Variable Effect of Nifedipine on Myocardial Blood Flow at Three Grades of Coronary Occlusion in the Dog

WILLIAM S. WEINTRAUB, SHIGEHIKO HATTORI, JAI AGARWAL, MONTY M. BODENHEIMER, VIDYA S. BANKA, AND RICHARD H. HELFANT

SUMMARY The effect of nifedipine on myocardial blood flow at various grades of coronary stenosis is unknown. Thus 22 open-chest dogs underwent carotid to left anterior descending perfusion with flow and perfusion pressure monitoring. Grades of coronary occlusion were defined by minimum diastolic perfusion pressure. Six dogs (group 1) underwent moderate occlusion to 50 to 55 mm Hg diastolic perfusion pressure; 10 (group 2), severe occlusion to 40 mm Hg perfusion pressure; and six (group 3), more severe occlusion at 25 mm Hg. Regional myocardial blood flow was measured with radioactive microspheres before and after the intracoronary injection of 10 μg of nifedipine. In group 1, nifedipine induced epicardial hyperemia and little change in endocardial flow in the ischemic zone. In group 2, nifedipine induced epicardial hyperemia from 1.06 to 1.39 ml/g per min, but endocardial flow decreased from 0.70 to 0.60 ml/g per min. In group 3, there was no change in blood flow. Thus the effect of nifedipine on myocardial blood flow depends on the extent of occlusion. Furthermore for certain degrees of occlusion, redistribution of blood flow from endocardium to epicardium has been shown to occur.

The calcium flux antagonist nifedipine has stimulated considerable recent interest as a potential treatment for coronary artery disease. Although nifedipine is a potent vasodilator (Kroneberg, 1975), its effect on myocardial blood flow during varying degrees of coronary occlusion is unknown. Thus, in the present study, we investigated the effect of intracoronary nifedipine on myocardial blood flow in open-chest dogs undergoing three distinct grades of coronary occlusion.

Methods

Experimental Preparation

Twenty-two dogs were anesthetized with pentobarbital and ventilated with a Harvard respirator. Arterial blood gases were monitored and PO_{2} maintained between 80 and 100 mm Hg and pH between 7.36 and 7.44. A catheter (7F) was passed into the right femoral artery and advanced to the thoracic aorta for arterial pressure monitoring. A stiff catheter 2 mm in internal diameter was placed in the left femoral artery and advanced to the abdominal aorta for blood withdrawal. A catheter was also placed in the right femoral vein for intravenous infusions.

A thoractomy then was performed in the 5th left

CORONARY heart disease is characterized by wide variability in the severity of obstructive lesions. Experimental studies have shown that the severity of partial coronary occlusion affects regional myocardial flow (Griggs and Nakamura, 1968). Blood flow is maintained until mean perfusion pressure reaches 60 mm Hg (Hoffman and Buckberg, 1977). Below that level, blood flow becomes linearly related to perfusion pressure (Guyton et al., 1977; Rouleau et al., 1979). In addition, it also has been demonstrated that, during coronary occlusion, epicardial blood flow is greater than endocardial blood flow (Hoffman and Buckberg, 1977; Rouleau et al., 1979).

Moreover, studies using the vasodilators, nitroglycerin and adenosine, have suggested that during partial coronary occlusion these drugs may cause a redistribution of myocardial blood flow from endocardium to epicardium (Forman et al., 1973; Gallagher et al., 1980).

