Metabolic Response to Prolonged Reduction of Myocardial Blood Flow Distal to a Severe Coronary Artery Stenosis

Frank A. Fedele, MD, Henry Gewirtz, MD, Robert J. Capone, MD, Barry Sharaf, MD, and Albert S. Most, MD

Limited data are available concerning the effects of mild-to-moderate, sustained reductions of coronary blood flow on myocardial aerobic metabolism. This study tested the hypothesis that a sustained flow reduction distal to a severe coronary artery stenosis may be well tolerated (after the initial insult is passed) because of gradual improvement in the balance between myocardial oxygen supply and demand. Studies were performed in eight sedated, closed-chest domestic swine that were instrumented with an artificial coronary arterial stenosis (80% diameter reduction). Hemodynamics, regional myocardial blood flow and oxygen, lactate, acid, and base metabolism were measured before stenosis and at 5, 20, 60, 120, and 180 minutes after stenosis insertion. Regional myocardial function (ultrasonic length sensors) was measured serially during 2 hours in three additional swine. After stenosis placement, endocardial and transmural flows declined ($p<0.05$) compared with flows before stenosis (from $1.54\pm0.37$ to $0.73\pm0.24$ ml/min/g [mean $\pm$ SD] and from $1.44\pm0.31$ to $1.19\pm0.25$ ml/min/g, respectively). Thereafter, flows remained unchanged for the duration of the study. Similarly, prestenosis heart rate ($135\pm7$ beats/min), aortic mean pressure ($113\pm17$ mm Hg), and tension time index ($27.1\pm3.6$ mm Hg · sec) remained constant for the duration of the study. In contrast, regional coronary venous pH declined ($p<0.05$) compared with prestenosis levels ($7.35\pm0.02$) 5 minutes after stenosis ($7.28\pm0.04$), but it returned to prestenosis levels during the next hour. Regional coronary venous $\text{PCO}_2$ exhibited a similar pattern (i.e., acute increase during poststenosis with gradual return to prestenosis levels). Lactate consumption at prestenosis ($36.7\pm27.3$ umol/min/100 g) changed to production 5 minutes poststenosis ($-80.3\pm46.8$; $p<0.05$) and then gradually returned toward consumption during the ensuing 3 hours ($1.6\pm10.7$ at 180 minutes, $p<0.05$ vs. 5 minutes). Regional myocardial oxygen consumption declined compared with poststenosis consumption ($16.8\pm4.1$ ml/min/100 g) at 5 minutes poststenosis ($13.7\pm2.8$, $p<0.05$) and remained unchanged thereafter. Regional shortening declined abruptly immediately after stenosis placement in a separate group of three animals and decreased further until a steady state was achieved 40 minutes after stenosis. Thus, the data demonstrate that metabolic indexes of myocardial ischemia improve over time in a clinically relevant animal model of human ischemic heart disease. Such changes occur in the absence of significant alterations in either regional myocardial blood flow or external determinants of myocardial oxygen demand. The mechanism that is involved likely is related to a time-dependent adjustment in which myocardial oxygen demand declines and stabilizes at a level more appropriate to reduced myocardial oxygen supply. (Circulation 1988;78:729–735)

Recent advances in the treatment of patients with ischemic heart disease, notably coronary angioplasty and thrombolysis, at times may result in only partial restoration of myocardial blood flow distal to a severe coronary arterial stenosis. The effects of a prolonged reduction, but not cessation, of myocardial blood flow on regional myocardial aerobic metabolism have not been well described. It is not known, for instance, whether a prolonged reduction in regional blood flow will result in a steady-state level of ischemia as defined by metabolic variables such as coronary venous pH and $\text{PCO}_2$ and regional lactate and oxygen metabolism or whether the degree of ischemia, metabolically defined, will continue to change (either improve

From the Division of Cardiology, Department of Medicine, Rhode Island Hospital, and the Brown University Program in Medicine, Providence, Rhode Island.

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Address for reprints: Henry Gewirtz, MD, Division of Cardiology, Rhode Island Hospital, Providence, RI 02903.

