (44)</td>
</tr>
<tr>
<td>6</td>
<td>43-48 (46)</td>
<td>46-47 (47)</td>
</tr>
<tr>
<td>7</td>
<td>40-42 (40)</td>
<td>37-40 (38)</td>
</tr>
<tr>
<td>8</td>
<td>46-49 (48)</td>
<td>46-47 (46)</td>
</tr>
<tr>
<td>9</td>
<td>30-32 (31)</td>
<td>32-33 (32)</td>
</tr>
<tr>
<td>10</td>
<td>41-43 (41)</td>
<td>36-39 (38)</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>43±5</td>
<td>42±5</td>
</tr>
</tbody>
</table>

CTRL-ADEN, during exercise with a coronary stenosis; ADEN-ADEN, during exercise with a coronary stenosis plus intracoronary adenosine infusion. Numbers in parentheses are average mean perfusion pressure.

### Table 3. Microsphere Myocardial Flow Data From Subepicardial to Subendocardial Layers

<table>
<thead>
<tr>
<th>Region</th>
<th>EPI</th>
<th>2</th>
<th>3</th>
<th>ENDO</th>
<th>Mean</th>
<th>ENDO/EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis (ml/min/g)</td>
<td>2.40±0.92</td>
<td>3.19±1.37</td>
<td>3.41±1.29</td>
<td>3.29±1.14</td>
<td>3.07±1.17</td>
<td>1.39±0.15</td>
</tr>
<tr>
<td>Stenosis+adenosine</td>
<td>2.17±0.61</td>
<td>2.93±0.87</td>
<td>3.23±0.87</td>
<td>3.16±0.79</td>
<td>2.87±0.75</td>
<td>1.49±0.30</td>
</tr>
<tr>
<td>Posterior region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis (ml/min/g)</td>
<td>1.66±0.39*</td>
<td>1.39±0.40*</td>
<td>0.94±0.44*</td>
<td>0.66±0.50*</td>
<td>1.16±0.36*</td>
<td>0.41±0.30*</td>
</tr>
<tr>
<td>Stenosis+adenosine</td>
<td>2.01±0.48</td>
<td>1.80±0.64**</td>
<td>1.31±0.65**</td>
<td>1.03±0.74**</td>
<td>1.54±0.59**</td>
<td>0.49±0.26*</td>
</tr>
<tr>
<td>Absolute increase</td>
<td>0.36</td>
<td>0.41</td>
<td>0.37</td>
<td>0.37</td>
<td>0.38</td>
<td></td>
</tr>
</tbody>
</table>

* p<0.05 compared with anterior region.
†p<0.05 compared with stenosis alone.

EPI, 2, 3, ENDO: myocardial layer from subepicardial (EPI) to subendocardial (ENDO); Mean, mean transmural flow; ENDO/EPI, ratio of subendocardial to subepicardial layer flows.
FIGURE 4. Graph showing anterior (nonischemic region) flow measured with radionuclide-labeled microspheres in 10 dogs during exercise with acute left circumflex coronary stenosis and during exercise plus intracoronary adenosine infusion into the left circumflex coronary artery in the presence of left circumflex coronary stenosis. Flow to four layers of myocardium from subepicardium (EPI) to subendocardium (ENDO) and mean flow are shown. ENDO/EPI, ratio of subendocardial to subepicardial layer flow. No significant differences are present.

Discussion

The most important finding in this study was that ischemia produced by exercise in the presence of a coronary stenosis did not cause maximal vasodilation of the coronary resistance vessels and that additional vasodilation of the coronary resistance vessels in response to exogenous adenosine significantly increased coronary blood flow and reduced the degree of myocardial hypoperfusion. Increased flow in this model was accompanied by reduced evidence of myocardial ischemia, as indicated by the improvement in ischemic region myocardial segment shortening. Despite the significant increase in inner-layer myocardial flow during vasodilation, posterior region subendocardial layer flow was still only 32% of flow to the subendocardial layer of the nonischemic anterior region, and regional contractile function, though improved modestly, remained significantly depressed.

