Contrasting effects of nifedipine and adenosine on regional myocardial flow distribution and metabolism distal to a severe coronary arterial stenosis: observations in sedated, closed-chest, domestic swine

HENRY GEWIRTZ, M.D., SHERRY L. GROSS, B.Sc., DAVID O. WILLIAMS, M.D., and ALBERT S. MOST, M.D.

ABSTRACT This study tested the hypothesis that intrinsic negative inotropic effects of a drug used to induce coronary vasodilation distal to a severe coronary arterial stenosis may influence the extent of redistribution of transmural flow and its metabolic consequences. To test this hypothesis, studies were conducted in eight closed-chest, sedated swine with severe (82% reduction in luminal diameter) coronary arterial stenoses. Measurement of hemodynamic parameters, regional myocardial blood flow (microsphere technique), lactate metabolism, and oxygen consumption were made (1) under control conditions, (2) after 10 min of intracoronary infusion of a vasodilator distal to the stenosis, and (3) under repeat control conditions. Each animal received both intracoronary adenosine (400 μg/min) and nifedipine (50 μg/min). The order of drug infusion was chosen at random and a control period separated administration of each. In response to nifedipine there was no significant change in the mean (± SD) value of endocardial flow (1.21 ± 0.34 vs 1.29 ± 0.61 ml/min·g⁻¹) distal to the stenosis. In contrast, epicardial flow increased in comparison with control to nifedipine (1.30 ± 0.58 to 1.79 ± 0.74 ml/min·g⁻¹; p < .05). Regional myocardial oxygen consumption (MVO₂) declined in comparison with control to nifedipine (14.0 ± 4.2 vs 11.1 ± 5.0 ml/min·100 g⁻¹; p < .05). Regional lactate extraction did not change in comparison with control after infusion of nifedipine (18.2 ± 22.4 vs 11.7 ± 16.8). In response to adenosine, endocardial blood flow distal to the stenosis declined in comparison with control (1.25 ± 0.53 vs 1.07 ± 0.38 ml/min·g⁻¹; p < .05); while epicardial flow increased (1.31 ± 0.55 vs 2.26 ± 0.59 ml/min·g⁻¹; p < .01). Regional MVO₂ also tended to decline in comparison with control after adenosine (13.4 ± 4.9 vs 11.7 ± 2.9 ml/min·100 g⁻¹) and was significantly (p < .05) reduced in comparison with postintervention control (14.6 ± 4.2 ml/min·100 g⁻¹). In contrast to nifedipine, adenosine caused a significant decline in regional lactate extraction in comparison with control (12.7 ± 23.2% vs 10.1 ± 55.0%; p < .01). Thus, administration of nifedipine, a negative inotropic agent, resulted in (1) a decline in regional MVO₂, (2) increased epicardial blood flow with variable effects on endocardial flow distal to the stenosis, and (3) no evidence of de novo or worsening ischemia, even in animals in which endocardial flow decreased. In contrast, coronary vasodilation induced by adenosine resulted in significant flow redistribution away from endocardial layers distal to the stenosis, with associated metabolic evidence of de novo or worsening myocardial ischemia. The results of the study support the proposed hypothesis.


VASODILATION of resistance vessels distal to a severe coronary arterial stenosis has been shown to result in redistribution of blood flow away from endocardial layers of the heart distal to the stenosis.1–7 Although extensively documented, the metabolic consequences of regional coronary "steal" have received relatively little attention, perhaps because it is assumed in the setting of a severe coronary stenosis that coronary vasodilation associated with a decline in endocardial blood flow results in precipitation or worsening of myocardial ischemia. This assumption, however, may not be warranted. Data from previous studies indicate that the magnitude and duration of the reactive hyperemic response to short-term coronary arterial occlusion may be modified by interventions that alter major de-
terminants of myocardial oxygen demand during the period of occlusion. This observation suggests that intrinsic negative inotropic properties of a drug used to induce vasodilation distal to a severe coronary arterial stenosis may influence not only the degree of flow redistribution that occurs but also the severity of ischemia (if any) that may result. We tested this hypothesis by administering both nifedipine and adenosine to a group of closed-chest, sedated swine with coronary arterial stenoses that reduced luminal diameter by 82%. The effects of each drug (administered by direct infusion distal to the stenosis) on regional myocardial blood flow, oxygen consumption, and lactate metabolism were compared to test the hypothesis that flow distribution and metabolic consequences of coronary vasodilation distal to a severe stenosis may be influenced by intrinsic negative inotropic properties of the vasodilator used.

Materials and methods

Animal preparation. Eight farm-bred pigs (mean weight 40.8 kg, range 34.8 to 47.7) were premedicated with ketamine (25 mg/kg) and then anesthetized with halothane (0.5% to 1.5%) and nitrous oxide. After this each animal was systemically anticoagulated with heparin (225 IU/kg iv). A No. 7F end-hole catheter in the arch of the aorta was used to monitor pressure and to obtain blood for determination of pH, P02, PC02, and regional myocardial blood flow. A No. 8F angiographic catheter was passed in a retrograde manner under fluoroscopic guidance from the femoral artery into the left atrium to allow administration of radioactive microspheres. A No. 7F “head hunter” catheter (USCI, Inc., Billerica, MA) inserted into the right internal jugular vein was advanced under fluoroscopic control to the proximal portion of the anterior interventricular vein.