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or worsen) over time. Furthermore, previous experiments in this area either have used coronary artery occlusion models or buffer-perfused, isolated hearts subjected to marked reductions in myocardial flow. Such models are of uncertain relevance to humans with severe coronary arterial stenosis and preserved, although reduced, antegrade blood flow distal to the lesion. Accordingly, the present study was performed in sedated, intact domestic swine instrumented with an intralumenal coronary arterial stenosis that reduced vessel diameter by 80% to test the hypothesis that metabolic evidence of ischemia would improve over time as reduced myocardial oxygen demand becomes better balanced with the available myocardial oxygen supply. The hypothesis is derived from the observation that myocardial "stunning" occurs after a period of reduced myocardial blood flow and from results of a previous study that demonstrated that recovery of systolic function is as rapid after prolonged ischemia as it is after brief ischemia.

**Materials and Methods**

**Animal Preparation**

After an overnight fast, farm-bred domestic swine (n = 8; mean weight, 42 kg; range, 37–49 kg) were premedicated with sodium thiamylol (total dose, 0.5–1.0 g i.v.), intubated, and anesthetized with halothane (0.5–1.0%) and nitrous oxide (60:40 mixture with oxygen). The animals were ventilated with a volume-cycled respirator through which supplemental oxygen was delivered at 2–3 l/min mixed with room air and anesthetic gases. Arterial blood gases were monitored frequently and were maintained at appropriate levels (pH 7.39–7.45; Pco2, 35–45 mm Hg; and Po2, 100–125 mm Hg) during each study. After induction of anesthesia, each animal was anticoagulated with heparin (225 IU/kg i.v.). Full anticoagulation was maintained by administration of approximately half the initial loading dose every 2–3 hours.

The animal was instrumented for the study as follows. A 7F Eppendorf catheter was advanced by fluoroscopic control from the right femoral artery to the left ventricle and then advanced retrogradely across the mitral valve to the left atrium. This catheter was used to administer radioactive microspheres for measurements of regional myocardial blood flow. The left femoral artery was used to introduce an 8F double-lumen catheter into the thoracic aorta just below the origin of the subclavian artery. This catheter was used to monitor arterial blood gases and for reference withdrawal for microsphere determinations of regional myocardial blood flow. An 8F pigtail catheter was inserted into the right brachial artery and then advanced to the apex of the left ventricle to monitor left ventricular pressure. The femoral veins were cannulated bilaterally with 8F catheters that were used to administer fluids and medications during the study.

Another 7F Eppendorf catheter was placed in the right internal jugular vein and advanced to the coronary sinus and thence to the middle portion of the anterior interventricular vein. In some animals, anterior interventricular catheterization was accomplished by a 3F angioplasty catheter that was guided to an appropriate position with the aid of a 9F introducing catheter and 0.014 angioplasty wire with a floppy distal end. When the angioplasty catheter was in place, the wire guide was removed, and the 9F guiding catheter was withdrawn to the proximal portion of the coronary sinus. Next, a 7F bipolar pacing catheter was inserted into the left internal jugular vein and was advanced to the coronary sinus. The pacing catheter was used to maintain the animal’s heart rate at 135–140 beats/min throughout the study.

Before placement of the coronary arterial stenosis (see below), halothane and nitrous oxide were discontinued, and the animal was permitted to awaken sufficiently to breathe spontaneously and exhibit modest tremulousness. A constant intravenous infusion of sodium thiamylol was begun at 10–40 ml/hr (20 mg/ml) to maintain sedation and ensure that the animal was free of pain. When the animal had stabilized for approximately 20 minutes, the experimental protocol was begun. In all instances, intravenous drugs and medications were administered in normal saline.

**Experimental Protocol**

First, a period of hemodynamic and arterial blood gas stability was documented by measuring arterial and anterior interventricular vein blood gases and by recording hemodynamic variables (i.e., heart rate and arterial and left ventricular pressures) every 5 minutes for 15–20 minutes. After demonstrating that three successive measurements of arterial and anterior interventricular vein pH differed by less than 0.2% (arterial vs. arterial, anterior interventricular vein vs. anterior interventricular vein), initial measurements of all experimental variables were obtained. Variables included hemodynamics, regional myocardial blood flow (microspheres), arterial and anterior interventricular blood gases and pH, and lactate and oxygen content of arterial and anterior interventricular vein blood. Next, an artificial coronary artery stenosis that reduced lumenal diameter by 80% was inserted into the animal’s left anterior descending coronary artery as previously described. Repeat measurements of all experimental variables were made at 5, 20, 60, 120, and 180 minutes after stenosis placement.