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intercostal space and the heart supported in a pericardial cradle. A catheter (7F) was passed into the left atrial appendage for microsphere injection. A 10-cm-long, 14-gauge stiff catheter was passed into the left ventricle through the apex for recording of pressure. A 5- to 10-cm segment of the left common carotid was isolated. After administration of heparin, the left anterior descending coronary artery was isolated at the level of the first or second diagonal branch, tied, and an arteriotomy 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 minimum internal diameter of 2 mm. Coronary perfusion pressure was monitored with a strain gauge (Stratham, P23dB) and coronary flow with an electromagnetic flow probe (Micron Instruments). The time from ligation of left anterior descending to establishment of cannula perfusion averaged 30 seconds, and all dogs in which cannulation took more than 120 seconds were excluded. During cannula perfusion of the left anterior descending artery in one dog, pressure at the tip of the cannula was measured with a 21-gauge needle passed into the artery distal to the cannula. The needle was attached to a Statham P23dB strain gauge. Cannula tip pressure and aortic pressure were identical. In addition, we checked the cannula system for stenosis in vitro using warm blood and a Harvard pump. Pressure was monitored in the proximal cannula system and at the tip, and no gradient was noted at flows of up to 46/ml per min. Diastolic perfusion pressure in the tubing was identical to aortic perfusion pressure at flows up to 100 ml/min in all dogs prior to occlusion. The presence of some coronary vascular reserve was determined by use of 10-second total occlusion followed by reperfusion. All dogs with less than 100% reactive hyperemia were rejected as having either inadequate coronary reserve on stenosis in the cannula system.

Microsphere Technique

Microspheres (9-μm diameter) labeled with 125I, 141Ce, 85Sr, or 46Sc were used to measure myocardial blood flow. Microspheres were suspended in saline and agitated in an ultrasonic bath for at least 15 minutes before injection. They were then shaken in a vortex whirler. Two to three million microspheres in 8 ml of saline were injected into the left atrium over a 15- to 20-second period followed by a 4-ml flush of microsphere-free saline. Starting before the injection of microspheres, we withdrew blood 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.

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. Dogs were randomized into three groups. Animals in group 1 (n = 6) were partially occluded to a minimum diastolic perfusion pressure of 50-55 mm Hg. Group 2 (n = 10) had partial occlusion to a minimum diastolic perfusion pressure of 40 mm Hg and Group 3 (n = 6) to a diastolic perfusion pressure of 25 mm Hg. The preparation then was allowed to stabilize for 10 minutes and a set of microspheres given. Then a bolus of 10 μg of nifedipine was given through the coronary cannula. Twenty seconds later, at the time of maximum increase in coronary flow as measured with a flow probe, a second set of microspheres was given. The time between the two microspheres injections was under 5 minutes.

Tissue Preparation

At the conclusion of the experiment but before death of the dog, Evans blue dye was injected into the coronary cannula with sufficient force to stain the ischemic region but insufficient to fill the visible intercoronary collaterals. The heart was excised, washed, dried, stuffed with gauge, wrapped with industrial strength aluminum foil, and frozen. The heart was sectioned while still frozen to facilitate accurate cutting. A 2- to 3-cm-wide ring of myocardium was cut with the path of the cut perpendicular to the blue line. A section of myocardium was taken from the remote normal zone. The ring was cut at the blue line with care to keep all the blue-stained tissue on the ischemic side. A 1-cm sample of myocardium was taken on the ischemic (blue) side labeled border ischemic sample, followed by a 1-cm central ischemic sample. All samples were divided into endocardial, mid-myocardial, 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 γ counter for 10 minutes each. Myocardial blood flow then was determined by the method of Heymann et al. (1977).

All data are expressed as mean ± sd. Differences for any parameter or sub-groups within the three groups described above were analyzed by a two-way analysis of variance by complete randomized blocks (Sokal and Rohlf, 1969). Differences between the three groups for any parameter were analyzed by a one-way analysis of variance (Sokal and Rohlf 1969).

