Attenuation of exercise-induced myocardial ischemia in dogs with recruitment of coronary vasodilator reserve by nifedipine

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ABSTRACT There is now evidence that under resting conditions coronary vasodilator reserve exists even in the presence of myocardial ischemia. Therefore, we tested the hypothesis that a vasodilator reserve may exist during exercise so that during exercise-induced ischemia a reduction in coronary constrictor tone can be produced that attenuates the decreases in regional myocardial blood flow and function distal to a severe coronary stenosis without changing the determinants of myocardial oxygen demand. Nine dogs were instrumented with an ameroid constrictor on the left circumflex coronary artery and were studied 2 to 3 weeks later. During a control treadmill run, heart rate increased from 119 ± 20 to 225 ± 20 beats/min and peak left ventricular pressure increased from 144 ± 17 to 163 ± 28 mm Hg. Poststenotic subendocardial blood flow (measured by a microsphere technique) fell from 1.19 ± 0.36 to 0.51 ± 0.30 ml/min·g and systolic wall thickening (by sonomicrometry) decreased from 24.3 ± 5.8% to 6.0 ± 6.1%. During an identical run after nifedipine (10 μg/kg iv), systemic hemodynamics were not significantly altered. However, subendocardial blood flow was increased to 0.85 ± 0.51 ml/min·g (p < .05) and systolic wall thickening to 11.4 ± 7.8% (p < .01). We conclude that in this study the amelioration of exercise-induced myocardial ischemia was due to the recruitment by nifedipine of coronary vasodilator reserve.


RECENT STUDIES indicate that the long-held concept of maximum coronary vasodilation during myocardial ischemia is not correct. Experiments on regional myocardial blood flow in anesthetized dogs1,2 and pigs3 with significant ischemia at rest have shown that at coronary perfusion pressures as low as 35 mm Hg, associated with a marked reduction of myocardial blood flow, vasodilator reserve remained, i.e., intracoronary infusion of adenosine increased myocardial blood flow. However, the effect on regional contractile function of the recruitment of persistent vasodilator reserve in these studies remains controversial.2,3

Significant α₂-adrenergic coronary vasoconstriction mediates the enhanced poststenotic myocardial ischemia observed in anesthetized dogs during cardiac sympathetic nerve stimulation.4 A recent study from our laboratory suggests that coronary vasodilator reserve is also not exhausted when myocardial ischemia is induced in conscious dogs by production of a coronary stenosis during exercise, since ischemia is attenuated by intracoronary α₂-blockade under these conditions.5

In the present study, we sought the existence of persistent coronary dilator reserve during exercise-induced ischemia in a conscious dog preparation of chronic coronary stenosis6 and to determine its functional importance. Our hypothesis was that a reduction of coronary constrictor tone would improve ischemic myocardial blood flow and function, without changing the determinants of global myocardial oxygen demand. Nifedipine was used as a vasodilator since its powerful coronary vasodilator action is associated with minor negative chronotropic and inotropic effects7,8 and it can functionally antagonize α₂-adrenergic coronary vasoconstriction during sympathetically induced myocardial ischemia.9 Also, nifedipine is
widely used in the clinical treatment of effort angina pectoris.\textsuperscript{10–13}

Methods

Ten mongrel dogs weighing 20 to 35 kg were instrumented during sterile surgery. They were premedicated, anesthetized with sodium pentobarbital (30 mg/kg iv), and maintained during intrathoracic surgery by techniques described previously.\textsuperscript{6, 14} For measurement of left ventricular pressure a high-fidelity Doppler flow probe (Konigsberg P7) and a fluid-filled tube were inserted through a stab wound in the apex, and the micromanometer was calibrated and zeroed at the estimated level of the right atrium.\textsuperscript{6} Silicon rubber catheters were inserted into the left atrium for injection of microspheres and drugs and into the descending thoracic aorta for withdrawal of reference blood samples during microsphere injection.