In each of six animals the heart was paced at a constant rate throughout the study by means of a No. 7F bipolar catheter positioned in the apex of the right ventricle. Complete heart block was induced in each of these animals by means of direct-current shock (two shocks of 400 J each) administered via an electrode catheter positioned over the bundle of His. This was done to prevent the marked increases in heart rate that often occur in response to the relatively large dose of nifedipine used in this study (see below). In two animals complete heart block could not be induced. However, both animals were included in the study because heart rate did not increase in response to nifedipine or adenosine (see below).

Next, a plastic stenosis (7.5 mm long, outer diameter 3.5 mm, inner diameter 0.625 mm) was placed in the proximal one-third of the left anterior descending coronary artery. The stenosis contained a second lumen into which the distal end of a 1.4 mm in diameter, 70 cm long plastic catheter had been attached before placement of the stenosis. The distal end of the catheter was open to the distal end of the stenosis and was used to infuse drugs into and record pressure from the distal arterial bed.

After instrumentation was accomplished, all cutdown sites were closed and anesthesia was discontinued. Small doses (20 to 40 mg) of sodium thioglycolate were then given intravenously throughout the study to ensure that the animal was comfortable and resting quietly. Although sedated, each animal breathed spontaneously, was awake, and had intact corneal reflexes. All animals remained intubated and were given supplemental oxygen (2 to 3 liter/min) during the study. Arterial blood gases were monitored frequently and remained at appropriate levels (pH = 7.38 to 7.45; PCO2 = 35 to 45; P02 = 100 to 125 mm Hg) throughout each experiment.

Study protocol — intracoronary adenosine and nifedipine. After the animal was stabilized for at least 30 min control measurements of hemodynamic parameters, regional myocardial blood flow, oxygen, and lactate metabolism were obtained (see below). Next, either adenosine (400 µg·min−1) or nifedipine (50 µg·min−1) was infused into the coronary circulation at a rate of 0.34 ml·min−1 × 10 min. At the end of this time, repeat measurements of all experimental parameters were obtained. The infusion was discontinued and 20 to 30 min later repeat control measurements were made. The vasodilator not used in the first intervention was then infused, again for 10 min at a rate of 0.34 ml·min−1. Measurements of all experimental parameters were made again at the end of 10 min, after which the infusion was discontinued. A final set of control measurements was made 20 to 30 min later.

The order in which the drugs were infused was determined by the toss of a coin before the start of each experiment. After the final set of measurements had been obtained, approximately 300,000 radioactive microspheres (total activity ~ 1.4 µCi) were injected into the coronary circulation distal to the stenosis to objectively label the myocardium that had been exposed to the drug. Each animal was then given a large intravenous dose of sodium thioglycolylate (200 to 300 mg) and 3 to 5 min later a lethal dose of KCl was administered. The heart was then removed and sectioned for determination of microsphere activity.

Before removal of the heart, the position of the distal end of the anterior interventricular venous catheter was noted with respect to the presence of any venous tributaries draining toward it from myocardium proximal to the stenosis. Two small venous tributaries of this type were noted in each of two animals, one small tributary was noted in each of four animals, and no such tributaries were found in the remaining two animals.

Determination of regional myocardial blood flow. For each experimental condition approximately 4 × 106 radiolabeled microspheres (15 µm in diameter, 85 to 105 µCi total radioactivity) were injected via the left atrial catheter to allow determination of regional myocardial blood flow. A different radioisotope was chosen at random for each flow determination. Microspheres were suspended in 2 ml of 20% dextran with 0.01% Tween-80 and mechanically dispersed by repeated injection between stock vial and syringe 2 min before each injection.

The anterior free wall along with the posterior and lateral walls of the left ventricle were removed from each excised heart, after which epicardial blood vessels and fat were carefully trimmed away. Next, the ventricle was cut into cubes weighing 1 to 3 g and the location of each was carefully noted on a diagram of the free wall of the ventricle. Each cube was divided into endocardial and epicardial halves. Each endocardial and epicardial half was again divided in half to obtain endocardial and epicardial layers that represented the innermost and outermost quarters of the left ventricular wall, respectively. Each quarter of the transmural cube weighed between 0.25 and 0.75 g. Radioactivity was measured in a gamma well-counter (Packard Instruments, Downer Grove, IL). A computer was used to correct for spillover of counts from one isotope into the window of another and to calculate regional myocardial blood flow in each tissue sample.

Tissue samples from the free wall of the left ventricle in the distribution of the left anterior descending coronary artery that received the drug infusion were designated the distal zone samples. These were readily identifiable because each contained a high concentration (~7000 g−1) of marker microspheres.
Tissue samples (n = 10 to 20 transmural cubes) obtained from myocardium at the posterobasal region of the left ventricle perfused by the nonstenosed circumflex coronary artery also were analyzed. This region of the left ventricle was used as a reference zone because it was physically remote from the distal zone and contained no marker microsphere radioactivity.

