The Effects of Nifedipine on Myocardial Blood Flow and Contraction During Ischemia in the Dog

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SUMMARY Nifedipine has been proposed as an agent to preserve viability and function of ischemic myocardium. We studied 23 open-chest dogs that underwent carotid-to-left anterior coronary artery perfusion with flow probe and perfusion pressure monitoring. Segment length was measured with ultrasonic crystals in the ischemic and nonischemic endocardium. Myocardial blood flow was measured with radioactive microspheres. Partial coronary occlusion was performed to 25 mm Hg diastolic perfusion pressure. Ten dogs received intracoronary nifedipine, 10 μg, and 13 dogs received i.v. nifedipine, 3 μg/kg/min. Nifedipine resulted in an increase in segmental shortening in both groups, but nonischemic zone shortening did not change in either group. Nifedipine did not affect myocardial blood flow in the ischemic zone, but increased flow in the nonischemic zone in the group that received i.v. nifedipine. Thus, nifedipine appears to have a direct beneficial effect on ischemic myocardium.

THE CALCIUM ANTAGONIST nifedipine has been proposed as an agent that may preserve myocardial function and structure during ischemia by preventing or attenuating calcium accumulation in mitochondria.1-8 It has also been suggested that nifedipine increases collateral blood flow to ischemic myocardium.2-8 However, nifedipine has negative inotropic effects on myocardial muscle strips in vitro.4 Preliminary in vivo studies in the dog suggest that nifedipine improves myocardial contraction during ischemia.8 Thus, the interrelationships between the effects of nifedipine on myocardial blood flow and function are unclear. In the present study, this relationship was investigated in open-chest dogs undergoing partial coronary occlusion, using tracer microspheres to assess myocardial blood flow and ultrasonic crystals to assess contraction.

Methods
Experimental Preparation
Twenty-three dogs were anesthetized with pento-barbital and placed on a Harvard respirator. Arterial blood gases were monitored and PO2 was maintained between 80 and 100 mm Hg and pH between 7.36 and 7.44. A #7F catheter was inserted into the right femoral artery and advanced to the thoracic aorta for arterial pressure monitoring. A stiff 2-mm-internal-diameter catheter was inserted into the left femoral artery and advanced to the abdominal aorta for blood withdrawal. A catheter was also inserted into the right femoral vein for i.v. infusions.

A thoracotomy was performed in the fifth left intercostal space and the heart was supported in a pericardial cradle. A #7F catheter was advanced into the left atrial appendage for microsphere injection (fig. 1). A 10-cm-long, 14-gauge, stiff catheter was passed into the left ventricle through the apex to record left ventricular pressure and dP/dt. A 5-10 cm segment of the left common carotid was exposed. After heparin was administered, the left anterior descending coronary artery was isolated at the level of the first or second diagonal branch, ligated and an arteriotomy was performed. A 14-gauge steel cannula was inserted into the left anterior descending artery, tied securely and continuously perfused from the left common carotid artery through plastic tubing with a minimal internal diameter of 2 mm. Coronary perfusion pressure was monitored with a Statham P23Db strain gauge and coronary flow with a 2-mm-internal-diameter electromagnetic flow probe (Micron Instruments). The time from ligation of the left anterior descending coronary artery to establishment of cannula perfusion averaged 50 seconds; dogs in which cannulation took more than 120 seconds were excluded from further study.

During cannula perfusion of the left anterior descending coronary artery, pressures at the tip of the cannula and in the tubing were identical. In addition, diastolic perfusion pressure in the tubing was identical to aortic perfusion pressure at flows up to 100 ml/min. The cannula system was tested in vitro with warm blood pumped through the system at rates from 1.1-46 ml/min; pressures were monitored in the proximal cannulation system and at the cannula tip, but no pressure gradient was observed.

The presence of coronary reserve was determined using a 10-second total occlusion followed by reperfusion. All dogs with less than 100% reactive hyperemia were rejected as having either inadequate coronary reserve or stenosis in the cannula system.

Placement of Ultrasonic Crystals
One pair of 2-mm ultrasonic crystals was placed in the nonischemic endocardium and one pair was placed in the ischemic endocardium (fig. 1). The crystals in

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Figure 1. Experimental preparation showing the carotid-to-left anterior descending coronary artery cannulation system, the port for drug injection, the electromagnetic flow probe and the screw-clamp constrictor. Perfusion pressure is measured distal to the constrictor. The potentially ischemic zone (hatched) is colored by the Evans blue dye. The ring of myocardium from which tissue samples are taken for blood flow analysis is indicated by the parallel broken lines. Both nonischemic zone and ischemic zone crystals are within this ring. Nonischemic zone and ischemic zone crystals and samples of tissue for blood flow were at least 1 cm from the border between nonischemic and ischemic zones. Ao = aorta; AoP = aortic pressure; CBF = coronary blood flow probe; CXL = circumflex coronary artery; LA cath = left atrial catheter; LAD = left anterior descending coronary artery; IZ crystal = ischemic zone crystal pair; NZ crystal = nonischemic zone crystal pair; LVP = left ventricular pressure; Perf P = perfusion pressure; PA = pulmonary artery.