The proximal segment of the left circumflex coronary artery was dissected free from surrounding tissue for a distance of 20 to 25 mm and instrumented with a single-crystal (10 MHz) Doppler flow probe (constructed in this laboratory). An ameroid constrictor was positioned distal to the flow probe. The ameroid constrictor was designed to induce gradual constriction of the left circumflex coronary artery and to stimulate the development of collaterals.\textsuperscript{13–17} The ameroid material (casein) was encased in a slotted stainless steel ring and was matched to produce a snug but nonconstrictive fit at the time of implantation. A hydraulic cuff occluder was placed distal to the ameroid constrictor to allow rapid, reversible coronary occlusions.

Regional myocardial function was analyzed by sonomicrometry (Trition Technology, San Diego). Two pairs of miniature ultrasonic crystals (5 MHz) were implanted in the left ventricular wall to measure regional myocardial wall thickness,\textsuperscript{18} care being taken to obtain proper orientation across the ventricular wall, which is important for reducing potential shear motion artifact.\textsuperscript{19} One pair of crystals was positioned in the left ventricular anterior wall perfused by the left anterior descending coronary artery to measure wall thickening in a nonischemic region. The other pair was placed in the left ventricular posterior wall, perfused by the left circumflex coronary artery, which was to be rendered ischemic. The proper position of this crystal pair within the potentially ischemic region was confirmed by the prompt development of wall dysfunction during a brief circumflex coronary artery occlusion during surgery. The appropriate alignment of each pair of crystals was confirmed by autoradiography. All subendocardial crystals were within the inner 2 mm of the left ventricular wall and were within the transmural projection of the larger, epicardial crystal. On histologic examination after trichrome staining, all dogs in this study had focal necrosis of part of the posterior papillary muscle, but no tissue damage was detected between the ultrasonic crystals in the ventricular free wall. The crystals were, however, surrounded by a fibrous rim (approximately 1 mm) of connective tissue, as described previously.\textsuperscript{20} One pair of crystals implanted to measure control wall thickness could not be used because the lead wires broke postoperatively.

After instrumentation the pericardium was left open, all wires and catheters were passed subcutaneously to the back of the animal and exteriorized between the scapulae, and the thoracotomy was repaired in layers. The pneumothorax was evacuated through a chest tube in the sixth intercostal space. Ampicillin (6.6 g/day) was administered for 3 days after surgery.

Measurement of regional myocardial blood flow. The reference withdrawal method was used to measure myocardial blood flow with radionuclide-labeled microspheres.\textsuperscript{21} Microspheres (15 μm diameter) labeled with one of the following radionuclides were used: \textsuperscript{153}Gd, \textsuperscript{141}Ce, \textsuperscript{51}Cr, \textsuperscript{111}In, \textsuperscript{52}Ru, \textsuperscript{95}Nb, or \textsuperscript{46}Sc (New England Nuclear). Due to the low number of spheres/milliliter, \textsuperscript{51}Cr was used exclusively for measurement of resting blood flow in the absence of ischemia to ensure that an adequate number of spheres was delivered. The other radionuclides were used randomly and injected in sufficient quantities (8 to 10 million spheres/1 to 2 ml injectate volume) into the left atrium. This resulted in greater than 4000 spheres in all tissue samples (0.5 to 1.0 g wet weight). The microspheres were suspended in 10% dextran with Tween 80 by the manufacturer, and the microsphere suspensions were vortex agitated before injection. Before injecting the first dose of microspheres, 2 ml of 10% dextran solution was injected through the left atrial catheter to test for sensitivity to this solution. The injection and sampling techniques used in this laboratory have been described.\textsuperscript{5, 20} Left ventricular pressure, left ventricular dimensions, and coronary blood flow velocity (in the dogs with an open artery at the time of the study) were monitored throughout the reference withdrawal period to confirm a steady state.