Flow values in endocardial and epicardial layers of each zone are based on data obtained from the innermost and outermost quarters of the myocardial wall, respectively. Transmural flow values, however, are based on activity of each isotope in all four quarters of each transmural cube. The value of transmural flow for each cube represents a weighted mean average of calculated flows for each of the four quarters comprising the cube. Tissue samples that exhibited control flow values greater than 2 SDs below mean flow for the distal zone were considered to be severely ischemic and thus were excluded from analysis.

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

**Determination of regional lactate metabolism.** Lactate concentration in arterial and AIV blood was determined by a spectrophotometric method with commercially available kits (Calbiochem Rapid Lactate Reagents, Calbiochem-Behring, La Jolla, CA). 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 frozen for subsequent analysis in duplicate. Regional extraction and production of lactate was calculated in standard fashion.

Concentrations of pyruvate in the anterior interventricular vein were measured with commercially available kits (Sigma Chemical Corp., St. Louis) by means of a spectrophotometric method. Blood samples were immediately deproteinized and centrifuged as described above and then stored at 4°C for subsequent analysis (always within 5 to 7 days after completion of the study). Values obtained for duplicate pairs varied by 5% or less in all cases. The ratio of [lactate]AIV to [pyruvate]AIV was used as an index of the redox state of the myocardium distal to the stenosis.

**Calculation of adenosine concentration in arterial plasma.** To estimate the molar concentration of adenosine in coronary arterial plasma during infusion of adenosine (400, 600 · min⁻¹), the following data were used: mean transmural blood flow distal to the stenosis during adenosine infusion (1.59 ± 0.40 ml·min⁻¹·g⁻¹), mean hematocrit (32 ± 3), mean distal zone weight (16 ± 2 g), and molecular weight of adenosine (267 g/M). Average calculated adenosine concentration in arterial plasma was 8.7 ± 10⁻⁶M during infusion of adenosine.

**Statistical methods.** The significance of mean group changes (vs control) in experimental parameters in response to infusion of drug was assessed by means of a blocked one-way analysis of variance and Dunnett’s test. Results were considered statistically significant p < .05. All values are expressed as mean ± SD.

**Validation protocols**

**Intracoronary adenosine (eight pigs without coronary stenoses).** Adenosine in micromolar concentrations blocks catecholamine-mediated increases in adenylate cyclase activity. In addition, higher adenosine concentrations (>10⁻⁶M), which stimulate intracellular P sites, are known to inhibit basal adenylate cyclase activity. Reduced levels of intracellular cyclic adenosine monophosphate resulting from decreased adenylate cyclase activity could in turn influence myocardial lactate metabolism as a result of inhibition of glycolysis. Thus, to test the hypothesis that adenosine could have influenced lactate metabolism independently of its effects on coronary flow distribution, eight additional pigs were studied as follows.

A plastic catheter, 1.4 mm in diameter, was placed in the proximal one-third of each animal’s left anterior descending coronary artery. The heart was paced at a constant rate throughout the study and coronary venous blood was sampled from a catheter inserted in the anterior interventricular vein (vide supra). After completion of instrumentation the animal was permitted to awake from general anesthesia and was then kept sedated with sodium thiampylal as described above.

Control measurements of hemodynamic parameters, regional myocardial blood flow, and arterial AIV lactate concentrations were made after the preparation had stabilized for at least 30 min. Next, adenosine was infused directly into the coronary circulation at 400 µg·min⁻¹ × 10 min via the infusion catheter in the animal’s left anterior descending coronary artery. At the end of this time repeat measurements of all experimental parameters were made. Following this the infusion was discontinued and 20 to 30 min later repeat measurements of all experimental parameters were obtained. The animal was then killed and the heart was removed for determination of microsphere activity.

**Effect of nifedipine on regional systolic function — direct assessment in four animals instrumented with ultrasonic length sensors.** The direct negative inotropic effects of nifedipine are well known. However, to demonstrate that these effects were operative under the conditions encountered in our study the following experiment was performed. Four pigs were instrumented with ultrasonic length sensors placed in endocardial layers of the heart that were perfused by the left anterior descending and circumflex coronary arteries. One week later, after the animal had recovered from surgery, it was returned to the laboratory for study.

Heart rate was controlled by atrial pacing throughout each experiment. Regional systolic function was evaluated with the aid of a laboratory PDP 11/40 computer system. An artificial coronary stenosis identical to the one described above was inserted into each animal’s left anterior descending coronary artery. Then, with the animal sedated (sodium thiampylol), control measurements of hemodynamic parameters and regional myocardial function were made at least 30 min after insertion of the stenosis. Nifedipine was then infused for 10 min at 50 µg·min⁻¹, as described above. Repeat measurements of hemodynamic parameters and regional systolic function were obtained. Nifedipine was discontinued and 20 to 30 min later a repeat set of control measurements was obtained. Measurements of regional myocardial blood flow, lactate metabolism, and oxygen consumption were also made at each measurement point in these experiments.

