Prevention by Nifedipine of Abnormal Coronary Vasoconstriction in Patients with Coronary Artery Disease

STEPHEN GUNThER, M.D., LAURENCE GREEN, M.D., JAMES E. MULLER, M.D., GILBERT H. MUDGE, JR., M.D., AND WILLIAM GROSSMAN, M.D.

SUMMARY The hemodynamic and myocardial metabolic responses to the cold pressor test were studied in 15 patients with coronary artery disease and stable exertional angina. Every patient had abnormal coronary vasoconstriction during a control cold pressor test, even though 14 were receiving propranolol and 12 were receiving long-acting nitrates. Mean coronary vascular resistance for the group increased 18 ± 6% (SD) (from 0.80 ± 0.12 to 0.94 ± 0.20 mm Hg/ml/min, p < 0.05); coronary sinus blood flow was unchanged, and the arterial–coronary sinus oxygen difference widened significantly (from 11.5 ± 1.2 to 12.3 ± 1.2 ml/100 ml, p < 0.05). Four patients developed angina, accompanied in each instance by a negative arterial–coronary sinus lactate difference. After the administration of nifedipine (10 mg buccally) in 10 patients, the coronary vascular responses to a repeat cold pressor test were normal in each patient. Mean coronary sinus blood flow increased 27 ± 12% (from 122 ± 32 to 153 ± 35 ml/min, p < 0.05), coronary vascular resistance decreased 10 ± 6% (from 0.85 ± 0.16 to 0.76 ± 0.16 mm Hg/ml/min, p < 0.05), and the arterial–coronary sinus oxygen difference was unchanged. No patient experienced angina. The hemodynamic and coronary vascular responses to a repeat cold pressor test in five patients given placebo were unaltered from control responses.

The protective effects of nifedipine were unaccompanied by any change in mean arterial pressure, left ventricular filling pressure or myocardial oxygen consumption either at rest or in response to the cold pressor test. Nifedipine appears to exert a selective antivasoconstrictor effect on the coronary vasculature.

CURRENT THERAPY of ischemic heart disease is directed at reducing myocardial oxygen demand by decreasing heart rate and myocardial contractility with β-adrenergic blockade and by reducing arterial and left ventricular filling pressures with nitrates. Such therapy is based on the assumption that myocardial oxygen supply is limited only by the fixed obstructive lesions of coronary artery disease. A growing body of evidence indicates, however, that myocardial ischemia may also result from abnormal coronary artery vasoreactivity. Spasm of coronary arteries has been well documented as the cause of Prinzmetal’s variant angina and similar mechanisms have been recently suggested in the pathogenesis of rest angina and myocardial infarction in certain patients with obstructive coronary disease. Frank coronary vasospasm, however, has not generally been considered an important feature of stable exertional angina and has been only rarely documented as a cause of myocardial ischemia in patients with this common disorder. It is possible that more subtle coronary vasoconstrictor mechanisms, not readily detectable by coronary arteriography, may exist in such patients. For example, direct measurement of coronary sinus blood flow during the physiologic stimulus of the cold pressor test has revealed that patients with coronary disease and exertional angina develop an abnormal increase in coronary vascular resistance. This vasoconstrictor response was sufficient to induce angina and ischemic electrocardiographic changes in some patients and to restrict myocardial blood flow inappropriately during a period of enhanced metabolic demand in all patients.

These demonstrations of abnormal coronary reactivity in the various forms of ischemic heart disease have stimulated renewed interest in the therapeutic value of coronary vasodilators. The calcium antagonist nifedipine is a potent vasodilator that has proved effective in preventing the coronary artery spasm associated with Prinzmetal’s angina, especially in patients refractory to conventional therapy. For this reason, we evaluated the effects of this agent on the abnormal vasoconstrictor response to the cold pressor test in a group of patients with coronary artery disease and exertional angina.

Methods

Patient Selection

Fifteen patients with stable exertional angina pectoris were studied during cardiac catheterization. Patients who predominantly had rest pain or other symptoms suggestive of Prinzmetal’s angina were excluded from the study. Thirteen patients had a positive maximal exercise tolerance test (Bruce protocol), defined as the development of ischemic chest pain and ≥ 1 mm of ST-segment depression in any electrocardiographic lead (except aVR) 80 msec after the end.
of the QRS complex anytime after exercise was begun. In two patients, exercise testing was nondiagnostic because of failure to reach target heart rate. Obstructive coronary artery disease (= 70% mean reduction in luminal diameter, as measured from multiple projections by two independent observers, of one or more of the major branches of the left coronary artery) was documented in each patient by coronary arteriography. All patients were maintained on their usual medications (including propranolol and long-acting nitrates) up to the time of catheterization. The protocol and investigational consent form were approved by the Human Subjects Committee of the Peter Bent Brigham Hospital.