After the study dogs were killed by an overdose of intravenous pentobarbital. Each heart was then excised and all instrumentation was removed except the ultrasonic crystals. The hearts were then immersed in 10% formalin for 48 to 96 hr to facilitate sectioning. The atria, right ventricle, and epicardial fat were then removed, and the left ventricle was cut into transverse slices perpendicular to the long axis. The slices containing the anterior and the posterior left ventricular dimension gauges were divided into eight to 10 transmural sections. Each transmural block of tissue was then divided into three pieces of approximately equal thickness from the endocardial to the epicardial surface. While only the data from the two transmural plugs containing the dimension gauges are reported, all other transmural samples also were analyzed to confirm that the sample that included the ischemic zone crystal pair was representative of the central ischemic zone.

Myocardial samples and arterial reference blood samples were placed in a Packard Autogamma Spectrometer (Model 5912) to determine the quantity and energy level of gamma radiation, and myocardial blood flow normalized to the weight of each sample was calculated as described previously.\textsuperscript{5, 20, 22}

Experimental protocol. Starting 7 days after surgery, each dog was studied every 1 to 2 days while resting quietly on its right side on a table. The hydraulic occluder was inflated for 10 sec and the amount of reactive hyperemia after the release of this occlusion, as well as the degree of regional myocardial dysfunction during the occlusion, were determined to assess the severity of stenosis caused by the ameroid constrictor and the degree of collateral development.\textsuperscript{17} When the reactive hyperemia response was depressed or regional dysfunction was reduced, a treadmill exercise evaluation was performed. This consisted of a brief run on the treadmill at 8% to 10% inclination and a speed (10 to 15 km/hr) sufficient to elicit a heart rate of greater than 200 beats/min.

If there was sufficient regional ischemic dysfunction during exercise, i.e., a reduction of systolic wall thickening by more than 40%, the experiment was performed the same day. If sufficient dysfunction did not occur, the experiment was delayed to allow the ameroid constrictor to narrow further. The definitive exercise studies were performed at an average of 16 days after surgery (range 14 to 21 days). At this time the ameroid had completely occluded the left circumflex coronary artery in six of 10 dogs and rendered the posterior myocardium completely collateral dependent. However, regional systolic wall thickening at rest was normal in all dogs studied. As observed previously in the same experimental preparation,\textsuperscript{6, 23–25} dogs with completely occluded coronary arteries do not appear to differ significantly from the other dogs with respect to regional myocardial flow and function at rest and during exercise.

Control measurements, including the first microsphere injec-
tion, were made in dogs standing quietly on the treadmill. The dogs were well trained and quiet while control measurements were taken, and the observed heart rate (119 ± 20 beats/min) undoubtedly reflected anticipation of running. The dogs were run at a predetermined speed and inclination for 4 to 5 min (range). Once a steady state was achieved, confirmed by a stable left ventricular pressure and a stable decrease in posterior wall thickening, a second microsphere injection was performed and the run continued until the 2 min arterial reference withdrawal was completed. The dog was then kept on the treadmill for 30 min to record the recovery from exercise. The treadmill exercise was repeated 3 hr later, with the same speed, inclination, and exercise duration. The reproducibility of hemodynamic responses to the same exercise protocol after 3 hr has been validated in our laboratory previously.8

Fifteen to 20 min before the second treadmill exercise bout, nifedipine (10 μg/kg) was infused into the left atrial catheter as a bolus. Nifedipine (10 mg) was dissolved in 15 ml polyethylene glycol, 15 ml ethyl alcohol, and 70 ml distilled water and protected from light. Intracoronary injection of 1 ml of the pure vehicle has been shown to have no detectable hemodynamic effect; in two preliminary experiments intravenous injection of 3 ml of the pure vehicle also induced no detectable hemodynamic effect. The third microsphere injection was administered to dogs at rest 15 min after the administration of nifedipine, after transient hypotension and reflex tachycardia had subsided. In a previous study by Bache and Tockman26 the same dose of nifedipine was demonstrated to be without any effect on resting coronary blood flow, heart rate, or blood pressure 15 min after its administration, whereas the anischemic effect on myocardial blood flow distribution persisted for at least 30 min. We chose this relatively low dose and this timing of administration to avoid major changes in systemic hemodynamics. The fourth microsphere injection was made during the run with nifedipine, once a steady state had been achieved.