**Results**

**Nifedipine intervention (eight animals with coronary stenoses)**

**Hemodynamics (table 1).** Aortic and distal coronary mean pressure as well as aortic diastolic pressure declined significantly (p < .01), albeit modestly, vs control 1 in response to infusion of nifedipine. Rate-pressure product (heart rate × systolic aortic pressure) also

**CIRCULATION**
Hemodynamic effects (mean ± SD) of intracoronary nifedipine

<table>
<thead>
<tr>
<th></th>
<th>Control 1</th>
<th>Nifedipine</th>
<th>Control 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>102 ± 17</td>
<td>103 ± 18</td>
<td>101 ± 17</td>
</tr>
<tr>
<td>Aortic pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>108 ± 19</td>
<td>99 ± 23</td>
<td>104 ± 18</td>
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<tr>
<td>Systolic</td>
<td>128 ± 24</td>
<td>120 ± 28</td>
<td>126 ± 20</td>
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<tr>
<td>Diastolic</td>
<td>93 ± 19</td>
<td>84 ± 22</td>
<td>91 ± 17</td>
</tr>
<tr>
<td>Distal coronary pressure (mm Hg)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>71 ± 18</td>
<td>58 ± 16</td>
<td>70 ± 15</td>
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<tr>
<td>Diastolic</td>
<td>42 ± 18</td>
<td>36 ± 11</td>
<td>44 ± 13</td>
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<tr>
<td>Rate-pressure product (mm Hg-min⁻¹)</td>
<td>13190 ± 4360</td>
<td>12490 ± 4310 &amp; 12890 ± 3660</td>
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</tr>
<tr>
<td>Mean left atrial pressure (mm Hg)</td>
<td>5.6 ± 5.8</td>
<td>6.4 ± 5.3</td>
<td>3.6 ± 5.5</td>
</tr>
</tbody>
</table>

*p < .01 vs control 1; *p < .05 vs control 1.

Regional myocardial blood flow (table 2). Endocardial, epicardial, and transmural blood flow distal to the stenosis was reduced (p < .01) vs flow in the circumflex zone (1.68 ± 0.61, 1.58 ± 0.51, and 1.72 ± 0.60 ml·min⁻¹·g⁻¹, respectively). In response to nifedipine, endocardial flow distal to the stenosis did not change vs control 1. In four animals, endocardial flow increased modestly, while in four others it declined modestly. Epicardial flow distal to the stenosis increased significantly (p < .05) vs control 1 during infusion of nifedipine. The increase in epicardial flow in response to nifedipine resulted in a significant (p < .01) decline in the endocardial/epicardial flow ratio distal to the stenosis. Calculated coronary arteriolar resistance (mean distal coronary pressure/regional myocardial blood flow) did not change vs control 1 in the endocardium (61.4 ± 15.5 to 54.9 ± 29.6 mm Hg/ml·min⁻¹·g⁻¹) but declined (p < .05) in the epicardium (58.4 ± 14.7 to 36.3 ± 13.8 mm Hg/ml·min⁻¹·g⁻¹) in response to nifedipine. Both values turned to control 1 levels by the second control (53.5 ± 16.1 and 50.0 ± 13.0 mm Hg/ml·min⁻¹·g⁻¹, respectively).

Regional myocardial oxygen metabolism (figure 1). Regional myocardial oxygen extraction declined (p < .01) vs control 1 during infusion of nifedipine. Oxygen extraction by the myocardium increased after discontinuation of nifedipine but remained depressed (p < .05) vs control 1 levels. Myocardial oxygen consumption also declined significantly (p < .05) vs control 1 during nifedipine and then returned to control levels after discontinuation of the drug. There was no correlation between percent change in regional myocardial oxygen consumption (control 1 to nifedipine) and percent change in rate-pressure product. Although rate-pressure product at control 2 was comparable to that observed during infusion of nifedipine, myocardial oxygen consumption at the second control was increased (p < .05) vs the value measured with nifedipine.

Regional myocardial lactate metabolism (table 3; figure 2). As shown in table 3 and figure 2, in the group as a whole nifedipine failed to produce significant changes in any parameters of regional myocardial lactate or pyruvate metabolism. It also should be noted that the four animals in whom endocardial blood flow declined in response to nifedipine exhibited similar changes in lactate extraction and AIV lactate/pyruvate ratio as the four animals in whom endocardial flow increased.

*See National Auxiliary Publication Service document No. 04174 for 5 pages of supplementary material. Order from NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163. Remit in advance in U.S. funds only $7.75 for photocopies or $4.00 for microfiche. Outside the U.S. and Canada add postage of $4.50 for the first 20 pages and $1.00 for each additional page; $1.50 for microfiche postage.

*See footnote opposite.
Adenosine intervention (eight animals with coronary arterial stenoses)

Hemodynamics (table 4). Aortic pressures (mean, systolic, and diastolic), rate-pressure product, and mean left atrial pressure also remained constant during the study. In contrast both mean and diastolic distal coronary pressures declined significantly (p < .01) in response to adenosine and then returned to control levels after discontinuation of the drug.