Autoregulatory changes in coronary vasomotor tone have generally been considered to precisely match coronary blood flow with myocardial oxygen demands,13,14 but these and previous data suggest that despite the intense metabolic stimulus for vasodilation present in ischemic myocardium, coronary beds may not be fully dilated during ischemia, and the residual vasomotor tone may affect myocardial hypoperfusion. The results of the current and previous studies5–9 imply that endogenous adenosine, formed during ischemia by the degradation of high-energy phosphorylated adenosine compounds and proposed as a major metabolic regulator of coronary blood flow,14 is either of less importance in mediating coronary vasodilation in the setting of ischemia or is unable to completely counteract whatever vasoconstrictor mechanisms are present. However, the role of endogenous adenosine was not examined in this study. These data demonstrate that the resistance vessels remain responsive to exogenous adenosine during ischemia.

Critique of Model and Methods

Both basal observations and responses to experimental interventions may be modified by acute surgical trauma and anesthesia, which may alter reflex control of the coronary vascular bed, autonomic responses, and coronary autoregulation.15–19 An awake, chronically instrumented canine model was used in the present study to avoid these potential confounding factors. Moderate exercise in the presence of a coronary stenosis sufficient to produce myocardial hypoperfusion and systolic dysfunction was used as a more physiological model of coronary vasomotor regulation in ischemic vascular beds.

Monitoring of coronary perfusion pressure distal to the stenosis and comparing myocardial blood flow at similar perfusion pressures during control and adenosine-vasodilated conditions obviates several potential problems with a stenosis model. With a fixed stenosis model, both coronary perfusion pressure and blood flow distal to a stenosis may change in parallel with changes in aortic pressure, in part due to compliance of the stenotic segment and within the hydraulic occluder system. This is in part because in the presence of a severe coronary stenosis, minor changes in stenosis geometry can significantly alter stenosis resistance and blood flow20 and minor changes in stenosis distending pressures can affect stenosis geometry and blood flow through the stenosis region.21 Additionally, blood flow distal to a severe fixed coronary stenosis may actually decrease in response to distal coronary vasodilation.21–23 This is presumably due to passive collapse of the vessel at or just distal to the stenosis when distending pressure decreases due to vasodilation distal to the stenosis21 but is also possibly due to active vasoconstriction at the site of stenosis due to sympathetic nervous system activation accompanying exercise or other stimuli24,25 (an example of this is shown in Figure 2). Performing studies at similar perfusion pressures allows greater confidence that any changes in blood flow observed are due to change in resistance at the level of the microvasculature rather than at the level of the arterial stenosis.

There are several potential limitations to the present study. The small intracoronary catheter required for successful chronic implantation in this model does not allow accurate phasic systolic and diastolic pressure determinations due to its size and compliance characteristics; thus, mean coronary perfusion pressures were reported for this study. We have previously reported on myocardial blood flow measured during exercise in the presence of a coronary stenosis resulting in myocardial ischemia in this model. Similar mean coronary perfusion pressures produced the same myocardial blood flow during separate exercise periods (in the absence of any intervention).26 The effect of chronic instrumentation with this type of intracoronary catheter has been
studied and reported not to affect myocardial blood flow or transmural distribution during exercise or in response to adenosine. In the current study, reactive hyperemic flow responses were normal with this instrumentation.

It is possible that under the ischemic conditions present during exercise with a coronary stenosis, the adenosine dose used was not a maximally vasodilating dose because the dose–response curves were carried out at rest and without a stenosis. For this reason, the dose used was four to 10 times that which produced maximal coronary flow at rest. If the adenosine dose did not cause maximal vasodilation, the results would underestimate the magnitude of the residual coronary vasodilator reserve. This model cannot completely exclude collateral inflow contributing to the total flow in the hypoperfused region. However, because driving pressure across the collateral vessels was not different between the control and adenosine conditions, this would not be expected to increase collateral flow into the hypoperfused region. Additionally, Messina et al. found that collateral flow to myocardium perfused at a reduced pressure, but with continued antegrade flow, was insignificant (<0.01 ml/min/g) at pressure gradients between the coronary arteries of up to 70 mm Hg (driving pressures similar to those in the current study). The effect of pharmacological doses of adenosine on collateral vessels is not known. Because the adenosine was infused into a vessel where the coronary perfusion pressure was considerably less than the perfusion pressure in adjacent coronary vessels, it is unlikely that adenosine would reach the collateral vessels. No systemic effects of the adenosine infusion were noted, and because adenosine is metabolized rapidly, recirculation of the drug into collateral channels is unlikely. Direct augmentation of myocardial contractility by adenosine, resulting in higher oxygen consumption and thus further metabolic stimulus for vasodilation (rather than a direct vasodilator effect of adenosine), might also produce the results found in this study. However, adenosine has been found not to have any direct inotropic effect or other direct effect on ventricular myocardial performance in vivo.

