Oxygen Consumption and Coronary Reactivity in Postischemic Myocardium

David D. Laxson, David C. Homans, Xue-Zheng Dai, Eugene Sublett, and Robert J. Bache

Coronary vascular responses in regions of reversible postischemic myocardial contractile dysfunction (stunned myocardium) were examined in chronically instrumented, awake dogs. Left anterior descending coronary artery blood flow and oxygen extraction, aortic and left ventricular pressures, and regional myocardial segment shortening were determined. Regional myocardial blood flow was measured with microspheres. Coronary reactive hyperemia and vasodilator reserve, and regional myocardial oxygen consumption were determined. Three sequential 10-minute left anterior descending coronary artery occlusions separated by 30-minute reperfusion periods resulted in progressive postischemic dysfunction so that 1 hour after the final coronary artery occlusion, myocardial segment shortening was reduced to 37% of baseline. Despite this decrease in contractile function, left anterior descending artery flow (19.6±2.6 vs. 18.4±3.0 ml/min), myocardial blood flow and the transmural distribution of flow measured with microspheres, and regional myocardial oxygen consumption were unchanged. Although the coronary vasodilator reserve in response to adenosine was unaltered (63±9 vs. 70±15 ml/min), the reactive hyperemia response to a 10-second coronary occlusion was decreased in intensity (debt repayment ratio=474±78% vs. 322±74%; p<0.05) and duration (57±9.1 vs. 35±4.5 seconds; p<0.05), while the peak flow response was unchanged (57±6.8 vs. 60±7.1 ml/min). Thus, in the intact awake animal postischemic myocardial contractile dysfunction was not associated with decreased myocardial oxygen consumption and did not impair the normal relation between coronary blood flow and myocardial oxygen utilization. Although coronary vessels showed a normal ability to vasodilate in response to adenosine, coronary reactive hyperemia was reduced. (Circulation Research 1989;64:9-20)

Brief episodes of ischemia that do not produce myocardial necrosis can result in reversible contractile dysfunction that persists long after relief of ischemia.1-3 This postischemic myocardial dysfunction has been termed stunned myocardium.1 While the biochemical abnormalities and mechanical dysfunction that characterize postischemic myocardium have been well described,1-6 little data is available examining the coronary vascular responses in regions of stunned myocardium.

Consequently, this study was carried out to determine whether regional myocardial blood flow, oxygen consumption, and their normal close coupling are altered in regions of severe postischemic contractile dysfunction, and to examine vasomotor regulation and coronary vasodilator reserve in stunned myocardium. Because cardiovascular and myocardial responses to experimental interventions may be modified by anesthesia and acute surgical trauma, studies were performed in a chronically instrumented canine model free of the effects of anesthesia and acute surgical trauma.

Materials and Methods

Surgical Preparation

Studies were carried out in 14 healthy adult mongrel dogs. Dogs were premedicated with fentanyl (0.4 mg i.m.) and droperidol (20 mg i.m.), anesthetized with sodium pentobarbital (30 mg/kg i.v.), intubated, and ventilated with a Harvard respirator (South Natick, Massachusetts) with supplemental oxygen. Under sterile conditions, a left thoracotomy was performed in the fifth intercostal
A heparin-filled catheter constructed of 3.0 mm o.d. polyvinyl chloride tubing was introduced through the left internal thoracic artery into the ascending aorta. The pericardium was opened, and a pericardial cradle was fashioned.

Another heparin-filled polyvinyl chloride catheter was introduced into the left atrium via the atrial appendage and secured with a purse-string suture. A similar catheter was introduced into the right atrium through the atrial appendage, engaged in the coronary sinus and advanced up into the great cardiac vein until the tip was in the anterior interventricular vein or at the junction of the anterior interventricular vein and great cardiac vein. A heparin-filled polyvinyl chloride catheter and a pressure transducer (P5, Konigsberg Instruments, Pasadena, California) were inserted into the left ventricle through stab wounds in the apical dimple and secured with purse-string sutures. Pairs of miniaturized piezoelectric ultrasonic crystals for the measurement of segment shortening were placed in a circumferential plane in the inner third of the anterior left ventricular wall in the distribution of the left anterior descending coronary artery and the posterior wall in the distribution of the circumflex coronary artery. A 1.5 cm segment of the left anterior descending coronary artery proximal to the major epicardial left ventricular branch was carefully dissected free and a Statham electromagnetic flowmeter probe (Gould Instruments, Cleveland, Ohio) or a cuff-type Doppler flow probe was then positioned around the coronary artery. A hydraulic occluder constructed of 2.7 mm o.d. polyvinyl chloride tubing was placed around the artery distal to the flowmeter probe but proximal to any arterial branches. The pericardium was then loosely closed. A hydraulic occluder was placed around the proximal descending thoracic aorta. All catheters and electrical leads were brought out between the ribs, tunneled subcutaneously, and exited through the skin at the base of the neck. A chest tube was brought out through a stab wound in the lateral chest wall. The thoracotomy incision was closed, the chest evacuated of air, and the animal allowed to recover. Catheters and leads were protected by a nylon vest the dogs were trained to wear. Catheters were flushed daily with heparinized saline. The dogs were allowed 10–14 days to recover before being studied.