Regional myocardial blood flow (table 5).* Under control conditions endocardial, epicardial, and transmural flow distal to the stenosis was reduced (p < .01) vs flow in the circumflex zone (1.77 ± 0.71, 1.63 ± 0.56, 1.74 ± 0.60 ml·min⁻¹·g⁻¹, respectively). The endocardial/epicardial flow ratio distal to the stenosis at control 1 also was reduced significantly (p < .05) vs that of the circumflex zone (1.08 ± 0.14 ml·min⁻¹·g⁻¹). In response to adenosine endocardial blood flow distal to the stenosis declined significantly (p < .05) vs control 1. Both epicardial and transmural blood flow in the distal zone increased vs control 1 during infusion of adenosine (p < .01 epicardium; p < .05 transmural). The distal zone endocardial/epicardial flow ratio declined substantially vs control 1 (p < .01) in response to adenosine. Coronary vascular resistance distal to the stenosis in both endocardium and epicardium decreased significantly (p < .01) vs control 1 during infusion of adenosine (60.9 ± 18.2 to 45.8 ± 17.8 and 57.0 ± 14.9 to 19.5 ± 2.4 ml·min⁻¹·g⁻¹, respectively) and then returned to control 1 levels after discontinuation of the drug (57.3 ± 21.0 and 52.5 ± 17.1 ml·min⁻¹·g⁻¹, respectively). Finally, circumflex zone flows failed to change significantly vs control 1 (1.77 ± 0.71, 1.63 ± 0.56, and 1.74 ± 0.60 ml·min⁻¹·g⁻¹, respectively, for endocardium, epicardium, and transmural) during infusion of adenosine to the distal zone (1.79 ± .65, 1.70 ± .47, and 1.83 ± .61 ml·min⁻¹·g⁻¹, respectively).

Regional myocardial oxygen metabolism (figure 1).* Infusion of adenosine distal to the stenosis resulted in a significant (p < .01) decline (vs control 1) in oxygen extraction by the myocardium. Although regional myocardial oxygen consumption did not change significantly vs control 1 during infusion of adenosine, it was depressed significantly (p < .05) vs control 2.

Regional myocardial lactate metabolism (table 6; figure 2). In contrast to results obtained with nifedipine, lactate extraction by the myocardium declined significantly (p < .01), albeit to a variable extent, vs control 1 in response to adenosine. It is important to note that in addition four of six animals went from net extraction at control 1 to net production in response to the infusion of adenosine. Each of these animals exhibited a reduction in endocardial blood flow in the distal zone in response to adenosine. Finally, the lactate/pyruvate ratio in AIV blood also increased significantly (p < .05) vs control 1 for the group as a whole during administration of adenosine.

Results of validation protocols

Influence of adenosine on regional lactate metabolism in animals (n = 8) without coronary arterial stenoses.* Under control conditions endocardial flows in the infusion zone (i.e., left anterior descending coronary arterial) were 1.69 ± 0.44 and 1.42 ± 0.35 ml·min⁻¹·g⁻¹, respectively. In response to intracoronary adenosine flows increased significantly (p < .01) in each layer; in the endocardium to 6.01 ± 2.90 ml·min⁻¹·g⁻¹ and in the epicardium to 5.75 ± 2.83 ml·min⁻¹·g⁻¹. Postin-

*See footnote on p 1051.

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**TABLE 3**

Effects (mean ± SD) of intracoronary nifedipine on regional myocardial lactate metabolism distal to stenosis

<table>
<thead>
<tr>
<th></th>
<th>Control 1</th>
<th>Nifedipine</th>
<th>Control 2</th>
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<tr>
<td>Arterial lactate (mM/l)</td>
<td>1.10 ± 0.55</td>
<td>1.13 ± 0.43</td>
<td>1.01 ± 0.36</td>
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<td>AIV lactate (mM/l)</td>
<td>0.95 ± 0.43</td>
<td>1.00 ± 0.26</td>
<td>0.86 ± 0.37</td>
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<td>Lactate extraction (%)</td>
<td>11.7 ± 16.8</td>
<td>18.2 ± 22.4</td>
<td>16.3 ± 12.1</td>
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<tr>
<td>AIV pyruvate (mM/l)</td>
<td>0.09 ± 0.03</td>
<td>0.08 ± 0.03</td>
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<tr>
<td>AIV lactate/pyruvate</td>
<td>10.6 ± 2.0</td>
<td>12.3 ± 2.3</td>
<td>11.2 ± 1.9</td>
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*See footnote on p 1051.
TABLE 4
Hemodynamic effects (mean ± SD) of intracoronary adenosine

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<th>Control 1</th>
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<tr>
<td>Heart rate (min⁻¹)</td>
<td>102 ± 17</td>
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<td>Mean</td>
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<td>Systolic</td>
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<tr>
<td>Diastolic</td>
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<td>Distal coronary pressure (mm Hg)</td>
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<tr>
<td>Mean</td>
<td>69 ± 19</td>
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<tr>
<td>Diastolic</td>
<td>42 ± 17</td>
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<td>Rate-pressure product  (mm Hg min⁻¹)</td>
<td>12690 ± 3740</td>
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<td>Mean left atrial pressure (mm Hg)</td>
<td>3.9 ± 4.8</td>
<td>5.2 ± 6.5</td>
<td>4.6 ± 6.3</td>
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</table>

*p < .01 vs control 1.