Microsphere Technique

Microspheres (9-μm diameter) labeled with 125I, 141Ce, 85Sr or 45Sc (3M Company) were used to measure myocardial blood flow. Microspheres were suspended in saline with a drop of Tween-80, agitated in an ultrasonic bath for at least 15 minutes and shaken in a vortex whirler before injection. Two to 3 million microspheres in 8 ml of saline were injected into the left atrium over 15-20 seconds, followed by a 4-ml saline flush. Starting before the injection of microspheres, blood was withdrawn from a femoral artery at 7.5 ml/min with a Harvard pump. Blood withdrawal was continued for 1 minute after completion of the saline flush to obtain a reference blood flow.

Experimental Protocol

The preparation was allowed to stabilize for at least 15 minutes after cannulation. Partial coronary occlusion was performed by occluding the cannulation tubing with a screw clamp device to a minimal diastolic perfusion pressure of 25 mm Hg. The preparation was allowed to stabilize for 5 minutes and then a first set of microspheres of one isotope was given. The dogs were randomized into two groups. Dogs in group 1 (n = 13) were given i.v. nifedipine, 3 μg/kg/min, for 15 minutes and then a second set of microspheres was given to assess the effects of nifedipine in the whole preparation. Dogs in group 2 (n = 10) were given 10 μg of intracoronary nifedipine through the coronary cannula to determine the effects of nifedipine on the subserved ischemic myocardium. Two minutes later (the time of near-maximal coronary flow in unoccluded arteries as measured with the flow probe in another series of dogs), a second set of microspheres of a different isotope was given. The time between the two microsphere injections in this group was less than 5 minutes. By giving two sets of microspheres of different energy levels, the blood flow before and after nifedipine administration can be determined.

Tissue Preparation

After the second microsphere injection, Evans blue dye was injected into the coronary cannula by handheld syringe with sufficient pressure to stain the myocardium but insufficient to fill the intercoronary collaterals. The dog was sacrificed; before removal of the crystals, their position was noted. The heart was washed, dried, stuffed with gauze and wrapped with aluminum foil and frozen. The heart was sectioned while still frozen to facilitate accurate cutting. A transmural ring of myocardium 2-3 cm wide was cut perpendicular to the border between blue-stained ischemic tissue and unstained nonischemic tissue (fig. 1). A section of myocardium was taken from the remote normal zone. The ring was cut at the blue border with care to keep all the blue-stained tissue on the ischemic side. A 1-cm sample of myocardium was taken on the ischemic side (border ischemic sample), followed by a 1-cm central ischemic sample. In all dogs, the central ischemic sample contained the crystal tracts. All samples were divided into endocardial, midmyocardial and epicardial thirds.

The tissue samples were weighed and counted along with the blood samples, pure isotope standards and a background tube in a Beckman 8000 well gamma counter for 10 minutes each. Myocardial blood flow was then determined by the method of Heymann et al.

Data Recording and Analysis

Hemodynamic data and myocardial shortening were obtained on an Electronics for Medicine VR-16 recorder. Myocardial shortening (%ΔL) was
FIGURE 2. Sample recordings showing the method for calculation of shortening. The panel on the left represents the control period, the panel on the right after an intervention. The top tracing is the ECG, the next is segment length representing the distance between the pair of crystals, and the straight line of 0-mm crystal separation. Then comes the first derivative of left ventricular pressure (LVP) with respect to time (dP/dt) and left ventricular pressure. End-diastolic length (EDL) and end-systolic length (ESL) are measured from the zero line to segment length line, and these lengths are timed from dP/dt according to the method of Theroux et al.8 Percent shortening was calculated as shown. Shortening was normalized to the fraction of the control period as shown. c = control; % ΔL = percent segment shortening; N% ΔL = fraction of control period shortening.

calculated by the method of Theroux et al.* and normalized to the control period (N%ΔL) (fig. 2). All data are expressed as mean ± SD. Differences for any variable of subgroups within the two groups described above were analyzed by a two-way analysis of variance by complete randomized blocks.9 Differences between the two groups were analyzed by a one-way analysis of variance.*

Results

Hemodynamics

Neither partial occlusion nor i.v. or intracoronary nifedipine affected left ventricular end-diastolic pressure or heart rate (table 1). Partial occlusion resulted in a slight decrease in aortic systolic and diastolic pressures. The decrease in diastolic pressure in the intracoronary group was not significant. Nifedipine caused a small but statistically significant decrease in aortic systolic and diastolic pressure in the i.v. group, but had no effect on systemic pressure in the intracoronary group.