Hemodynamic Measurements

Aortic pressure was measured using a Gould P23XL pressure transducer. Left ventricular systolic and end-diastolic pressures were obtained from the Konigsberg pressure transducer. Coronary artery blood flow was measured with a Statham SP2202 electromagnetic flowmeter or with a Hartley Doppler flowmeter. Electromagnetic flowmeter probes were calibrated in vitro using normal saline, while Doppler probes were calibrated in situ with measured flows of heparinized blood using a Harvard peristaltic pump.

Doppler flow probes were used in three dogs while electromagnetic probes were used in the remainder. All pressures and coronary blood flow, as well as segment shortening data, were recorded on a direct-writing eight-channel oscillograph (model 8000, Hewlett-Packard, Palo Alto, California).

Regional Function Measurements

Segment length measurements were obtained by activating the implanted piezoelectric crystals with a Triton model 120 ultrasonic system (San Diego, California) synchronized to the flowmeter. Crystal separation for each channel was sampled at 1 KHz and converted to an analog voltage. The minimum resolution with 5 MHz crystals is approximately 0.07 mm. End-diastolic segment length was measured just before the onset of the upstroke of the left ventricular pressure tracing, while end-systolic segment length was taken at 20 msec prior to peak negative left ventricular dP/dt. Percent segment shortening was defined as end-diastolic length minus end-systolic length divided by end-diastolic length multiplied by 100. A minimum of five beats or at least one respiratory cycle were averaged for each determination of regional function.

Myocardial Regional 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, 59Co, 31Cr, 85Sr, 113Sn, or 42Sc. Microspheres were agitated in an ultrasonic mixer for at least 15 minutes prior to injection. Approximately 3×10⁶ microspheres were injected into the left atrial catheter and flushed with 5 ml of normal saline for each measurement. A reference arterial blood specimen was withdrawn via the aortic catheter at a rate of 15 ml/min beginning 5 seconds before the injection and continuing for 120 seconds.

After completion of the study, the dogs were killed with a lethal dose of pentobarbital and the heart removed. The left main coronary artery and the left anterior descending coronary artery distal to the hydraulic occluder were cannulated with separate catheters. The region at risk (the area of left ventricle supplied by the left anterior descending coronary artery distal to the hydraulic occluder) was perfused with normal saline while simultaneously the left main coronary artery was perfused with Evans blue dye at pressures equal to mean aortic pressure. With this technique, the unstained area represented the region at risk. The heart was then sectioned into four transverse rings from base to apex such that a myocardial ring 1.5 cm in thickness included the crystal pairs. The myocardial rings were then incubated in triphenyltetrazolium chloride for 15 minutes, examined for evidence of abnormalities of triphenyltetrazolium chloride staining in the anterior wall, and fixed in 10% buffered formalin. After fixation, samples of myo-
cardium between the anterior crystal pair, and completely within the unstained region, as well as samples of myocardium from between the posterior crystal pair and completely within stained myocardium were removed, divided into four transmural layers of equal thickness from epicardium to endocardium, weighed on an analytical balance, and placed in counting vials.

Radioactivity in myocardial specimens and blood reference vials was determined using a gamma spectrometer (model 5912, Packard Instruments, Downers Grove, Illinois) 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 were entered into a digital computer programmed to correct the counts recorded in each window for contaminant activity contributed by the associated isotopes, as well as for background activity, and to compute the correct counts per minute per gram of myocardium. Knowing the rate of withdrawal of the reference sample (Qs), the radioactivity in the reference sample (Cs), 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: Qm = Qs x Cm/Cs. Blood flows were expressed as milliliters per minute per gram of myocardium.

**Oxygen Consumption**

Arterial and coronary venous blood samples were obtained anaerobically for determination of pH, PO2, and PCO2 by withdrawal of 3.0 ml of blood from the aortic and anterior interventricular vein catheters simultaneously. Hemoglobin content was determined with the cyanmethemoglobin method. Hemoglobin saturation was computed from the blood PO2, pH, and temperature, using the oxygen desaturation curve for dog blood.8 Oxygen content was calculated as hemoglobin x 1.34 x percent oxygen saturation + (0.031 x PO2). Oxygen consumption in the region of myocardium perfused by the anterior descending coronary artery was computed by multiplying the arteriovenous oxygen difference by coronary blood flow determined with the flowmeter probe. Since anterior interventricular vein blood flow corresponds to left anterior descending coronary artery influx,9,11 this method allowed determination of myocardial oxygen consumption in the region perfused by the anterior descending coronary artery.

**Reactive Hyperemia**

Blood flow during reactive hyperemia was determined by electrical integration of the flowmeter signal. Calculation of blood flow debt, excess flow during reactive hyperemia, and debt repayment were made as described by Olsson and Gregg12: Blood flow debt (ml) = control flow rate (ml/min) x duration of occlusion; excess flow during reactive hyperemia (ml) = total flow during reactive hyperemia (ml) - [control flow rate (ml/sec) x duration of reactive hyperemia (sec)]; blood flow debt repayment (%) = [excess flow during reactive hyperemia (ml)/blood flow debt (ml)] x 100.