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FIGURE 2. Individual response of regional myocardial lactate extraction to nifedipine (NF50) and adenosine (Ado). Note the substantial decline in lactate extraction in response to adenosine in five of eight animals. In contrast, lactate extraction improved modestly in response to nifedipine in several animals and failed to deteriorate substantially in any. C₁ = control 1; C₂ = control 2.

fusion (i.e., control 2) flows were available for six of eight animals (data could not be obtained in the other two). In these animals flow values at control 2 did not differ significantly from those at control 1 (endocardium and epicardium 1.84 to 0.39 and 1.50 ± 0.48 ml·min⁻¹·g⁻¹, respectively).

Regional lactate extraction under control conditions was 38.0 ± 15.5%. In response to intracoronary adenosine there was a modest but significant reduction in regional lactate extraction (23.8 ± 7.1%; p < .05), but actual lactate production was not observed in any animal in response to adenosine. Furthermore, calculated regional lactate uptake (arterial-AIV lactate difference × transmural left anterior descending coronary arterial blood flow) under control conditions (0.051 ± 0.015 mM/min/100 g) actually increased in response to adenosine (0.137 ± 0.091 mM/min/100 g; p < .05). In contrast, in animals with coronary arterial stenoses lactate uptake under control conditions (0.028 ± 0.045 mM/min/100 g) was transformed to production during administration of adenosine (−0.041 ± 0.048 mM/min/100 g; p < .01); it did not change during infusion of nifedipine (0.021 ± 0.048 mM/min/100 g).

Influence of nifedipine on regional contractile function in the presence of coronary arterial stenosis (four animals with ultrasonic length sensors). Regional shortening fraction distal to the stenosis declined vs control levels (0.14 ± 0.10) in four of four animals in response to nifedipine (0.07 ± 0.06; p < .05). A continuous record from one of the animals used in the study is shown in figure 3. After discontinuation of the infusion of nifedipine regional systolic function returned to control levels in all animals (0.15 ± 0.09). In addition, it should be noted that distal zone end-systolic length increased vs control (11.3 ± 4.2 mm) in response to nifedipine (12.5 ± 1.9 mm; p < .05) in each animal. Finally, fractional shortening in the circumflex zone did not change vs control (0.16 ± 0.04) during infusion of nifedipine (0.15 ± 0.04).

Under control conditions endocardial and epicardial flows distal to the stenosis were 1.08 ± 0.34 and 1.42 ± 0.46 ml·min⁻¹·g⁻¹, respectively. In response to intracoronary nifedipine endocardial flow declined vs

TABLE 5
Effects (mean ± SD) of intracoronary adenosine on regional myocardial blood flow (ml·min⁻¹·g⁻¹) distal to stenosis

<table>
<thead>
<tr>
<th></th>
<th>Control 1</th>
<th>Adenosine</th>
<th>Control 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocardium</td>
<td>1.25 ± 0.53</td>
<td>1.07 ± 0.38</td>
<td>1.35 ± 0.46</td>
</tr>
<tr>
<td>Epicardium</td>
<td>1.31 ± 0.55</td>
<td>2.26 ± 0.59</td>
<td>1.46 ± 0.59</td>
</tr>
<tr>
<td>Transmural</td>
<td>1.36 ± 0.54</td>
<td>1.59 ± 0.40</td>
<td>1.49 ± 0.51</td>
</tr>
<tr>
<td>Endo/epi ratio</td>
<td>0.96 ± 0.19</td>
<td>0.47 ± 0.14</td>
<td>0.95 ± 0.18</td>
</tr>
</tbody>
</table>

*p < .01 vs control 1; #p < .05 vs control 1.

*See footnote on p 1051.
TABLE 6
Effects (mean ± SD) of intracoronary adenosine on regional myocardial lactate metabolism distal to stenosis

<table>
<thead>
<tr>
<th></th>
<th>Control 1</th>
<th>Adenosine</th>
<th>Control 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial lactate (mM/l)</td>
<td>1.26 ± 0.40</td>
<td>1.13 ± 0.45</td>
<td>0.92 ± 0.23</td>
</tr>
<tr>
<td>AIV lactate (mM/l)</td>
<td>1.09 ± 0.45</td>
<td>1.43 ± 0.55</td>
<td>0.80 ± 0.23</td>
</tr>
<tr>
<td>Lactate extraction (%)</td>
<td>12.7 ± 23.2</td>
<td>-40.6 ± 55.0</td>
<td>11.2 ± 21.1</td>
</tr>
<tr>
<td>AIV pyruvate (mM/l)</td>
<td>0.09 ± 0.02</td>
<td>0.08 ± 0.02</td>
<td>0.08 ± 0.02</td>
</tr>
<tr>
<td>AIV lactate/pyruvate</td>
<td>12.1 ± 3.2</td>
<td>17.1 ± 4.8</td>
<td>10.5 ± 2.5</td>
</tr>
</tbody>
</table>

control in each animal (0.81 ± 0.28 ml·min⁻¹·100 g⁻¹; *p < .01*). Epicardial blood flow distal to the stenosis increased vs control in two animals but declined slightly in two others (mean 1.34 ± 0.12 ml·min⁻¹·1g⁻¹). After discontinuation of nifedipine flows in each layer returned to preinfusion levels (0.92 ± 0.21 and 1.41 ± 0.23 ml·min⁻¹·g⁻¹ for endocardium and epicardium, respectively).