At the conclusion of the study, myocardium distal to the stenosis was marked by injecting radiolabeled microspheres through the coronary infusion catheter attached to the stenosis. The animal was given a large intravenous dose of sodium thiamylol and killed 5 minutes later by an intravenous injection of potassium chloride. The chest was opened, and the location of the distal end of the
anterior interventricular vein catheter was diagrammed according to the position of the stenosis in the left anterior descending coronary artery. The stenosis-catheter system was removed from the left anterior descending coronary artery, and the vessel itself was inspected for evidence of gross intimal damage. The heart was rinsed thoroughly with tap water, refrigerated in buffered saline, and sectioned for determination of microsphere activity (see below).

**Hemodynamics**

Heart rate (lead II of the surface electrocardiogram) and arterial, left ventricular, left atrial, and distal coronary artery pressures were monitored continuously throughout the study and recorded on chart paper with a Hewlett-Packard eight-channel recorder (model 5588A, Palo Alto, California). Intravascular and intracardiac pressures were recorded from fluid-filled catheters connected to Hewlett-Packard force transducers (Model 1280A). Analog recordings were made, and recordings were also digitized, displayed, and stored on line with an IBM-AT laboratory computer system. Software developed in our laboratory to record and analyze data has been described previously.13

**Regional Myocardial Blood Flow**

For each experimental condition, approximately $4 \times 10^6$ radiolabeled microspheres (15-µm diameter, 85–105 µCi total radioactivity) were injected through the left atrial catheter to determine regional myocardial blood flow.14 A different radioisotope was chosen at random for each flow determination. Details of microsphere methods used in our laboratory have been published.10,11

**Regional Myocardial Oxygen Metabolism**

Paired samples (2–3 ml) of arterial and anterior interventricular venous blood were obtained for determination of oxygen content (Lex-O2–CON Instrument, Lexington Instruments, Waltham, Massachusetts) during each phase of the study. Oxygen content (vol%) was determined in duplicate for each sample, and values were accepted only when the difference between them was less than 0.2 ml/O2/dl. Regional myocardial oxygen consumption (ml/min/100 g) was calculated as the product of transmural regional myocardial blood flow distal to the stenosis and the arterial and anterior interventricular venous oxygen difference.

**Regional Myocardial Lactate Metabolism**

Lactate concentration in arterial and anterior interventricular vein blood was determined by a spectrophotometric method with commercially available kits (Calbiochem Rapid Lactate Reagents, Calbiochem-Behring, La Jolla, California). Samples of blood (5 ml) were immediately deproteinized by placing them in cold perchloric acid (8% vol/vol). The samples were centrifuged, and the supernatant was frozen for subsequent analysis in duplicate.

Regional lactate consumption was calculated as the product of transmural regional myocardial blood flow distal to the stenosis and the arterial and anterior interventricular vein lactate difference.

**Regional Myocardial Function**

Serial measurements of regional myocardial function were obtained with ultrasonic length sensors in three additional animals. Each animal was prepared for the study as described previously.8 These animals were studied during open-chest, fully anesthetized conditions. Heart rates were controlled by atrial pacing throughout the study. Regional shortening fraction in endocardium distal to the stenosis and in a region supplied by the circumflex coronary artery was measured before and every 10–15 minutes for 2 hours after stenosis placement.

**Statistics**

The significance of group-mean changes in hemodynamics, regional myocardial blood flow, and metabolic variables was assessed by means of a blocked one-way analysis of variance and Dunnett’s test.13 Comparisons were made between prestenosis and poststenosis values and between 5-minute poststenosis and poststenosis values from later points in time. Results were considered statistically significant when $p$ was less than 0.05. All values are expressed as mean ± SD.