**Study Protocol**

Studies were carried out with the dogs quietly standing in a sling. Aortic pressure, left ventricular pressure, and dP/dt from the Konigsberg pressure transducer, left anterior descending coronary blood flow, and segment shortening from anterior and posterior left ventricle were monitored continuously throughout the study. Initial hemodynamic measurements, arterial and coronary vein blood gas samples, and a microsphere injection for determination of regional blood flow were made during control conditions. Reactive hyperemia was observed in duplicate following 10-second coronary artery occlusions in seven animals, and following 20-second occlusions in six animals. In seven animals, the vasodilator response to infusion of adenosine (1 mg/kg/min i.v.) was also determined. This dose of adenosine has been found in this laboratory to cause maximum coronary vasodilation. Mean aortic pressure was maintained constant during the adenosine infusion by inflating the aortic occluder as needed. A second injection of microspheres was administered for determination of regional myocardial blood flow during adenosine vasodilation.

After completion of these control measurements, a 10-minute occlusion of the left anterior descending coronary artery was carried out. The flowmeter signal was continuously monitored to ensure total cessation of blood flow. Two minutes after the onset of this coronary occlusion, a third injection of microspheres was administered to evaluate collateral flow into the anterior descending myocardial region. If akinesis, rather than dyskinesis, of the anterior region was seen, isoproterenol was given intravenously to increase heart rate by 75–100%. This was done in five of 14 dogs. In these animals, the addition of isoproterenol resulted in development of dyskinesis in every case. At the end of 10 minutes, the occlusion was completely released to allow a 30-minute period of unimpeded reflow. This was followed by a second 10-minute coronary artery occlusion, a second 30-minute reflow period, and a final 10-minute coronary artery occlusion. After the third 10-minute occlusion, the occluder was released completely.

One hour after the final coronary artery occlusion, coronary venous and arterial blood samples were withdrawn for determination of regional myocardial oxygen consumption, and microspheres were injected for determination of regional blood flow. In the same group of seven animals in which the coronary vasodilator response to adenosine had been measured during control conditions, adenosine infusion was repeated to produce maximal
coronary vasodilation, and microspheres were again injected. Finally, reactive hyperemia responses to 10- and 20-second coronary artery occlusions were determined in the same animals in which reactive hyperemia responses had been measured during control conditions. Hemodynamic and segment shortening data were monitored for 3 hours after the final coronary occlusion and were again measured at 24 hours after the final coronary occlusion. If systolic shortening in the anterior left ventricular wall had returned to baseline at the 24-hour measurement, the animal was then killed. If regional function had not returned to the baseline value at 24 hours, measurements were obtained periodically until function returned to the control value, and then the animal was killed.

Data Analysis

Coronary blood flow, regional myocardial blood flow as measured with microspheres, regional segment shortening, myocardial oxygen consumption, and hemodynamics were analyzed by a one-way analysis of variance; significance was defined as \( p<0.05 \) value. When results were found to be significant by analysis of variance, individual comparisons were made with Duncan's test.

Results

Fourteen animals were studied. One dog developed ventricular fibrillation during the first reperfusion period and died. Two dogs failed to develop prolonged postsischemic dysfunction (regional shortening \( \geq 80\% \) of baseline at 1 hour following coronary occlusions) and were not studied further. Results from the remaining 11 dogs are reported (mean±SEM). Triphenyltetrazolium chloride produced uniform staining in all hearts studied, with no evidence of myocardial necrosis. Results from the dogs that received isoproterenol infusion during coronary occlusion were initially analyzed separately. Since the results were not different from the animals that did not receive isoproterenol (except for slightly but not statistically higher collateral blood flow; see below and Table 3), results from all 11 animals were combined.

Hemodynamic Measurements

Heart rate, aortic pressure, left ventricular systolic and end-diastolic pressures, left ventricular \( \Delta P/\Delta t \), and coronary blood flow are shown in Table 1. In comparison with baseline control measurements, there was no difference in any of these variables at the end of each reperfusion period, at 1 hour after the third occlusion, and at the time of the final measurements. Hemodynamic data obtained during vasodilation in the seven animals that underwent adenosine infusion are shown in Table 2. There was no difference at 1 hour after the final coronary occlusion compared with baseline.

### Table 1. Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>AoS (mm Hg)</th>
<th>AoD (mm Hg)</th>
<th>AoM (mm Hg)</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>LV ( \Delta P/\Delta t ) (mm Hg/sec)</th>
<th>CBF (ml/min)</th>
<th>Ant SS (%)</th>
<th>Post SS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>89±3</td>
<td>132±6</td>
<td>80±4</td>
<td>103±6</td>
<td>132±5</td>
<td>8.5±1.8</td>
<td>2,810±303</td>
<td>21.2±2.5</td>
<td>14.7±1.2</td>
<td>14.9±1.3</td>
</tr>
<tr>
<td>CAO</td>
<td>126±9</td>
<td>126±5</td>
<td>78±6</td>
<td>95±2</td>
<td>128±5</td>
<td>10.2±2.2</td>
<td>2,810±294</td>
<td>0.0*</td>
<td>-6.3±1.4</td>
<td>15.8±1.1</td>
</tr>
<tr>
<td>1 Hr</td>
<td>96±5</td>
<td>130±4</td>
<td>81±3</td>
<td>102±3</td>
<td>131±3</td>
<td>10.1±1.9</td>
<td>2,660±287</td>
<td>20.9±2.9</td>
<td>5.4±0.4</td>
<td>15.0±1.2</td>
</tr>
<tr>
<td>Final</td>
<td>108±7</td>
<td>127±6</td>
<td>79±4</td>
<td>102±5</td>
<td>131±6</td>
<td>10.1±1.6</td>
<td>2,870±280</td>
<td>21.3±2.7</td>
<td>13.8±1.2</td>
<td>14.0±1.3</td>
</tr>
</tbody>
</table>