Left ventricular end-diastolic pressure was slightly but not significantly lower during adenosine infusion. This raises the question whether an improved gradient between coronary perfusion pressure and left ventricular filling pressure, due to an effect of adenosine on filling pressures other than improved myocardial perfusion, might contribute to the increased myocardial flow present during adenosine infusion. However, increased ischemic region flow was seen in animals in which there was no change in left ventricular filling pressure; adenosine is not known to have inotropic effects on ventricular myocardium that might decrease end-diastolic pressure by a direct mechanism, and there was no other evidence for a systemic effect of adenosine at this dose (e.g., change in heart rate, aortic pressure, left ventricular systolic pressure, or left anterior descending region myocardial blood flow) that would contribute to diminishing left ventricular end-diastolic pressure.

Comparison With Other Studies

Several previous studies have examined the concept of paradoxical coronary vasoconstriction during myocardial ischemia. In open-chest dog studies, coronary blood flow before and during intracoronary adenosine infusion at coronary perfusion pressures of 35–50 mm Hg have reported that myocardial blood flow was increased to the subendocardial layer as well as the subepicardial layer during adenosine-induced vasodilation, even when evidence of tissue ischemia was present. The magnitude of increase in subendocardial layer flow in response to adenosine in the present study (0.37 ml/min/g at coronary perfusion pressure, 42 mm Hg) is similar to that reported in open-chest studies by Aversano et al. (0.29 ml/min/g at coronary perfusion pressure, 35 mm Hg) and Grattan et al. (0.36 ml/min/g at coronary perfusion pressure, 40 mm Hg) at similar heart rates. Regional myocardial systolic function was also evaluated and improved during adenosine vasodilation in the study of Aversano. However, in a study of vasodilator reserve during ischemia in open-chest swine, adenosine-recruitable increases in myocardial flow were not associated with improved myocardial systolic function or in improved metabolic indexes of ischemia.

Conversely, Gewirtz et al. using a fixed stenosis model and nonischemic conditions, reported only subepicardial flow reserve distal to a severe stenosis in response to vasodilation with adenosine or nifedipine. They also found that subendocardial flow fell during adenosine infusion and that this was accompanied by evidence of myocardial ischemia. The issue of the behavior of the stenosis and of the vessel just distal to the stenosis changing geometry during marked changes in distal perfusion pressure, as discussed above, may be confounding factors in interpreting the results of this model as demonstrating the absence of subendocardial layer flow reserve.

In contrast to the study of Gerwitz, Heusch et al. examined myocardial flow to an ischemic bed distal to a stenosis or in collateral dependent myocardial regions before and after intravenous nifedipine in exercising dogs and found increased blood flow to, and improved contractile function of, the ischemic myocardium after nifedipine. The differential effects on collateral versus nifedipine. The differential effects on collateral versus coronary dilation were not distinguished in this study.

When pharmacologically recruitable vasodilator reserve has been found in hypoperfused myocardium, the amount of flow reserve has generally been greater or similar in the subepicardial than in the subendocardial layer; the latter case was present in the current study. Myocardial oxygen requirements are greater in the inner than outer layers of the left ventricle, and ischemia occurs earlier and to a greater degree in the inner layers during hypoperfusion. Thus, the stimulus for vasodilation during moderate (nontransmural) ischemia is greater in the inner
layers of myocardium, and outer layer flow reserve might be expected to be greater. The extent to which subepicardial layer flow reserve exceeds or is similar to subendocardial flow reserve may depend on the severity of hypoperfusion (and thus the intensity of the metabolic stimulus for outer layer vasodilation). However, subendocardial flow reserve during severe ischemia has also been reported to greatly exceed subepicardial reserve.33