**Results**

**Hemodynamics**

Heart rate did not change significantly compared with prestenosis (135 ± 2 beats/min) at any time during the study (Table 1). Similarly, mean aortic pressure and tension time index both remained constant compared with prestenosis levels (113 ± 17 mm Hg and 27 ± 4 mm Hg · sec, respectively) for the duration of the study. Mean left atrial pressure during prestenosis (2 ± 2 mm Hg) did not differ significantly from values at 5 (5 ± 2 mm Hg) and 20 minutes (6 ± 2 mm Hg) poststenosis, but it was lower ($p<0.05$) than values at 1, 2, and 3 hours (8 ± 4, 9 ± 6, and 6 ± 6 mm Hg, respectively) during poststenosis.

**Regional Myocardial Blood Flow**

Distal zone endocardial blood flow declined ($p<0.05$) compared with prestenosis at 5 minutes poststenosis (0.73 ± 0.24 ml/min/g) and then remained unchanged for the duration of the study (Table 2). Epicardial blood flow in the distal zone increased ($p<0.05$) compared with prestenosis at 5, 20, and 60 minutes poststenosis and then declined to levels that did not differ significantly from prestenosis at 2 and 3 hours poststenosis. Distal zone transmural flow was reduced ($p<0.05$) compared with prestenosis at 5, 60, and 120 minutes poststenosis. Values of distal zone transmural flow at 20 minutes and 3 hours poststenosis, although lower, were not signif-
significantly different from prestenosis levels. Finally, it should be emphasized that values of epicardial flow at 5, 20, 60, and 120 minutes poststenosis did not differ significantly from one another. The same was true for endocardial flow, transmural flow, and the endocardial-epicardial flow ratio.

Five minutes after placement of the stenosis, flow in each layer of the circumflex zone increased compared with prestenosis values (endocardium, 1.63 ± 0.40 to 1.87 ± 0.27 ml/min/g; epicardium, 1.28 ± 0.25 to 1.47 ± 0.21 ml/min/g) although the changes did not attain statistical significance. Flows in each layer increased modestly thereafter and were significantly elevated (p < 0.05) compared with prestenosis levels at 3 hours (endocardium, 2.07 ± 0.04 ml/min/g; epicardium, 1.59 ± 0.28 ml/min/g).

Acid-Base Metabolism

The PCO₂ of arterial blood modestly declined (p < 0.05) compared with prestenosis (43 ± 3 mm Hg) at 3 hours poststenosis (39 ± 4 mm Hg). Anterior interventricular vein PCO₂ increased (p < 0.05) compared with prestenosis (57 ± 4 mm Hg) at 5 (64 ± 6 mm Hg) and 20 minutes (63 ± 8 mm Hg) poststenosis but then declined to levels that did not differ significantly from prestenosis at 1, 2, and 3 hours (59 ± 8, 57 ± 6, and 54 ± 4 mm Hg, respectively) after stenosis placement (Figure 1, left). Values at 2 and 3 hours poststenosis were statistically different (p < 0.05) compared with the value at 5 minutes poststenosis.

Arterial pH did not change significantly compared with prestenosis (7.41 ± 0.02) during the entire study. In contrast, anterior interventricular vein pH decreased (p < 0.01) compared with prestenosis pH (7.35 ± 0.02) at 5 minutes (7.28 ± 0.04) and at 20 minutes (7.29 ± 0.05) poststenosis (p < 0.05) (Figure 1, right). The pH of anterior interventricular vein blood increased at 1, 2, and 3 hours (7.32 ± 0.04, 7.32 ± 0.04, and 7.35 ± 0.03, respectively) poststenosis. These values were statistically different (p < 0.05) compared with 5 and 20 minutes poststenosis and did not differ significantly from prestenosis values.

Aerobic Metabolism

Both arterial and anterior interventricular vein PO₂ were unchanged compared with prestenosis (113 ± 12 and 18 ± 3 mm Hg, respectively) for the duration of the study. Arterial oxygen content remained unchanged compared with prestenosis (13.8 ± 1.1 ml/dl) for the 1st hour after stenosis placement but then declined (p < 0.05) at 2 and 3 hours (13.1 ± 1.3 and 12.8 ± 1.3 ml/dl, respectively). Anterior interventricular vein oxygen content and myocardial oxygen extraction both remained unchanged compared with prestenosis (2.2 ± 0.7 ml/dl and 84 ± 4%, respectively) for the duration of the study. In contrast, regional myocardial oxygen consumption declined (p < 0.05) compared with prestenosis (16.8 ± 4.1 ml/min/100 g) at 5-minutes poststenosis (13.7 ± 2.8 ml/min/100 g) and remained constant thereafter (Figure 2, left).