HR, heart rate; AoS, aortic systolic pressure; AoD, aortic diastolic pressure; AoM, aortic mean pressure; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; LV \( \Delta P/\Delta t \), left ventricular \( \Delta P/\Delta t \); CBF, coronary blood flow; Ant SS, anterior region myocardial segment shortening; Post SS, posterior region myocardial segment shortening. BL, baseline; CAO, coronary artery occlusion; 1 Hr, 1 hour post last coronary artery occlusion period, Final, ≥24 hours following last coronary artery occlusion period.

*\( p<0.05 \) compared with baseline. Values are mean±SEM.

### Table 2. Hemodynamics During Adenosine Infusion (\( n=7 \))

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>AoM (mm Hg)</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>LV ( \Delta P/\Delta t ) (mm Hg/sec)</th>
<th>CBF (ml/min)</th>
<th>Ant SS (%)</th>
<th>Post SS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>92±3</td>
<td>96±6</td>
<td>127±6</td>
<td>7±2.0</td>
<td>2,635±303</td>
<td>21.1±3.3</td>
<td>15.5±1.5</td>
<td>16.5±1.6</td>
</tr>
<tr>
<td>Adenosine</td>
<td>102±8</td>
<td>94±6</td>
<td>140±8</td>
<td>11.2±2.2</td>
<td>3,200±330</td>
<td>63.0±9</td>
<td>17.8±2.0</td>
<td>16.6±1.7</td>
</tr>
<tr>
<td>1 Hr</td>
<td>103±5</td>
<td>98±4</td>
<td>127±6</td>
<td>10.5±2.4</td>
<td>2,514±316</td>
<td>21.6±4.2</td>
<td>5.8±0.3</td>
<td>16.0±1.6</td>
</tr>
<tr>
<td>Adenosine</td>
<td>115±8</td>
<td>91±5</td>
<td>137±8</td>
<td>11.8±2.6</td>
<td>2,914±383</td>
<td>69.7±15</td>
<td>14.1±1.5</td>
<td>16.6±1.6</td>
</tr>
<tr>
<td>Final</td>
<td>108±6</td>
<td>95±7</td>
<td>124±7</td>
<td>11.0±1.9</td>
<td>2,614±367</td>
<td>22.5±3.2</td>
<td>13.9±1.4</td>
<td>14.2±2.0</td>
</tr>
<tr>
<td>Adenosine</td>
<td>106±8</td>
<td>88±4</td>
<td>132±3</td>
<td>11.6±3.1</td>
<td>2,616±225</td>
<td>66±13</td>
<td>13.7±1.6</td>
<td>14.1±1.2</td>
</tr>
</tbody>
</table>

HR, heart rate; AoM, aortic mean pressure; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; LV \( \Delta P/\Delta t \), left ventricular \( \Delta P/\Delta t \); CBF, coronary blood flow; Ant SS, anterior region myocardial segment shortening; Post SS, posterior region myocardial segment shortening. 1 Hr, 1 hour after last coronary artery occlusion period, Final, ≥24 hours following last coronary artery occlusion period.

*\( p<0.05 \) compared with baseline control. Values are mean±SEM.

\( t_p<0.05 \) compared with segment shortening without adenosine infusion at 1 hour following the final coronary artery occlusion period.
Regional Myocardial Blood Flow

Myocardial blood flow measured with microspheres is shown in Figure 1. During control conditions mean myocardial blood flow was 0.85±0.08 ml/min (mean±SEM), and subendocardial flow significantly exceeded subepicardial flow (endocardial-to-epicardial flow ratio, 1.33±0.05). During occlusion of the anterior descending coronary artery there was a significant decrease in blood flow to all layers of the anterior region myocardium and a reversal of the normal endocardial-to-epicardial flow ratio (Figure 1). Collateral flow tended to be slightly higher in the subgroup of dogs that required isoproterenol to produce dyskinesis during occlusion, but this difference was not statistically significant (Table 3). In comparison with control values, there was no difference in anterior region microsphere flow or the ratio of subendocardial-to-subepicardial flow at 1 hour after the final occlusion. Microsphere blood flows during vasodilation with adenosine were not different at 1 hour after the final occlusion compared with preocclusion vasodilated flows (Figure 2).

Regional Myocardial Function

Systolic segment shortening in the anterior myocardial region is shown in Figure 3. During control conditions systolic shortening in the anterior wall was 14.7±1.2%. Anterior region segment shortening was significantly reduced at 30 minutes after the first occlusion (8.1±1.3%) and underwent a significant further decrease by 30 minutes after the third coronary artery occlusion (4.3±0.7%). Shortening remained significantly depressed at 1 hour after the final occlusion compared with control (5.4±0.4%). End-diastolic segment length was slightly but not significantly greater at 1 hour after the final coronary occlusion compared with baseline (14.9±0.8 vs. 15.5±0.8 mm).