Perfusion pressure in the cannulated left anterior descending coronary artery is presented in table 2. Partial occlusion resulted in decreased systolic and diastolic perfusion pressures. The diastolic pressures were essentially identical to the 25 mm Hg diastolic pressure selected initially. There was no difference in either preocclusion or postocclusion perfusion pressure between the two groups. Nifedipine had no significant effect on systolic or diastolic perfusion pressure in either the i.v. or intracoronary group. In the i.v. group, nifedipine did not affect perfusion pressure despite a decrease in systemic blood pressure.

Myocardial Shortening

The effect of nifedipine on myocardial shortening is presented in table 3. Partial occlusion resulted in a decrease in myocardial shortening in the ischemic zone, but had no significant effect in the nonischemic zone in either group. In the ischemic zone, i.v. nifedipine resulted in an increase in shortening from 19% to 47% of control. Similarly, intracoronary nifedipine increased ischemic zone shortening, from 20% to 33% of control. Partial occlusion did not affect nonischemic zone shortening and neither i.v. nor intracoronary

### Table 1. Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Group I Intravenous</th>
<th>Group II Intracorony</th>
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<tbody>
<tr>
<td></td>
<td>Control Post occlusion Nifedipine</td>
<td>Control Post occlusion Nifedipine</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>3.8 ± 1.8 4.3 ± 1.6 4.0 ± 1.8</td>
<td>5.2 ± 2.7 6.1 ± 3.3 6.5 ± 3.5</td>
</tr>
<tr>
<td>AoP (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>116 ± 18 108 ± 17* 104 ± 15*</td>
<td>116 ± 15 107 ± 15* 103 ± 19</td>
</tr>
<tr>
<td>Diastolic</td>
<td>91 ± 16 85 ± 19* 78 ± 18*</td>
<td>87 ± 16 79 ± 17 78 ± 23</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>144 ± 22 139 ± 25 134 ± 23</td>
<td>153 ± 26 150 ± 30 145 ± 27</td>
</tr>
</tbody>
</table>

*p < 0.05 compared with value to left.

Abbreviations: LVEDP = left ventricular end-diastolic pressure; AoP = aortic pressure.

### Table 2. Perfusion Pressure (mm Hg)

<table>
<thead>
<tr>
<th></th>
<th>Group I Intravenous</th>
<th>Group II Intracorony</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>Preocclusion 117 ± 15 116 ± 13 Postocclusion 62 ± 8* 63 ± 9* Nifedipine 61 ± 7 61 ± 14</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>Preocclusion 89 ± 18 86 ± 17 Postocclusion 24 ± 5* 25 ± 7* Nifedipine 22 ± 3 23 ± 4</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.001 vs preocclusion value.
nifedipine changed shortening in the nonischemic zone.

**Total Coronary Blood Flow**

Table 4 presents values for coronary blood flow measured with an electromagnetic flow probe in the cannulation system. Partial occlusion resulted in a decrease in coronary flow in both groups. Neither i.v. nor intracoronary nifedipine affected coronary flow to the subserved ischemic zone.

**Regional Myocardial Blood Flow**

Regional myocardial blood flow data are presented in Table 5. After partial coronary occlusion, subendocardial and subepicardial flows in the ischemic zone were significantly lower \( p < 0.01 \) than corresponding flows in the nonischemic zone in both groups. Nifedipine had no effect on either subendocardial or subepicardial blood flow to the ischemic zone in either the i.v. or the intracoronary group. Partial occlusion did not affect nonischemic zone myocardial blood flow. In contrast to ischemic zone findings, nifedipine resulted in an increase in myocardial blood flow to the subendocardium and subepicardium in the nonischemic zone in the i.v. group. In the intracoronary group, however, neither partial occlusion nor nifedipine affected either endocardial or epicardial nonischemic zone flow.

**Discussion**

Both i.v. and intracoronary nifedipine caused an increase in ischemic subendocardial segmental shortening in the setting of partial coronary occlusion. The partial coronary occlusion in both groups to a minimal diastolic perfusion pressure of 25 mm Hg caused an approximately 80% decrease in shortening from the control level. Intravenous nifedipine increased shortening from 19% to 47% of the control value, whereas intracoronary administration increased shortening from 20% to 33% of control.