Regional myocardial oxygen consumption declined vs control levels (12.53 ± 1.89 ml/min⁻¹·100 g⁻¹) in each animal in response to nifedipine (8.33 ± 1.47 ml/min⁻¹·100 g⁻¹; *p < .02*). After discontinuation of nifedipine regional myocardial oxygen consumption returned to control levels (10.41 ± 1.53 ml/min⁻¹·100 g⁻¹). In contrast, regional lactate extraction by the myocardium did not change vs control (-3.1 ± 13.8%) in response to nifedipine (3.7 ± 4.3%). Individual values for lactate extraction at control were -1.0%, 10.9%, -22.9%, and 0.0%. During infusion of nifedipine the individual values were 2.4%, 2.4%, 0.0%, and 9.8%, respectively.

**Discussion**

The results of this study support the hypothesis that negative inotropic properties of an agent used to induce coronary vasodilatation distal to a severe coronary arterial stenosis may influence the extent of flow redistribution that occurs as well as the metabolic consequences of the redistribution. Thus, we observed that (1) nifedipine failed to consistently produce a redistribution of blood flow away from endocardium distal to a severe coronary stenosis and (2) that even when an endocardial steal was induced by the drug, metabolic evidence of worsening or de novo ischemia as assessed by regional lactate metabolism did not result (figure 4). In
contrast adenosine caused (1) a significant decline in endocardial blood flow distal to the stenosis, (2) a consistent although variable reduction in regional lactate extraction in each animal, and (3) metabolic evidence of de novo myocardial ischemia in four of six animals with net lactate extraction under control conditions.

Although adenosine has been reported to exert a negative inotropic effect on the myocardium,17-19 this property of the nucleoside has been demonstrated only in isolated preparations simultaneously exposed to exogenous catecholamine stimulation. Thus, while adenosine in physiologic concentrations (-10^{-5}M) may antagonize the increase in myocardial contractility ordinarily seen in response to catecholamine stimulation, it does not exert a primary negative inotropic effect when administered in the absence of exogenous catecholamines unless very high concentrations (10^{-3}M) of the nucleoside are used.17, 19 Such receptor concentrations, however, almost certainly could not have been achieved in the present study (see Methods). In addition, observations in our laboratory indicate that adenosine does not depress regional myocardial function, even in doses of 800 μg·min^{-1}.25 It is therefore reasonable to conclude that adenosine functioned only as a coronary vasodilator in the experiments described in this report.

Support for the concept that adenosine did not influence myocardial lactate metabolism independently of its effects on coronary flow distribution is provided by lactate results after adenosine was given to eight animals without coronary arterial stenoses. None of these animals exhibited lactate production in response to adenosine. Although net lactate extraction was reduced modestly by adenosine in control animals, actual myocardial uptake of lactate increased twofold in response to the nucleoside. The same dose of adenosine, it should be recalled, caused a marked reduction in lactate uptake with resulting de novo or increased net myocardial release of lactate in five of eight animals with stenoses (figure 2). Finally, previous studies17-19 have shown that the effect of adenosine on myocardial adenylate cyclase activity is inhibitory. Accordingly, one would predict that the nucleoside, if it had exerted a primary effect on myocardial adenylate cyclase activity, would have produced changes in myocardial lactate metabolism in a direction opposite that observed in the group with stenoses.

In the absence of any intrinsic inotropic effects on the myocardium adenosine, by inducing a redistribution of blood flow away from endocardium distal to a severe coronary stenosis, would be expected to either precipitate or worsen myocardial ischemia. The observation during administration of adenosine that lactate extraction decreased with de novo or increased production in five of eight animals and that coronary venous lactate/pyruvate ratio increased is consistent with this view. The fact that myocardial oxygen consumption distal to the stenosis tended to decline in response to the infusion of adenosine also suggests that endocardial steal induced by the drug resulted in ischemic impairment of regional myocardial function. Thus, when coronary vasodilation is induced by an agent that does not affect major determinants of myocardial oxygen demand, regional redistribution of blood flow away from endocardium distal to a severe coronary stenosis results in metabolic evidence of myocardial ischemia.