There was a gradual subsequent recovery of function, although shortening remained significantly depressed at 3 hours after the final coronary artery occlusion. Function returned to baseline levels in all animals; in eight dogs recovery occurred within 24 hours, while in three dogs recovery occurred in 48 to 72 hours. Regional shortening in the nonischemic posterior wall was 14.9±1.3% at baseline and did not change significantly during the course of the study.

Regional segment shortening in the subset of seven dogs that underwent adenosine infusion was 15.5±1.5% during control conditions and 17.8±2.0% during control adenosine infusion (Table 2, Figure 4). At 1 hour after the final coronary artery occlusion, adenosine infusion resulted in a significant and marked

<table>
<thead>
<tr>
<th>Treatment</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>+ Isoproterenol</td>
<td>0.27±0.02</td>
<td>0.17±0.03</td>
<td>0.15±0.01</td>
<td>0.11±0.01</td>
<td>0.18±0.01</td>
<td>0.44±0.07</td>
</tr>
<tr>
<td>- Isoproterenol</td>
<td>0.21±0.12</td>
<td>0.11±0.05</td>
<td>0.09±0.03</td>
<td>0.07±0.03</td>
<td>0.12±0.05</td>
<td>0.35±0.12</td>
</tr>
</tbody>
</table>

Endo/Epi, ratio of endocardial to epicardial layer flow. Values are mean±SEM.
improvement in anterior region shortening. This occurred despite no change in left ventricular systolic or end-diastolic pressures, although heart rate during adenosine infusion tended to be higher than control (103±5 vs. 115±8 beats/min).

**Myocardial Oxygen Consumption**

Regional myocardial oxygen consumption measured in nine animals during control conditions and in posts ischemic myocardium are shown in Table 4. One hour after the final coronary occlusion hemodynamic variables and regional function were not different in this group of nine dogs as compared with the total group of 11 dogs. In comparison with control measurements, coronary venous Po2 was slightly but significantly decreased in posts ischemic myocardium, coronary blood flow was unchanged, and myocardial oxygen consumption was slightly, but not significantly, higher.

**Coronary Reactive Hyperemia**

Measurements of coronary reactive hyperemia are shown in Table 5. Reactive hyperemia duration and blood flow debt repayment after 10-second occlusions were significantly reduced in posts ischemic myocardium as compared with control at similar blood pressures, while peak flow was unchanged. A similar result was seen after 20-second occlusions, but the decrease in duration and blood flow debt repayment was of borderline statistical significance (each p=0.07).

**Discussion**

There were several important new findings in the present study. First, despite marked reductions of systolic function, oxygen consumption was unchanged in posts ischemic myocardium. Second, the coronary vessels maintained a normal relation between myocardial oxygen consumption and blood flow, so that the coronary arteriovenous oxygen content gradient was unchanged. Finally, despite normal vasodilator reserve during adenosine infusion, coronary reactive hyperemia was depressed in posts ischemic myocardium. Each of these observations will be discussed in detail.

**Myocardial Oxygen Consumption and Coronary Blood Flow**

In the present study myocardial oxygen consumption, total coronary blood flow and the transmural distribution of perfusion were not different from control in posts ischemic myocardium. Similarly, Lange et al., using open chest dogs, found that myocardial blood flow was unchanged in posts ischemic myocardium.

---

**Figure 2.** Ischemic (anterior) region myocardial blood flow by layer from epicardium (1) to endocardium (4) and mean flow during coronary vasodilation with intravenous adenosine infusion at baseline (BL) and at 1 hour of reperfusion following the final coronary occlusion period (1 hr). No difference in myocardial blood flow was present between the two periods.

**Figure 3.** Ischemic (anterior) region myocardial segment shortening at baseline (BL); during each coronary artery occlusion (CAO); following 30 minutes of reperfusion after the first (X1), second (X2), and third (X3) coronary artery occlusions; and at 1 hour (1 hr), 2 hours (2 hr), 3 hours (3 hr), and ≥24 hours (final) of reperfusion following the final coronary occlusion. *p<0.05 compared with baseline; †p<0.05 compared with 30 minutes after the first CAO.
The decrease in coronary blood flow and myocardial oxygen consumption was not measured. In a preliminary report of studies in open chest dogs in which oxygen saturation was measured spectrophotometrically in transmural biopsy specimens, Stahl et al.

In contrast, several investigators have reported decreased coronary blood flow and myocardial oxygen consumption in postischemic myocardium. Smith, using open chest dogs in which a single 10-minute occlusion of the left anterior descending coronary artery was used to produce postischemic myocardium; oxygen consumption was not measured.

The finding of unchanged myocardial oxygen consumption in the presence of severely reduced contractile function is problematic. The anterior interventricular vein, from which venous blood was withdrawn for determination of oxygen consumption, drains left anterior descending artery inflow and is essentially free of contamination by venous drainage from the left circumflex artery in the dog. Additionally, septal artery inflow does not contribute to anterior interventricular vein flow in the dog. Therefore, contamination of venous blood by drainage from nonischemic myocardium cannot explain the finding of unchanged myocardial oxygen consumption in postischemic myocardium. Systolic wall tension is a major determinant of myocardial oxygen consumption, but the ultrasonic microcrystal technique used in this study actually measures myocardial segment shortening, which makes a comparatively minor contribution to energy consumption. It is possible that the unchanged oxygen consumption in stunned myocardium was due to an increase in wall tension or to ongoing tension development in the face of impaired shortening of the contractile apparatus. However, the absence of ...