Results

Hemodynamic data for the three groups are summarized in Table 1. There were no significant hemodynamic differences between these groups prior to partial occlusion. Following partial occlusion, group III showed a slight rise in left ventricular end-diastolic pressure and a slight fall in aortic systolic blood pressure (P < 0.05). Nifedipine had
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TABLE 1  Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP (mm Hg)</td>
<td>Control 7 ± 3</td>
<td>Post-occlusion 6 ± 3</td>
<td>Nifedipine 7 ± 3</td>
</tr>
<tr>
<td>Aortic pressure (mm Hg)</td>
<td>Control 118 ± 15</td>
<td>Post-occlusion 114 ± 17</td>
<td>Nifedipine 114 ± 19</td>
</tr>
<tr>
<td>Systolic</td>
<td>91 ± 17</td>
<td>91 ± 17</td>
<td>90 ± 17</td>
</tr>
<tr>
<td>Heart rate</td>
<td>136 ± 33</td>
<td>134 ± 33</td>
<td>134 ± 33</td>
</tr>
</tbody>
</table>

LVEDP = left ventricular end-diastolic pressure.

Table 1 shows the effect of nifedipine on coronary perfusion pressure.

TABLE 2  Perfusion Pressure in the Cannulated Left Anterior Descending Coronary Artery

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>Pre-occlusion 115 ± 11</td>
<td>Post-occlusion 97 ± 13</td>
<td>Nifedipine 90 ± 14</td>
</tr>
<tr>
<td></td>
<td>92 ± 11</td>
<td>95 ± 12</td>
<td>77 ± 12†</td>
</tr>
<tr>
<td>Diastolic</td>
<td>Pre-occlusion 88 ± 15</td>
<td>Post-occlusion 52 ± 5</td>
<td>Nifedipine 45 ± 7</td>
</tr>
<tr>
<td></td>
<td>92 ± 16</td>
<td>37 ± 7†</td>
<td>34 ± 6†</td>
</tr>
</tbody>
</table>

* Compared to left P < 0.01; †compared to above P < 0.01.

Effect of Nifedipine on Coronary Flow

Table 3 shows the effect of nifedipine on coronary flow measured with an electromagnetic flow probe. Both total flow in ml/g per min and normalized flow expressed as a fraction of control flow are presented. There was no difference in coronary flow in these groups prior to occlusion. Nifedipine caused a significant increase in coronary flow in groups 1 and 2 (P < 0.01) but no significant change in group 3. Intracoronary nifedipine resulted in a larger increment in coronary blood flow (%ACF) with moderate coronary occlusion (group 1), a lesser increase with more severe coronary occlusion (group 2), and no significant change with the most severe degree of partial coronary occlusion (group 3).

Normal Zone Myocardial Blood Flow

Normal zone myocardial blood flow is presented in Table 4. Nifedipine had no effect on normal zone flow in either the epicardium or endocardium. There was no significant difference in blood flow between the three groups in either the epicardium or endocardium.
The Effect of Nifedipine on Ischemic Zone Myocardial Blood Flow

The effect of nifedipine on ischemic zone myocardial blood flow is shown in Table 5. In group 1, nifedipine caused a significant increase in epicardial blood flow from 1.15 to 1.96 (P = 0.0014). However, the change in endocardial blood flow from 1.06 to 1.14 was not significant. In group 1, ischemic zone endocardial blood flow was slightly lower than normal zone (1.06 vs. 1.29) before nifedipine, but the difference was not significant. In contrast, in group 2, nifedipine caused a significant increase in epicardial blood flow from 1.06 to 1.39 (P = 0.0017), whereas endocardial blood fell from 0.70 to 0.60 (P = 0.0064). In group 2, ischemic zone endocardial blood flow was significantly lower than normal zone flow prior to nifedipine (0.70 vs. 1.28 P = 0.0006). In contrast, at the most severe degree of coronary occlusion nifedipine had no significant effect on either endocardial or epicardial blood flow.