Data analysis. Recordings of each study were made on a Brush forced-ink recorder and on magnetic tape for later playback and computation. The systemic hemodynamic variables analyzed were heart rate, left ventricular peak systolic and end-diastolic pressures, and peak positive and negative dP/dt. The double product (peak left ventricular systolic pressure × heart rate) was also calculated. Regional myocardial wall thickness in the anterior and posterior left ventricular walls were analyzed at end-diastole and end-systole (defined as the time of maximal systolic wall thickness within 20 msec before peak negative dP/dt) according to the method of Theroux et al.27 Wall thickening during systole was calculated as the percent change from end-diastolic wall thickness. In addition, the mean systolic wall thickening velocity was determined. Mean circumflex coronary arterial blood flow velocity was measured in four dogs with an open artery at the time of the study.

Hemodynamic and dimension data were digitized from magnetic tape with a computer system (PDP 11/03). Twenty consecutive cardiac cycles were averaged for each observation. Data from one dog that exhibited a significant decrease in heart rate during exercise after nifedipine were not included in the statistical analysis. The criteria for excluding data from this dog were derived from a previous reproducibility study in which differences in hemodynamic responses to two identical runs completed 3 hr apart were determined.6 This dog showed a typical improvement of ischemic regional myocardial blood flow and function during the nifedipine run. However, since a reduction in exercise heart rate per se has been demonstrated to attenuate exercise-induced ischemia in this experimental preparation,25 we chose to eliminate data from this dog to focus on vasodilator reserve rather than on effects of nifedipine that might be secondary to hemodynamic responses. The difference in systemic hemodynamics during the control and the nifedipine runs in the remaining nine dogs was less than the mean ± 1SD of the differences in the reproducibility study.

Data are presented as mean values with their SDs. Statistical analysis was performed with a two-way analysis of variance for repeated measurements.28 When there was a significant overall effect, Tukey’s test was applied to compare single mean values. A two-dimensional analysis of regional systolic wall thickening vs regional subendocardial blood flow was performed with Hotelling’s multivariate t test for two variables. To facilitate statistical analyses, hemodynamic and dimension data were analyzed at the same time points for which myocardial blood flow data were available: resting control, control steady-state exercise, resting control after nifedipine, and steady-state exercise after nifedipine. Although not used in the statistical analysis, additional time points during the runs were compared to confirm the existence of hemodynamic and functional steady states to validate the microsphere determination of myocardial blood flow. A p value of .05 or less was considered to indicate a significant difference between mean values.

Results

A representative example of original recordings of systemic hemodynamics and regional myocardial dimensions during a control run and a run after administration of nifedipine is shown in figure 1.

Systemic hemodynamics. During the control run, heart rate, peak left ventricular systolic pressure, and left ventricular dP/dt immediately increased; maximum responses occurred within 10 sec. Subsequently these values decreased, reaching a steady state after 1 to 2 min, but were still substantially elevated compared with the resting values (table 1). Left ventricular end-diastolic pressure and the double product were also markedly increased.

After the bolus infusion of nifedipine (10 μg/kg iv) there was an immediate decrease in blood pressure and a reflex tachycardia. However, these responses subsided within 10 to 15 min. Neither the steady-state hemodynamic resting values nor the hemodynamic responses to exercise were different during the control and nifedipine runs (table 1). In the four dogs with an open left circumflex coronary artery at the time of the study, coronary arterial blood flow velocity increased to a similar extent during the control and the nifedipine run (table 1).

Regional myocardial function. During the control run, systolic wall thickening in the ischemic region decreased by 76% from the resting value at the time regional myocardial blood flow was measured with microspheres (table 2). Mean systolic wall thickening velocity also decreased (table 2). Systolic wall thickening and mean systolic wall thickening velocity of the control region were significantly increased.

After nifedipine, resting function in both the control and the potentially ischemic myocardium were un-
changed. However, during the run systolic wall thickening in the ischemic region was reduced by only 51% from the resting value, a significant (p < .01) improvement compared with that during the control run (table 2). Mean systolic wall thickening velocity was also significantly higher than during the control run (table 2). Function in the control region during the nifedipine run was increased to the same extent as during the control run.