**TABLE 4. Myocardial Oxygen Consumption (n=9)**

<table>
<thead>
<tr>
<th></th>
<th>$\text{PaO}_2$ (mm Hg)</th>
<th>$\text{PVO}_2$ (mm Hg)</th>
<th>$\text{AVO}_2$ (ml O$_2$/100 ml)</th>
<th>$\text{CBF}$ (ml/min)</th>
<th>$\text{MVVO}_2$ (ml/min)</th>
<th>$\text{HR}$ (beats/min)</th>
<th>$\text{AoM}$ (mm Hg)</th>
<th>$\text{LVSP}$ (mm Hg)</th>
<th>$\text{LVEDP}$ (mm Hg)</th>
<th>$\text{LV dP/dt}$ (mm Hg/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>89±2</td>
<td>26.1±1.3</td>
<td>9.1±0.7</td>
<td>19.6±2.6</td>
<td>1.78±0.2</td>
<td>90±4</td>
<td>107±5</td>
<td>136±5</td>
<td>8.8±2</td>
<td>3,100±311</td>
</tr>
<tr>
<td><strong>1 Hr</strong></td>
<td>83±2</td>
<td>22.6±0.4</td>
<td>10.5±0.7</td>
<td>18.4±3.0</td>
<td>1.93±0.3</td>
<td>95±6</td>
<td>106±4</td>
<td>137±4</td>
<td>10.6±1.8</td>
<td>2,900±300</td>
</tr>
</tbody>
</table>

* $\text{PaO}_2$, arterial pressure of oxygen; $\text{PVO}_2$, coronary venous partial pressure of oxygen; $\text{AVO}_2$, arterial venous oxygen content difference; $\text{CBF}$, coronary blood flow; $\text{MVVO}_2$, myocardial oxygen consumption; $\text{HR}$, heart rate; $\text{AoM}$, mean aortic pressure; $\text{LVSP}$, left ventricular systolic pressure; $\text{LVEDP}$, left ventricular end-diastolic pressure; $\text{LV dP/dt}$, left ventricular dP/dt; 1 Hr, 1 hour after final coronary artery occlusion period. Values are mean±SEM.

* $p<0.05$ compared with baseline.
TABLE 5. Reactive Hyperemia Data

<table>
<thead>
<tr>
<th>Control</th>
<th>Occlusion duration (sec)</th>
<th>Blood flow debt (ml)</th>
<th>RH duration (sec)</th>
<th>Excess flow (ml)</th>
<th>BFDR (%)</th>
<th>Peak flow (ml/min)</th>
<th>mAoP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-second occlusion (n=7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>20.1±2.9</td>
<td>10.3±0.16</td>
<td>3.40±0.50</td>
<td>57.4±9.1</td>
<td>15.9±2.4</td>
<td>474±78</td>
<td>56.6±6.8</td>
</tr>
<tr>
<td>1 Hr</td>
<td>18.1±2.8</td>
<td>10.3±0.15</td>
<td>3.10±0.50</td>
<td>35.2±4.5</td>
<td>9.3±1.6</td>
<td>327±74</td>
<td>59.5±7.1</td>
</tr>
<tr>
<td>20-second occlusion (n=6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>16.5±2.1</td>
<td>20.2±0.15</td>
<td>5.60±0.70</td>
<td>29.5±14.0</td>
<td>28.2±4.0</td>
<td>530±96</td>
<td>61±8.8</td>
</tr>
<tr>
<td>1 Hr</td>
<td>14.3±2.1</td>
<td>20.1±0.17</td>
<td>4.80±0.70</td>
<td>56.0±8.2</td>
<td>17.2±4.1</td>
<td>356±78</td>
<td>59±9.2</td>
</tr>
</tbody>
</table>

CBF, coronary blood flow; BFDR, blood flow debt repayment; RH, reactive hyperemia; mAoP, mean aortic pressure during reactive hyperemia. Values are mean±SEM.

*p<0.05 compared with baseline.

an increase in end-diastolic segment length or changes in preload or afterload does not support the former possibility, while the temporal pattern of myocardial segment shortening in postischemic myocardium, shown in Figure 5 and typical of that seen in all dogs, appears inconsistent with the latter explanation. During isovolumic systole there was prominent lengthening of the stunned myocardial segment. It was not until well into the ejection phase of systole, when rapid ventricular emptying and geometric changes in the ventricle resulted in changes in loading conditions, that shortening of the stunned segment occurred. The presence of systolic segment lengthening in stunned myocardium during the isovolumic contraction phase, similar to that seen in severely ischemic myocardium, suggests that tension development was impaired. This concept is supported by reports that in isolated, perfused isovolumetrically beating hearts postischemic dysfunction is manifested by impaired pressure development.25,26 Thus, it is unlikely that ongoing tension development without appropriate systolic shortening could account for the normal oxygen consumption in stunned myocardium.