In contrast, for any given degree of endocardial steal induced by a drug with intrinsic negative inotropic effects, the metabolic consequences should be less severe. The effects of nifedipine on regional myocardial lactate metabolism in the four animals in whom a steal
occurred support this view. While endocardial flow declined in these animals to much the same extent as it did with adenosine infusion (figure 4), there was little, if any, change in regional lactate extraction or coronary venous lactate/pyruvate ratio. Data obtained in four additional animals studied with ultrasonic length sensors also failed to demonstrate any deterioration in lactate metabolism in response to nifedipine, even though endocardial flow declined in each. This point is further illustrated by data from four animals in which endocardial flow declined in response to both adenosine and nifedipine. We observed net lactate production in three of four of these animals during infusion of adenosine vs in none of four during infusion of nifedipine. Accordingly, while it would have been preferable to produce the same degree of coronary vasodilation with each drug in each animal, the fact that this could not be achieved does not invalidate the basic conclusions of the study. As shown in figure 4, comparable degrees of reduction in endocardial flow in response to both drugs were generally associated with worsening of lactate metabolism only after adenosine.

The fact that nifedipine exerted a negative inotropic effect on the myocardium is confirmed by the observed reduction in regional shortening fraction measured in four of four animals studied with ultrasonic length sensors. Since lactate metabolism failed to deteriorate during nifedipine (figure 4), it is unlikely that myocardial ischemia impaired regional shortening. Reduced myocardial oxygen consumption measured during nifedipine infusion also probably reflects, for the most part, a primary reduction in myocardial contractility induced by the drug. However, rate-pressure product declined slightly (6% to 8%), albeit significantly, during infusion of nifedipine, and thus we cannot exclude the possibility that this factor may also have contributed to a limited extent to reduced distal zone oxygen consumption.

One likely explanation for the observed differences in the propensity of the two drugs to cause regional steal could be related to the negative inotropic effects of nifedipine. Since nifedipine depresses myocardial contractility, its primary vasodilating effects may have been partially offset by an autoregulatory increase in coronary vascular tone. This response should predominate in epicardial layers distal to a stenosis where flow reserve is greatest. Thus, epicardial tone should be reduced to a lesser extent by nifedipine than by adenosine and as a result the tendency of nifedipine to cause regional steal should also be less. The patterns of flow distribution distal to the stenosis and calculated coronary vascular resistances during infusion of nifedipine and adenosine support this hypothesis. The tendency for nifedipine to partially antagonize its own vasodilating effects (particularly when reflexly mediated increases in myocardial contractility do not occur) may also help to explain, at least in part, its reduced potency as a coronary vasodilator in comparison with other drugs, such as adenosine.

Comparison of the results obtained in our study with those reported in other recent investigations in which nifedipine was administered to animals with stenosed but patent coronary arteries is difficult because of differences in experimental preparations, dose (one-fifth to one-half of that used in the present study), and route of administration of nifedipine. Furthermore, in these studies the effects of nifedipine on endocardial flow distal to the stenosis varied. In one report endocardial flow increased in response to nifedipine, while in the others it either decreased or remained the same. The variability in the response of endocardial flow to nifedipine and in its induction of regional steal in the setting of coronary arterial stenosis probably reflects the above-noted differences in experimental design.

In our study endocardial vasodilatory reserve was present distal to the stenosis, even though the endocardial flow was reduced under control conditions. This observation is consistent with results of previous studies, which have shown that coronary arteriolar tone may be greater than minimal despite the presence of reduced myocardial blood flow. Although the mechanism responsible for persistent endocardial vasodilatory reserve in the setting of reduced coronary blood flow is unknown, the presence of such reserve would serve to reduce the extent of flow redistribution that occurs in response to any given degree of epicardial vasodilation. This fact, however, is unlikely to have influenced the metabolic results of our study since the effect of residual endocardial flow reserve would apply equally to both nifedipine and adenosine interventions.

One methodologic aspect of the study that should be considered relates to the suitability of AIV blood samples for assessing changes in regional myocardial oxygen and lactate metabolism. It is recognized that these samples must contain a mixture of blood originating from both endocardial and epicardial layers of the heart distal to the stenosis and that they may be contaminated to a certain extent by blood originating from myocardium proximal to the stenosis. Accordingly, it is apparent that biochemical manifestations of endocardial ischemia distal to the stenosis may be diluted to some degree by (1) relative overrepresentation of nonischemic or only mildly ischemic distal zone
epicardial blood and (2) admixture of blood originating from normally perfused regions. The magnitude of this dilutional effect is probably small since direct inspection of the heart at the end of each study indicated that the majority of venous tributaries emptying into the anterior interventricular vein came from myocardium distal to the stenosis. Furthermore, since adenosine caused more epicardial vasodilation than nifedipine this fact would tend to minimize rather than accentuate measured biochemical differences that were observed in response to each drug. Accordingly, the distinct worsening in regional lactate metabolism observed in five of eight animals during administration of adenosine is noteworthy.

In conclusion the data obtained in the present study demonstrate that the extent of redistribution of flow and the metabolic consequences of coronary vasodilation distal to a severe coronary arterial stenosis may be influenced by the intrinsic negative inotropic effects of a drug used to produce vasodilation. As a corollary we may also infer from the data that, in the setting of a severe coronary arterial stenosis, redistribution of flow away from the endocardium may not result in de novo or worsening myocardial ischemia if major determinants of myocardial oxygen demand also are reduced at the same time.

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