This improvement in the function of ischemic muscle has several possible explanations. Decreased afterload due to a vasodilator could cause improved shortening. This could at least partially explain improved shortening in the i.v. group, but not in the intracoronary group. Decreased afterload would not be expected and was not observed with a small dose (10 \( \mu g \)) of intracoronary nifedipine. Thus, decreased afterload per se does not explain these findings. Similarly, although increased preload through the Frank-Starling mechanism could cause shortening to increase, neither i.v. nor intracoronary nifedipine affected left ventricular end-diastolic pressure. In addition, the fact that neither i.v. nor intracoronary nifedipine affected normal zone shortening argues against a primary hemodynamic mechanism for improvement in shortening.

Another obvious mechanism for improved function would be increased blood flow to the ischemic zone with decreased ischemia. Several investigators have shown that subendocardial shortening decreases as the degree of partial occlusion is increased.\(^{10-12}\) Our data show that myocardial shortening decreases over a narrow range of blood flow. Thus, a relatively modest increase in blood flow could increase shortening. However, at the level of partial occlusion, neither i.v. nor intracoronary nifedipine affected ischemic zone blood flow. The dose of intracoronary nifedipine used in this study (10 \( \mu g \)) results in an increase in coronary blood flow in an unoccluded coronary comparable in magnitude to the increase in blood flow due to reactive hyperemia after 10 seconds of coronary occlusion. Thus, myocardial shortening increased by a mechanism other than increased regional blood flow, even though the dose of intracoronary nifedipine used can cause hyperemia in normal myocardium. The fact that neither i.v. nor intracoronary nifedipine affected ischemic zone flow suggests that at this level of occlusion (25 mm Hg diastolic perfusion pressure), coronary reserve is exhausted and the microvascular resistance vessels responsible for autoregulation are fully dilated. Intravenous nifedipine might, however, change blood flow in the ischemic zone by way of intracoronary collaterals, because nifedipine is a powerful vasodilator.\(^{14}\) However, this was not observed in the present study.

A positive inotropic action of nifedipine in the ischemic zone would be consistent with our results. Failure to affect nonischemic zone function in the i.v. group makes this explanation unlikely. Moreover, nifedipine has been shown to have negative inotropic effects or to cause relaxation of in vitro smooth muscle strips.\(^{4}\)

Another possible mechanism of improvement in shortening is that nifedipine directly mitigates the effect of ischemia. Experimental studies have shown that ischemia results in excessive accumulation of calcium in mitochondria.\(^{15, 16}\) Nifedipine may improve

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**Table 3. Myocardial Shortening**

<table>
<thead>
<tr>
<th></th>
<th>Group I Intravenous</th>
<th>Group II Intracoronary</th>
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</thead>
<tbody>
<tr>
<td>Ischemic zone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preocclusion</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Postocclusion</td>
<td>0.19 ± 17*</td>
<td>0.20 ± 50*</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>0.47 ± 21*</td>
<td>0.33 ± 49*</td>
</tr>
</tbody>
</table>

**Table 4. Coronary Flow by Flow Probe (ml/min)**

<table>
<thead>
<tr>
<th></th>
<th>Group I Intravenous</th>
<th>Group II Intracoronary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preocclusion</td>
<td>45 ± 15</td>
<td>45 ± 21</td>
</tr>
<tr>
<td>Postocclusion</td>
<td>15 ± 8*</td>
<td>22 ± 14*</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>15 ± 7</td>
<td>21 ± 12</td>
</tr>
</tbody>
</table>

\(^{*}p < 0.005\) compared with value above.
ischemic zone contraction by blocking or decreasing this excess uptake.\(^1\) It should be apparent, however, that this effect may be dose-dependent; thus, higher doses could result in ischemic zone dysfunction, consistent with results obtained in isolated muscle strips. In this regard, Selwyn et al.\(^3\) suggested that while 1 mg/kg/min of nifedipine can preserve ischemic myocardium, higher doses may be detrimental. Additional studies are needed to clarify the effect of nifedipine on the intramyocardial and mitochondrial calcium compartments during ischemia.

**Acknowledgment**

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**References**


**TABLE 5. Myocardial Blood Flow (ml/g/min)**

<table>
<thead>
<tr>
<th>Ischemic zone</th>
<th>Group I Intravenous</th>
<th>Group II Intracoronary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endocardium</td>
<td>Epicardium</td>
</tr>
<tr>
<td>Postocclusion</td>
<td>0.39 ± 0.18</td>
<td>0.66 ± 0.19</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>0.38 ± 0.21</td>
<td>0.82 ± 0.22</td>
</tr>
<tr>
<td>Nonischemic zone</td>
<td>1.14 ± 0.44</td>
<td>1.24 ± 0.28</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>1.51 ± 0.67*</td>
<td>1.63 ± 0.45*</td>
</tr>
</tbody>
</table>

*\(p < 0.05\) compared with postocclusion value.
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