It is possible that microvascular heterogeneity in oxygen consumption, with some areas of increased consumption or extraction, could obscure other parallel perfused areas of reduced oxygen demand. This would not have been detected, since only regional oxygen consumption was measured. However, the extent to which this could occur is very limited, since the high average rate of oxygen extraction in the heart limits the degree to which areas of further increased oxygen extraction could occur. The distribution of myocardial blood flow across the wall of the left ventricle was unchanged in postischemic myocardium, suggesting that the distribution of oxygen consumption across the wall was also unchanged. This is in agreement with the preliminary report of Stahl et al15 that in an open-

FIGURE 5. Left ventricular pressure and dP/dt, regional segment shortening, and coronary blood flow from a dog at baseline (A), during coronary vasodilation with intravenous adenosine at baseline (B), during left anterior descending coronary artery occlusion (C), at 1 hour of reperfusion after the final coronary artery occlusion period before (D) and during (E) coronary vasodilation with adenosine, and at ≥24 hours of reperfusion after the last coronary artery occlusion period (F). The vertical dashed lines mark end diastole and end systole for each tracing.
chest canine model of stunned myocardium, transmural oxygen consumption was normal to slightly increased across the left ventricular wall. Thus, the mechanism for unchanged myocardial oxygen consumption in the presence of decreased contractile function is unclear. Mitochondrial respiration appears intact in stunned myocardium, so that uncoupling of oxidation phosphorylation pathways does not explain this finding.6,22,27 These results are, however, compatible with abnormalities in energy utilization or electromechanical coupling. Shunting of energy supplies towards cellular repair processes might also contribute to the unexpectedly high oxygen utilization of stunned myocardium.

Coronary Vasodilator Responsiveness

The increase in coronary blood flow in response to infusion of the potent coronary vasodilator adenosine was unchanged in the postischemic myocardium, demonstrating that coronary vasodilator reserve was not impaired. Despite normal vasodilator reserve, coronary reactive hyperemia was briefer and total excess flow during reactive hyperemia was less in postischemic than in normal myocardium. These changes were statistically significant after 10-second coronary occlusions and of borderline significance after 20-second occlusions. Decreased reactive hyperemia could have resulted from 1) decreased sensitivity of the coronary resistance vessels to the metabolic vasodilators that mediate the reactive hyperemic response, 2) increases of extravascular compressive forces within the postischemic myocardium (such as edema), which act on the intramural coronary vasculature to limit maximum coronary flow rates, or 3) reduced production of vasodilator messengers during ischemia. Peak flows after both 10- and 20-second occlusions were unchanged. In addition, maximum flow rates during adenosine infusion were not reduced in postischemic myocardium. The finding of normal vasodilator capacity in the postischemic myocardium indicates that myocardial or endothelial cell swelling sufficient to cause extrinsic compression of intramural coronary vasculature to impair maximum flow rates did not occur in response to ischemia. In addition, the response to adenosine, which may act as a messenger coupling myocardial metabolic demands to coronary flow, was preserved.28,29 These data do not support alterations in vessel sensitivity to mediators of vasodilation, or structural or mechanical changes in vessels or myocardium as major contributors to the decreased reactive hyperemia.

Adenosine is a potent coronary vasodilator that accumulates in myocardium during ischemia,29,30 and that appears to contribute to the reactive hyperemic response.31 Thus, Saito et al32 found that adenosine-receptor blockade with theophylline or intracoronary adenosine deaminase decreased the volume of reactive hyperemic blood flow by approximately 33%. Of interest was the finding that these interventions that antagonize the action of adenosine shortened the hyperemia but did not decrease peak flow rates. A similar alteration of the reactive hyperemic response was observed in postischemic myocardium in this study, that is, decreased debt repayment and duration without a change in peak flow. The high energy adenine nucleotide pool, which is the precursor of myocardial adenosine production, is substantially decreased in postischemic myocardium.21,27 Catabolism of nucleotides to nucleosides and bases, leading to adenosine formation during ischemia, has been reported to occur mainly during the initial ischemic episode, with little further reduction of the adenosine nucleotide pool during subsequent ischemic episodes.21 While the present study was not designed to evaluate changes in myocardial adenine nucleotide pools, the findings suggest the possibility that a decrease in the adenosine nucleotide pool during the initial 10-minute coronary occlusions resulted in decreased adenosine formation during the subsequent brief periods of ischemia, thereby decreasing the reactive hyperemic response.

Postischemic Myocardial Dysfunction

In the present study, serial coronary occlusions resulted in progressive myocardial dysfunction. Previous reports examining the effects of multiple short coronary occlusion periods have supported27,33,34 or disputed14 the occurrence of progressive myocardial dysfunction with repetitive ischemic episodes. These studies have used variable occlusion and reperfusion protocols (ranging from three to 15 occlusions), and were carried out in open-chest, anesthetized models. The absence of cardiac-depressant effects of general anesthesia, the lower levels of basal oxygen consumption, which are characteristic of the chronically instrumented awake animal preparation, and the long-term stability of the preparation used in this study make comparisons of results difficult.