Regional myocardial blood flow. Average blood flow data from the ischemic and control regions are presented in figure 2 and table 3. At rest there was no difference in myocardial blood flow in the potentially ischemic posterior and the control anterior wall. During the control run, in the ischemic region a marked transmural gradient developed, with a decrease in subendocardial and midmyocardial blood flow and an increase in subepicardial blood flow (figure 2; table 3). Myocardial blood flow in the control region increased substantially in all transmural layers.

**TABLE 1**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Nifedipine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>119 ± 20</td>
<td>225 ± 20^b</td>
</tr>
<tr>
<td>PLVSP (mm Hg)</td>
<td>144 ± 17</td>
<td>163 ± 28^A</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>14.8 ± 5.0</td>
<td>30.5 ± 7.0^b</td>
</tr>
<tr>
<td>+ dP/dt (mm Hg/sec)</td>
<td>3322 ± 594</td>
<td>5150 ± 827^b</td>
</tr>
<tr>
<td>− dP/dt (mm Hg/sec)</td>
<td>2490 ± 893</td>
<td>3352 ± 460^b</td>
</tr>
<tr>
<td>DP (mm Hg × bpm × 100)</td>
<td>176 ± 42</td>
<td>372 ± 80^b</td>
</tr>
<tr>
<td>CBFV (n = 4; cm/sec)</td>
<td>32.7 ± 14.8</td>
<td>44.0 ± 15.8^A</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

HR = heart rate; PLVSP = peak left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; DP = double product; CBFV = mean coronary blood flow velocity.

^p < .05; ^b < .01 exercise vs rest. None of the exercise values after nifedipine is significantly different from control exercise values.
TABLE 2
Regional myocardial dimensions during control exercise and exercise after nifedipine

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 9)</th>
<th>Nifedipine (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDT (mm)</td>
<td>10.5 ± 2.0</td>
<td>10.6 ± 1.7</td>
</tr>
<tr>
<td>EST (mm)</td>
<td>13.0 ± 2.5</td>
<td>13.1 ± 2.5</td>
</tr>
<tr>
<td>ST (%)</td>
<td>24.3 ± 5.8</td>
<td>22.8 ± 5.1</td>
</tr>
<tr>
<td>MSTV (mm/sec)</td>
<td>13.2 ± 4.7</td>
<td>13.4 ± 5.0</td>
</tr>
</tbody>
</table>

Control wall

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDT (mm)</td>
<td>10.3 ± 2.3</td>
<td>10.9 ± 2.3</td>
</tr>
<tr>
<td>EST (mm)</td>
<td>13.7 ± 2.4</td>
<td>14.2 ± 2.3</td>
</tr>
<tr>
<td>ST (%)</td>
<td>34.0 ± 12.2</td>
<td>32.7 ± 15.1</td>
</tr>
<tr>
<td>MSTV (mm/sec)</td>
<td>17.5 ± 4.7</td>
<td>18.0 ± 5.7</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

EDT = end-diastolic thickness; EST = end-systolic thickness; ST = systolic thickening; MSTV = mean systolic thickening velocity.

*p < .05; **p < .01 exercise vs rest.
†p < .01 nifedipine vs control.

Fifteen min after administration of nifedipine, when transient hypotension and tachycardia had subsided, there was no change in myocardial blood flow at rest in either the ischemic or the control regions. In the ischemic zone, blood flow during the run after administration of nifedipine was higher in all transmural layers; this difference from the control run was significant for subendocardial, midmyocardial, and mean transmural blood flow, but not for subepicardial blood flow, and subendocardial and midmyocardial values were not different from those at rest (figure 2; table 3). Subendocardial blood flow in the ischemic zone was markedly increased in one of the dogs studied (from 0.54 to 1.79 ml/min·g), and it was essentially unchanged in two dogs; in the remaining six dogs there was a moderate increase, as reflected in the mean values. When data from the dog with the most pronounced improvement in blood flow were excluded from the statistical analysis, a significant increase in subendocardial blood flow was still noted (p = .045 vs .012).