Figure 1 shows the contrasting effects on epicardial blood flow caused by nifedipine at the three levels of occlusion. The increase in epicardial blood flow was larger in group 1 than in group 2 and larger in group 2 than in group 3. Similarly, Figure 2 shows the contrasting changes in endocardial blood flow induced by nifedipine at the three levels of coronary occlusion. Whereas blood flow tended to increase in the endocardium in group 1, it decreased after nifedipine in group 2. In group 3, there was little change in blood flow. This confirms that there is a significant difference in the way the coronary vasculature responds to nifedipine at different levels of partial coronary occlusion.
Discussion

The results of this study cast new light on the response of the coronary vasculature to vasodilators. We have shown that the response of the microvasculature to a vasodilator depends on the severity of coronary stenosis (Table 5). In the group with moderate stenosis, nifedipine caused hyperemia in the epicardium but little change in the endocardium. In the group with more severe stenosis, epicardial blood flow rose and endocardial blood flow fell. In the group with most severe stenosis, there was little change in flow in either the epicardium or the endocardium. Thus we may postulate several degrees of coronary stenosis.

With more moderate stenosis at a diastolic perfusion pressure of 52 ± 5 mm Hg, myocardial blood flow to the endocardium and the epicardium was preserved (Table 5). Due to the presence of residual autoregulatory reserve, vasodilation caused a marked increase in flow along with a decrease in perfusion pressure. The autoregulatory reserve was mostly in the epicardium with a marked increase in its flow. However, some reserve must have been present in the endocardium because the blood flow was maintained in spite of a decrease in perfusion pressure. At a slightly higher degree of coronary stenosis (group 2), with a diastolic perfusion pressure of 37 ± 7 mm Hg, the endocardial reserve was completely exhausted, as indicated by a decrease in endocardial blood flow. However, some epicardial reserve is still present. Vasodilation in group 2 caused hyperemia exclusively in the epicardial area. This caused a slight increase in total coronary flow and slight fall in perfusion pressure. As the endocardial reserve was exhausted, this slight fall in perfusion pressure caused a reduction in endocardial blood flow. Thus, in this relatively severe stenosis, vasodilation caused redistribution of flow away from the endocardium. Finally, with the most severe grade of coronary obstruction, no autoregulatory reserve was present. Vasodilators then have no effect on the perfusion pressure, total perfusion, or endocardial and epicardial flow. Similar results to our group 2 have been noted by Forman, et al. (1973) with nitroglycerin and by Gallagher et al. (1980) with adenosine. Nifedipine now may be added to the list of vasodilators that, in certain settings, may cause a redistribution of blood flow from endocardium to epicardium.

Rubio and Berne (1975) and others (Olsen et al., 1979) have suggested that the control of myocardial blood flow is at the local level and is mediated by an endogenous vasodilator thought to be adenosine. Furthermore, Rouleau et al. (1979) have suggested that the different myocardial layers have independent local control of myocardial blood flow. Our data showing redistribution in group 2 support this concept. At this level, the epicardium was capable of dilating and the endocardium probably was responding passively to altered hemodynamics and, thus, different myocardial levels are functioning independently in this situation.

In this study we examined the effect of a potent vasodilator on the coronary vasculature by direct intracoronary injection. This permitted us to determine the direct effect of nifedipine on the coronary vasculature. When given intravenously, the effect will be a complex interaction of direct effect, effects on collateral flow and on systemic hemodynamics.

Implications

Redistribution of blood flow from endocardium to epicardium is most likely a deleterious effect. However, redistribution of flow seems to happen only in a well-defined pathological situation, and whether it ever happens in clinical settings is unknown. Our study suggests that redistribution of flow does not occur until endocardial coronary reserve is exhausted and endocardial flow falls below nonischemic zone flow. Gould et al. (1974) have suggested that blood flow and, presumably, some vascular reserve are maintained until the coronary is 80% obstructed. With lesions greater than 80%, blood flow falls. Presumably, redistribution of blood flow would not be expected until this level of stenosis. With the most severe lesions, transmural coronary reserve would be exhausted and a vasodilator should have little effect. The effect we measured in our model was relatively small with a 15% reduction in endocardial blood flow. Just how important this flow reduction would be for myocardial function or possibly even myocardial survival will require further study.

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