The protocol employed in the current study was designed in part to evaluate the effect of several ischemic insults on the development of postischemic dysfunction and is most comparable to the report of Lange et al,14 where three serial 5- or 15-minute occlusions separated by 30-minute reperfusion periods were made in an open-chest canine model. In that study, regional segment shortening was reduced at 30 minutes after the initial coronary occlusion, but repetitive occlusions did not produce further cumulative myocardial dysfunction. In contrast, while the greatest decrease in segment shortening in the present study developed after the initial ischemic episode, progressive dysfunction also occurred, so that segment shortening at 30 minutes after the third occlusion was significantly less than at the same interval after the initial coronary occlusion. The mechanism for this difference in behavior of postischemic myocardium between awake and open-chest animals is of interest. Heart rate and left ventricular systolic pressures were lower in the
Regional Myocardial Function During Vasodilator Infusion

Despite the severe reduction in myocardial segment shortening in postischemic myocardium, adenosine infusion dramatically improved segment shortening to postischemic myocardium. In these same animals, there was little change in shortening in response to adenosine infusions during baseline conditions. In addition, regional myocardial segment shortening in the posterior wall did not change significantly in response to adenosine infusion either at baseline or after myocardial stunning. Although mean aortic pressure was reduced slightly during adenosine infusion, this was not statistically significant, and left ventricular systolic pressure and heart rate tended to be higher. Global left ventricular pressure and dimension measurements do not necessarily reflect regional loading conditions, however. Stahl et al also reported improved contractile function in stunned myocardium of open-chest dogs during coronary vasodilation with papaverine or dipyridamole. In that study, the regional left ventricular end-systolic pressure-volume relation was used to provide a load independent measure of regional myocardial contractility. This relation has been validated principally with global end-systolic pressure-volume relations, so that the possibility that changes in regional left ventricular loading conditions contributed to the change in segment shortening during adenosine infusion cannot be entirely excluded.

In normal myocardium, myocardial blood flow is closely coupled to myocardial metabolic needs so that contractile function is not limited by flow; thus, during normal conditions an increase in blood flow does not result in an improvement in function. Since the relation between myocardial oxygen consumption and coronary blood flow was normal in the stunned region during basal conditions, it is unclear why further increasing flow would improve contractile function. As discussed earlier, this study measured regional myocardial oxygen consumption and cannot exclude microvascular heterogeneity with adjacent areas of increased and decreased oxygen consumption within the postischemic myocardium. If such a situation did exist, vasodilation with adenosine might improve flow to underperfused areas and result in improved regional function. If this occurred, regional oxygen consumption might be expected to increase during adenosine infusion. Unfortunately, myocardial oxygen consumption was not measured during adenosine infusion, so this mechanism could not be addressed by the current study. Stunned myocardium has been shown to remain responsive to inotropic stimuli; although adenosine does not exert a direct positive inotropic effect upon the myocardium, adenosine induced vasodilation might result in reflex activation of sympathetic activity resulting in inotropic stimulation of the myocardium. Although the mechanism of the improvement in contractile function during adenosine infusion remains unresolved, changes in regional left ventricular loading and reflex sympathetic responses to systemic vasodilation may be of importance.

Effect of Isoproterenol During Coronary Occlusion

Five dogs received isoproterenol during coronary artery occlusions. In these animals, the anterior segment demonstrated severe hypokinesis or akinesia during the initial coronary occlusion, but did not develop dyskinesis. With the addition of isoproterenol, there was prompt development of sustained dyskinesis throughout the occlusion period. Infusion of isoproterenol was associated with a significant increase in heart rate, no change in left ventricular systolic pressure, a modest decrease in mean and diastolic aortic pressure, and an increase in nonischemic region segment shortening. Although coronary collateral flow measured with microspheres tended to be higher in the group that required isoproterenol to produce dyskinesis, this difference did not achieve statistical significance. Heart rates during coronary occlusion in the animals receiving isoproterenol infusion (155 ± 4 beats/
min) were similar to those commonly seen in open-chest studies with pentobarbital anesthesia, while heart rates during occlusion in animals not receiving isoproterenol were much lower (109±9). The increased heart rate and contractility in response to isoproterenol appeared to overcome the effect of slightly higher ischemic region blood flow.

Summary
Repeated brief coronary artery occlusions resulted in progressive, severe, but reversible decreases in regional myocardial segment shortening without necrosis. Despite severe contractile dysfunction, regional myocardial oxygen consumption was unchanged. Total coronary blood flow, the transmural distribution of perfusion and myocardial oxygen extraction were also unchanged, demonstrating that the normal coupling between oxygen demands and coronary flow was maintained in stunned myocardium. Reactive hyperemia blood flow was significantly decreased, although peak hyperemic blood flow rates and the vasodilator response to adenosine were not impaired following myocardial stunning. Finally, regional function in stunned myocardium was dramatically and significantly improved during systemic vasodilator-induced increases in coronary blood flow.

Acknowledgments
The authors would like to thank Melanie Crampston and Paul Lindstrom for their valuable technical assistance.

References
15. Stahl L, Weiss HR, Becker LC: Increased O2 consumption and heterogeneous extraction in stunned vs. normal myocardium (abstract). Circulation 1986;74(suppl II):II-493
22. Przyklenk K, Kloner RA: Superoxide dismutase plus cata-


Key Words: coronary circulation • myocardial function • myocardial ischemia • myocardial oxygen consumption • myocardial reperfusion • adenosine
Oxygen consumption and coronary reactivity in postischemic myocardium.
D D Laxson, D C Homans, X Z Dai, E Sublett and R J Bache

Circ Res. 1989;64:9-20
doi: 10.1161/01.RES.64.1.9

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/64/1/9

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/