In the control zone, there was a slightly more pronounced but not significantly different increase in blood flow to all transmural layers.

Relationship between regional myocardial blood flow and function. The relationship between regional subendocardial blood flow and systolic wall thickening in the

FIGURE 2. Transmural distribution of regional myocardial blood flow in the ischemic (left) and control (right) regions at rest and during exercise. At rest, blood flow distribution in the ischemic area was not different from that in the control area. During the control run, however, myocardial blood flow in the control region increased in all transmural layers, whereas in the ischemic region a marked transmural gradient with a decrease in subendocardial blood flow and an increase in subepicardial blood flow developed. Nifedipine did not change myocardial blood flow at rest in either region. However, the decreases in blood flow to the subendocardium and the midmyocardium of the ischemic region during exercise were significantly attenuated. Open circle = control rest; closed circle = control exercise; open triangle = nifedipine rest; closed triangle = nifedipine exercise; ENDO = subendocardium; MID = midmyocardium; EPI = subepicardium; TM = mean transmural myocardial blood flow. Bars indicate 1 SD. *p < .05; **p < .01 exercise vs rest. †p < .05 nifedipine vs control.
TABLE 3
Regional myocardial blood flow during control exercise and exercise after nifedipine (n = 9)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Nifedipine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
</tr>
<tr>
<td>Ischemic wall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo</td>
<td>1.19 ± 0.36</td>
<td>0.51 ± 0.30A</td>
</tr>
<tr>
<td>Mid</td>
<td>1.39 ± 0.45</td>
<td>0.80 ± 0.43A</td>
</tr>
<tr>
<td>Epi</td>
<td>1.05 ± 0.34</td>
<td>1.45 ± 0.73</td>
</tr>
<tr>
<td>TM</td>
<td>1.20 ± 0.37</td>
<td>0.92 ± 0.43</td>
</tr>
<tr>
<td>Control wall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo</td>
<td>1.35 ± 0.35</td>
<td>3.10 ± 1.25A</td>
</tr>
<tr>
<td>Mid</td>
<td>1.28 ± 0.29</td>
<td>2.93 ± 0.95B</td>
</tr>
<tr>
<td>Epi</td>
<td>1.03 ± 0.38</td>
<td>2.34 ± 0.61B</td>
</tr>
<tr>
<td>TM</td>
<td>1.22 ± 0.30</td>
<td>2.78 ± 0.91B</td>
</tr>
</tbody>
</table>

Data are mean ± SD, ml/min·g.

Endo = subendocardial blood flow; Mid = midmyocardial blood flow; Epi = subepicardial blood flow; TM = mean transmural blood flow.

*p < .05; **p < .01 exercise vs rest.

Ischemic region is graphically presented in figure 3. During the control run there was a marked decrease in subendocardial blood flow associated with a similarly pronounced decrease in systolic wall thickening. Resting values after administration of nifedipine were not different from control. However, during the run after nifedipine an increase in subendocardial blood flow was associated with an increase in systolic wall thickening.

Discussion

The major finding of this study is that a significant coronary vasodilator reserve exists during exercise-induced myocardial ischemia. When this vasodilator reserve is recruited by nifedipine, an improvement in ischemic regional myocardial blood flow and function during exercise ensues.

In none of the dogs reported did nifedipine in the dose used attenuate exercise-induced increases in heart rate, left ventricular pressure, or regional myocardial function in the nonischemic region. This finding is in contrast to findings with all other pharmacologic interventions previously investigated in this experimental preparation of exercise-induced regional myocardial ischemia, including isosorbide dinitrate, 30 β-blockade with atenolol, 25 and calcium-channel blockade with verapamil 31 and diltiazem. 6 Since in this study nifedipine did not affect the responses of systemic hemodynamics during exercise, its effects can be attributed exclusively to coronary or coronary collateral vasodilatation. Even though nifedipine did not affect the responses of systemic hemodynamics (and therefore presumably the determinants of myocardial oxygen consumption), the magnitude of the improvement in ischemic regional myocardial function induced by nifedipine was comparable to that produced by atenolol, verapamil, or diltiazem when administered alone, although less marked than that with a combination of these agents. 24, 25