The mechanism of residual vasodilator reserve at reduced perfusion pressures and in the face of tissue ischemia remains uncertain, but recent data implicate adrenergic influences as a factor in maintaining coronary vasomotor tone during hypoperfusion. Coronary resistance vessels, the main source of coronary vascular resistance, contain both postsynaptic α1- and α2-adrenoceptors.34 Liang and Jones35 studied an open-chest dog model in which left coronary perfusion pressure was decreased and the effect of intracoronary infusions of selective α1- and α2-adrenergic receptor antagonists (prazosin and yohimbine, respectively) was examined. During hypoperfusion, α1-receptor blockade but not α2-receptor blockade increased coronary blood flow and myocardial oxygen consumption. In a study of exercising dogs pretreated with propranolol and subjected to an acute severe coronary stenosis, Seitelberger et al33 reported that intracoronary infusions of the α2-adrenoceptor antagonist idazoxan increased ischemic region inner and midlayer blood flow and improved regional contractile function. Conversely, in an exercising dog model similar to that of the current study in which coronary perfusion pressure was controlled, selective α1-adrenergic receptor blockade but not α2-receptor blockade increased inner and midlayer myocardial blood flow in myocardium made acutely ischemic by a coronary stenosis.26 These last two studies may not be directly comparable due to differences in experimental conditions—different intensities of myocardial ischemia, the presence of β-adrenergic receptor blockade in the former but not the latter study, and the control of coronary perfusion pressure in the latter but not the former study.

Studies also suggest that one effect of residual vasoconstrictor tone in regions of myocardial hypoperfusion may be to lessen the degree of subepicardial steal during intense coronary vasodilation.26–28 Coronary vasoconstrictor tone may act to some extent, then, to preserve subendocardial flow in hypoperfused regions under some conditions. This may be of functional significance because it has been reported both at rest and during exercise that myocardial contractile function is closely related to subendocardial layer flow but not to subepicardial layer flow.39–41

Clinical Implications

Persistence of vasoconstrictor tone may have several potential clinical implications. As previously discussed, it may act to decrease subepicardial steal of coronary flow during intense vasodilation. Addi-

tionally, it has been shown in patients with coronary artery disease that, in comparison with rest, sites of discrete coronary stenosis may become more severe during exercise.24 The mechanism of this decrease in stenosis lumen is unknown, but both active vasoconstriction at the stenosis and/or passive narrowing due to distal vasodilation with a subsequent decrease in stenosis distending pressure have been suggested as possible mechanisms. Moreover, it has been reported that intracoronary propranolol can prevent this loss of stenosis lumen diameter during exercise and ameliorate clinical indexes of myocardial ischemia.25 One mechanism that could explain this result is that intracoronary propranolol decreased the amount of coronary vasodilation distal to the stenosis during exercise, thus ameliorating the passive worsening of stenosis severity, resulting in greater flow than would otherwise be the case and lessening the intensity of ischemia. As discussed previously, such a mechanism of passive worsening of stenosis severity ensuing from distal coronary vasodilation can be demonstrated in animal models. Through this type of mechanism, one could speculate that persistent vasoconstrictor tone may impact upon the degree of myocardial hypoperfusion, and thus ischemia, during exercise when significant coronary artery disease is present.

Summary

This study demonstrated residual adenosine-recruitable coronary vasoconstrictor tone in ischemic myocardium distal to a coronary stenosis in the exercising dog. Myocardial blood flow to the inner and midwall layers and mean transmural flow were increased during intracoronary infusion of adenosine. The increased blood flow was accompanied by a modest but significant improvement in myocardial segment shortening. These findings suggest that residual vasoconstrictor tone in the coronary microvasculature may affect the degree of myocardial hypoperfusion that occurs when a proximal coronary stenosis results in myocardial ischemia.

Acknowledgments

The authors would like to extend their appreciation to Eugene Sublett, Melanie Crampton, Paul Lindstrom, and Todd Pavik for their excellent technical contributions to this study.

References


Key Words • adenosine • myocardial ischemia • coronary circulation • coronary stenosis
Coronary vasodilator reserve in ischemic myocardium of the exercising dog.
D D Laxson, X Z Dai, D C Homans and R J Bache

Circulation. 1992;85:313-322
doi: 10.1161/01.CIR.85.1.313

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

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