Arterial lactate concentration remained constant compared with prestenosis levels (1.0 ± 0.7 mM) for the duration of the study. In contrast, anterior interventricular vein lactate levels increased significantly compared with prestenosis (0.7 ± 0.5 mM) at 5 and 20 minutes (1.8 ± 0.9 and 1.3 ± 0.6 mM, respectively) poststenosis. Lactate concentration at 1, 2,

### Table 1. Hemodynamics

<table>
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<th>Variable</th>
<th>Prestenosis</th>
<th>5</th>
<th>20</th>
<th>60</th>
<th>120</th>
<th>180</th>
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<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>135 ± 2</td>
<td>136 ± 2</td>
<td>135 ± 2</td>
<td>135 ± 3</td>
<td>140 ± 11</td>
<td>137 ± 6</td>
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<td>Mean pressure aorta (mm Hg)</td>
<td>113 ± 17</td>
<td>111 ± 16</td>
<td>121 ± 17</td>
<td>123 ± 12</td>
<td>121 ± 8</td>
<td>116 ± 15</td>
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<tr>
<td>Mean pressure left atrium (mm Hg)</td>
<td>1.9 ± 2.0</td>
<td>5.2 ± 2.4</td>
<td>5.6 ± 2.4</td>
<td>7.6 ± 4.4*</td>
<td>8.7 ± 6.3†</td>
<td>6.4 ± 6.3*</td>
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<tr>
<td>Tension time index (mm Hg · sec)</td>
<td>27 ± 4</td>
<td>27 ± 3</td>
<td>29 ± 3</td>
<td>29 ± 3</td>
<td>27 ± 3</td>
<td>25 ± 5</td>
</tr>
</tbody>
</table>

All values are mean ± SD.

* p < 0.05 vs. prestenosis; † p < 0.01 vs. prestenosis.

### Table 2. Natural History Study: Regional Myocardial Blood Flow

<table>
<thead>
<tr>
<th>Distal zone flow (ml/min/g)</th>
<th>Prestenosis</th>
<th>5</th>
<th>20</th>
<th>60</th>
<th>120</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocardium</td>
<td>1.53 ± 0.37</td>
<td>0.73 ± 0.24*</td>
<td>0.81 ± 0.25*</td>
<td>0.81 ± 0.25*</td>
<td>0.79 ± 0.18*</td>
<td>0.94 ± 0.29*</td>
</tr>
<tr>
<td>Epicardium</td>
<td>1.25 ± 0.29</td>
<td>1.52 ± 0.26†</td>
<td>1.57 ± 0.23†</td>
<td>1.46 ± 0.27†</td>
<td>1.38 ± 0.28</td>
<td>1.41 ± 0.37</td>
</tr>
<tr>
<td>Transmural</td>
<td>1.43 ± 0.31</td>
<td>1.18 ± 0.25†</td>
<td>1.27 ± 0.21</td>
<td>1.21 ± 0.22†</td>
<td>1.17 ± 0.22†</td>
<td>1.24 ± 0.32</td>
</tr>
<tr>
<td>Endo:epi ratio</td>
<td>1.22 ± 0.10</td>
<td>0.48 ± 0.14*</td>
<td>0.51 ± 0.13*</td>
<td>0.55 ± 0.15*</td>
<td>0.58 ± 0.11*</td>
<td>0.66 ± 0.15*</td>
</tr>
</tbody>
</table>

Values are mean ± SD, n = 8.