Conflicting results have been reported on the ability of nifedipine to increase blood flow and function of an ischemic myocardial region. Intravenous nifedipine has been shown to increase myocardial blood flow distal to a complete coronary occlusion, 32, 33 but others

FIGURE 3. Relationships between subendocardial blood flow and systolic wall thickening in the ischemic region. In the control run, a significant reduction in subendocardial blood flow was associated with a similarly pronounced decrease in regional myocardial function. Nifedipine did not affect regional myocardial blood flow or function at rest. However, in the run after nifedipine there was significant improvement in both flow and function. Bars indicate 1 SD.
have shown no effect on ischemic myocardial blood flow at a coronary perfusion pressure of 25 mm Hg, whereas ischemic myocardial segment shortening was observed to increase. Intracoronary nifedipine may even depress ischemic myocardial function without changing regional myocardial blood flow. Nifedipine has also been reported to increase subepicardial flow without changing subendocardial flow, while decreasing regional oxygen consumption distal to an 82% coronary obstruction in sedated swine. Apart from a possible direct negative inotropic effect of intracoronary nifedipine on ischemic myocardium, the two major determinants of the action of the intravenous drug are the degree of ischemia, and thus the degree to which coronary vasodilator reserve is already exhausted, and the degree of nifedipine-induced hypotension and the associated decrease in coronary perfusion pressure. With respect to these two determinants, a beneficial effect of intravenous nifedipine on ischemic myocardial blood flow and function during exercise was to be expected in our study, since (1) the degree of ischemia in the control run was only moderate (subendocardial blood flow 0.51 ± 0.30 ml/min·g) due to extensive collateral development during the gradual closure of the ameroid constrictor, and (2) coronary perfusion pressure was probably not decreased in the nifedipine run, since systolic pressure was unchanged and the transient hypotensive effect had subsided 15 min after bolus infusion of nifedipine. A direct negative inotropic effect of nifedipine was not observed at rest or during exercise in either the control or ischemic regions.

The nifedipine-induced increase in regional myocardial blood flow during exercise does not appear to be based on nonspecific coronary vasodilatation, since myocardial blood flow at rest 15 min after nifedipine was not increased. Recovery of heart rate and blood pressure responses as well as an unchanged coronary blood flow 15 min after administration of the same dose of nifedipine as used in our study (10 µg/kg iv) have previously been demonstrated by Bache and Tockman. These authors found that nifedipine limits postocclusive reactive hyperemia and also inhibits transmural redistribution of flow from the subendocardium to the subepicardium in the presence of a severe coronary stenosis; these effects were independent of changes in myocardial oxygen consumption. We did not find a large transmural redistribution of myocardial blood flow by nifedipine during exercise-induced ischemia (endocardial/epicardial ratio 0.39 ± 0.22 during the control run vs 0.53 ± 0.29 in the run after nifedipine, p = NS). However, the increase in blood flow to all transmural layers was significant only in the subendocardium and the midmyocardium, with a favorable flow redistribution.

The site and mechanism underlying the increase in regional myocardial blood flow during exercise after administration of nifedipine remain speculative. Nifedipine can induce a substantial dilation of large epicardial coronary arteries, and this effect persists even after the systemic hemodynamic effects and the increase in coronary blood flow have subsided. Such large vessel dilation proximal and distal to the ameroid constrictor may have been involved in the four dogs with an open coronary artery on the day of the study, but it cannot explain the increase in ischemic zone myocardial blood flow in the five dogs with coronary occlusion and a completely collateral-dependent myocardium in which similar blood flow increases occurred.