* p < 0.01 vs. prestenosis; † p < 0.05 vs. prestenosis.
and 3 hours (1.0 ± 0.4, 0.8 ± 0.3, and 0.7 ± 0.3 mM, respectively) poststenosis, however, did not differ significantly from prestenosis levels. Lactate consumption during prestenosis (36.7 ± 27.3 μmol/min/100 g) changed to lactate production at 5, 20, and 60 minutes (−80.3 ± 46.8, −18.0 ± 25.1, and −11.8 ± 30.3 μmol/min/100 g, respectively) poststenosis (all were significant, p<0.01) (Figure 2, right). After 2 and 3 hours, lactate consumption resumed (1.7 ± 11.2 and 1.6 ± 10.7 μmol/min/100 g, respectively). Values at each time point were significantly different (p<0.05) both from prestenosis and from 5 minutes poststenosis. Lactate production or consumption at 20, 60, 120, and 180 minutes was significantly reduced (i.e., less production) (p<0.01) compared with 5 minutes poststenosis.

**Regional Myocardial Function**

Heart rate (about 140 beats/min) and mean aortic pressure (80–100 mm Hg) remained stable and varied less than 10% for each animal during the study. Endocardial fractional shortening declined, as anticipated, immediately after stenosis placement. However, systolic function (i.e., fractional shortening) for the group did not reach its nadir immediately (Figure 3). After the initial steep decline, there was a further gradual reduction in distal zone shortening throughout the next 30–40 minutes after stenosis placement. Regional myocardial function stabilized at a level roughly 30% of control after the 40-minute time point. Endocardial fractional shortening in the circumflex region exhibited a very modest decline in the 1st hour after stenosis placement but returned to control levels during the 2nd hour of study.

**Discussion**

This study may be summarized as follows. Immediately after placement of a severe coronary arterial stenosis, endocardial blood flow declined approximately 50% compared with prestenosis levels and remained unchanged for the duration of the study (3 hours). Also, a modest (approximately 20%) increase in distal zone epicardial blood occurred but only for the 1st hour after stenosis placement. Thereafter, epicardial flow declined by about 10% to levels that did not differ significantly from prestenosis. Accordingly, after stenosis placement, distal zone endocardial and epicardial blood flow remained essentially unchanged (Table 2) for the duration of the study. The same was true of external determinants of myocardial oxygen demand.

In contrast to the pattern observed with myocardial blood flow and hemodynamics, metabolic evidence of myocardial ischemia, that is, reduced coronary venous pH, elevated coronary venous PCO2, and regional myocardial lactate production, all changed in the direction of improvement. Indeed, after 1 hour, coronary venous pH and PCO2 returned.

**Figure 1.** Bar graphs of PCO2 and pH of anterior interventricular vein (AIV) blood is shown in the left-hand and right-hand panels, respectively. Both variables exhibit substantial worsening 5 minutes after stenosis placement with gradual return to prestenosis levels during 3 hours. *p<0.05 vs. prestenosis, **p<0.01 vs. prestenosis, #p<0.05 vs. 5 minutes poststenosis, ##p<0.01 vs. 5 minutes poststenosis. STNS, stenosis.

**Figure 2.** Bar graphs of regional myocardial oxygen (MVO2) and lactate consumption. Oxygen consumption declined 5 minutes after stenosis placement and then remained unchanged for the duration of the study. Lactate production was maximal immediately after stenosis insertion and then reversed toward consumption during the next 3 hours. *p<0.05 vs. prestenosis, **p<0.01 vs. prestenosis, ##p<0.01 vs. 5 minutes poststenosis. STNS, stenosis.
to and remained at values that did not differ significantly from prestenosis levels (Figure 1). Marked lactate production observed immediately after placement of the stenosis declined significantly and reverted toward consumption during the 3-hour observation period (Figure 2). Thus, metabolic evidence of myocardial ischemia declined over time despite the fact that regional myocardial blood flow and external determinants of myocardial oxygen demand remained constant. It should be emphasized that the distal zone endocardial:epicardial flow ratio, as well as the absolute values of flow in each layer (Table 2), did not change significantly between 5 and 60 minutes poststenosis (i.e., during the time that metabolic changes were most prominent). Accordingly, metabolic improvement cannot be explained on the basis of a simple change in the proportion of distal zone endocardial and epicardial blood that contributed to the anterior interventricular vein blood sample.