A possible mechanism underlying the beneficial effects of nifedipine in our study is a functional antagonism against α-adrenergic constrictor tone in the ischemic coronary vasculature. Such an effect may persist after the initial coronary and peripheral vasodilatation have subsided, similar to the favorable transmural blood flow redistribution observed by Bache and Tockman and the large vessel coronary vasodilatation observed by Vatner and Hintze. Significant α-adrenergic vasoconstriction in response to the intracoronary infusion of norepinephrine has been observed by Buffington and Feigl in the inner and outer myocardial layers of anesthetized dogs when coronary perfusion pressure was reduced to 50 mm Hg, and significant α-adrenoceptor-mediated coronary constriction tone has been shown in the presence of myocardial ischemia in anesthetized dogs during cardiac sympathetic nerve stimulation and in conscious dogs during exercise. Also, nifedipine has been shown to antagonize α-adrenergic coronary vasoconstriction and to attenuate ischemic myocardial dysfunction in anesthetized dogs during cardiac sympathetic nerve stimulation. The hypothesis of a functional antagonism of nifedipine to α-adrenergic coronary constriction during ischemia is supported by our finding that nifedipine did not increase myocardial blood flow at rest, but only during exercise when sympathetic tone was high. In addition, it should be emphasized that previous studies demonstrating vasodilator reserve in the presence of myocardial ischemia have been performed in anesthetized preparations, in which sympathetic tone is also high.

Whether the prevention of α-adrenergic coronary constriction by nifedipine occurs in the ischemic terminalsegmental vascular bed or in the coronary collaterals cannot be determined in our study. However, both sites of
action appear to be possible. The prevention of α2-adrenergic poststenotic vasoconstriction during cardiac sympathetic nerve stimulation by the intracoronary infusion of nifedipine distal to a coronary stenosis indicates an effect in the ischemic terminal vascular bed. On the other hand, calcium-channel blockade with intravenous diltiazem can prevent sympathetic vasoconstriction of normal and diseased epicardial coronary arteries in patients during isometric handgrip exercise, and collaterals could be affected as well at their origin from these epicardial vessels.

The improved myocardial relaxation and diastolic compliance produce by nifedipine could have been a possible contributing factor to the increase in myocardial blood flow by increasing the perfusion pressure gradient to the subendocardium. However, there were no differences in left ventricular end-diastolic pressure or peak negative dP/dt during the control and nifedipine runs (table 1). No effect of sublingual nifedipine on diastolic myocardial properties, apart from its peripheral arterial dilator action, has been reported in patients with impaired baseline ventricular function, and impaired early relaxation has been reported in patients with coronary artery disease. Nevertheless, mechanisms other than prevention of adrenergic vasoconstriction may underly the presence of vasodilator reserve during exercise-induced myocardial ischemia.

In conclusion, we have demonstrated the presence of significant coronary vasodilator reserve during exercise-induced myocardial ischemia in conscious dogs and that nifedipine can recruit this reserve and induce an improvement of ischemic regional myocardial blood flow and function without major effects on systemic hemodynamics. Although some studies suggest that the coronary vasodilator effect of nifedipine at rest may be less pronounced in man than in dog, it could nevertheless be effective in preventing sympathetically mediated increases in coronary tone.

We are grateful to Elizabeth Gilpin for the statistical analyses and to Dr. Thomas Widmann for the development and maintenance of the data reduction program. We also thank Margaret Hill, Denise Jio, Kathy Kohilhaas, and Sergio Martinez for their technical assistance.

References

26. Bache RJ, Tockman BA: Effect of nitroglycerin and nifedipine on...
35. Lamping KA, Gross GJ: Differential effects of intravenous vs. intracoronary nifedipine on myocardial segment function in ischemic canine hearts. J Pharmacol Exp Ther 228: 28, 1984
44. Kjekshus JK: Mechanism for flow distribution in normal and ischemic myocardium during increased ventricular preload in the dog. Circ Res 33: 489, 1973
Attenuation of exercise-induced myocardial ischemia in dogs with recruitment of coronary vasodilator reserve by nifedipine.
G Heusch, B D Guth, R Seitelberger and J Ross, Jr

Circulation. 1987;75:482-490
doi: 10.1161/01.CIR.75.2.482

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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