The mechanisms responsible for apparent spontaneous improvement in myocardial ischemia during the conditions of this study were not determined with certainty but very likely are related to an improvement in the balance between myocardial oxygen demand and myocardial oxygen supply. Immediately after stenosis, coronary vascular resistance declined but not sufficiently to prevent a reduction in endocardial blood flow. Because endocardial resistance was substantially reduced (although not minimal), endocardial flow was largely determined by coronary perfusion pressure and tended to remain constant because perfusion pressure did not change. Simultaneously, myocardial contractile function in the endocardium also declined but not, we hypothesize, to its nadir. Progressive reduction, followed by stabilization of distal zone endocardial systolic function observed in a group of three animals that were studied with ultrasonic length sensors provides experimental evidence in support of this hypothesis (Figure 3). Thus, the mismatch between available myocardial oxygen supply and myocardial oxygen demand was accentuated soon after stenosis in comparison with later time points when myocardial contractility was more depressed. Because regional myocardial oxygen consumption remained constant after stenosis insertion does not invalidate this hypothesis because changes in endocardial function and oxygen consumption may have been masked to some degree by opposite changes in the epicardium.

Other mechanisms that could potentially explain the observations of the study also should be considered. A time-dependent decline in lactate production has been reported previously. Apstein et al. observed this phenomenon in an isolated, buffer-perfused heart preparation. However, in their study, the decline in lactate production with time was most prominent in moderately and severely ischemic hearts and was only marginally apparent in hearts with "mild" ischemia (defined as flow 60% of "normal"). Apstein and coworkers proposed that any or all of the following mechanisms might be involved: 1) progressive tissue acidosis, 2) tissue lactate accumulation with subsequent inhibition of glycolysis, 3) myocardial glycogen depletion, 4) loss of glycolytic cofactors such as inorganic phosphate or adenosine. Their data did not permit them to choose among these alternatives, all of which were postulated on the results of other studies involving severe myocardial ischemia and infarction.

It is unlikely that any of the above noted explanations are applicable to the present study. First, the degree of transmural flow reduction (approximately 15% below normal) observed in our animals was less than that produced even in the "mild" ischemia group (flow 40% below normal) of Apstein et al. Accordingly, factors such as tissue acidosis and lactate accumulation, glycogen depletion, or cofactor loss are unlikely to have played a major role. Indeed, the extent of tissue acidosis was measured, although indirectly (regional coronary venous pH and PCO2), and was shown to lessen, not increase, over time. Second, regional myocardial blood flow in the endocardium was maintained at least at 50% of control throughout the 3-hour observation period of the present study. In a previous study in which distal zone endocardial blood flow was maintained at levels very similar to those observed in the present study, we demonstrated that recovery of regional systolic function after prolonged (i.e., 30 minutes) pacing-induced myocardial ischemia was not impaired when compared with a brief (5-minute) ischemic period. Because animals in our previous study could recover systolic function at least as well after prolonged ischemia as after brief ischemia also argues against progressive metabolic deterioration (i.e., lactate accumulation, tissue acidosis, loss of glycolytic cofactors, etc.) as
an explanation for reduced lactate production over time in the present study.

In summary, therefore, this investigation demonstrates that during severe coronary arterial stenosis with reduced antegrade blood flow the metabolic sequelae of myocardial ischemia exhibit a natural tendency to resolve over time. It is important to emphasize that improvement was observed in face of constant external determinants of myocardial oxygen demand and unaltered regional myocardial blood flow. Because the level of flow reduction was not severe, it is unlikely that metabolic paralysis can account for the observation. Rather, it is more likely that myocardial contractile function declines abruptly (but not to its nadir) with the onset of ischemia and then further declines to reach an eventual steady state in which myocardial oxygen demand more closely matches myocardial oxygen supply with concomitant reduction in metabolic evidence of ischemia. Regional function data (Figure 3) obtained in a group of three animals studied with ultrasonic length sensors support this hypothesis. The data are important clinically because they indicate that 1) other things being equal, prolonged reduction of myocardial blood flow of a mild-to-moderate degree may be well tolerated by patients and 2) that clinical trials designed to evaluate treatment of myocardial ischemia must take into account the natural tendency for metabolic markers of ischemia to move in the direction of improvement over time.

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References


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