Experimental Protocol

Coronary sinus blood flow was measured by the thermodilution technique, as previously described. Stable positioning of the thermodilution catheter during the study was verified by frequent fluoroscopic monitoring. To avoid potential artifacts from coronary sinus reflux due to tricuspid regurgitation, recordings in which extrasystoles of any kind occurred during flow measurements were excluded. Mean and phasic arterial pressures were recorded from a catheter percutaneously placed in either the femoral or brachial artery. Left ventricular diastolic pressure (LVDP) was recorded at high gain and paper speed with a catheter positioned retrogradely from the femoral artery. Heart rate was controlled by coronary sinus pacing through electrodes in the thermodilution catheter at a constant rate of 90-95 beats/min throughout the study. Blood oxygen content was measured directly (Lex-O2-Con, Lexington Instruments), and plasma lactate levels were measured spectrophotometrically by the enzymatic reduction of NAD.

The cold pressor test was performed in each patient before and 15 minutes after the administration of nifedipine (10 mg buccally) in 10 patients or placebo (lactose capsules buccally) in five patients. Baseline recordings of coronary sinus blood flow, mean and phasic arterial pressures and LVDP were made, and paired samples of arterial and coronary sinus blood obtained for determination of oxygen content and lactate levels. The patient's hand and forearm were then immersed in ice water for 1 minute while continuous recordings of coronary sinus blood flow and pressure measurements were made. At the peak of the pressor response or, if sooner, at the onset of angina, blood samples were again obtained. When the patient's blood pressure and coronary sinus flow had returned to baseline (within 5-8 minutes), nifedipine or placebo was administered, and the cold pressor test was repeated 15 minutes later. Measurements were thus obtained for each patient under four conditions.

Data Analysis

Coronary vascular resistance was calculated as the quotient of mean arterial pressure divided by coronary sinus blood flow, and expressed as mm Hg/ml/min. To determine whether changes in coronary vascular resistance could be ascribed to increased diastolic compression of intramyocardial vessels from elevated left ventricular filling pressures, resistances were also calculated as the quotient of (mean arterial pressure − mean LVDP)/coronary sinus flow, where mean LVDP was determined by planimetry as the average of five consecutive beats. Myocardial oxygen consumption was calculated as (arterial oxygen content − coronary sinus oxygen content) × coronary sinus blood flow, and expressed as ml oxygen/min.

Three types of statistical analysis were performed. Because each of the two patient populations was studied under four conditions, the experimental protocol yielded eight groups of data for each measured or calculated variable. The null hypothesis that the means of these eight groups were equal was tested for each variable by analysis of variance, using the BMD-P14 ANOVA program (University of California Press) and an IBM Systems 370 computer. For variables for which the resulting F value (variance ratio) was sufficiently high to reject the null hypothesis at the p = 0.05 level, pair-wise comparisons of the eight group means were performed by the Scheffé method to determine which means were significantly different from the others. This method allowed multiple comparisons of the group means both within and between the two patient groups. Analysis of variance was similarly used to test the null hypothesis that the percentage changes in mean arterial pressure, myocardial oxygen consumption and LVDP during the cold pressor test were equal before and after treatment in both patient groups. The hypothesis that there were no significant differences between the placebo- and nifedipine-treated groups in terms of clinical features was tested by unpaired t test (for age and ejection fraction) or by chi-square analysis (for severity of coronary artery disease and presence or absence of each type of drug therapy). The null hypothesis in each analysis was rejected when p < 0.05. All data are presented as mean ± sd.

Results

Clinical Data

The clinical features and diagnostic catheterization data of the patient population are summarized in table 1. The mean ages were 50 ± 8 years for the nifedipine-treated group and 55 ± 8 years for the placebo-treated group (p > 0.1). Three-vessel coronary artery disease was present in 40% of both patient groups (four of 10 nifedipine-treated patients and two of five placebo-treated patients). One patient in each group had an isolated stenosis of one coronary artery. Three patients in the nifedipine-treated group and one patient in the placebo-treated group had left ventricular dysfunction (ejection fraction < 55%) (p > 0.10). None of these patients had either symptoms or radiographic evidence of congestive heart failure at the time of study. Overall, 14 of the 15 patients were receiving propranolol at the time of catheterization.
(mean dose 240 ± 102 mg/day), and 12 of 15 were receiving long-acting nitrates (mean dose 24 ± 15 mg/day). There were no significant differences between the two groups in terms of drug therapy.

**Control Cold Pressor Test**

The responses of both patient groups to the control (pretreatment) cold pressor test were similar (table 2). The cold pressor test caused a mean increase in coronary vascular resistance of 18 ± 6% (from 0.80 ± 0.12 to 0.94 ± 0.20 mm Hg/ml/min, \( p < 0.05 \)). Thus, despite an increase in myocardial oxygen consumption, coronary sinus blood flow remained unchanged and the arterial–coronary sinus oxygen difference widened significantly. In the four patients who experienced angina, the arterial–coronary sinus lactate difference changed from positive to negative. Coronary vasoconstriction was observed in each of the 15 patients, even though 14 were receiving propranolol and 12 were receiving long-acting nitrates.

**Cold Pressor Test After Placebo**

The hemodynamic responses to a repeat cold pressor test in the five patients given placebo were un-

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**Table 1. Clinical and Diagnostic Data**

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Age (years)</th>
<th>CAD (% stenosis)</th>
<th>LVP (mm Hg)</th>
<th>EF</th>
<th>Digoxin (mg/day)</th>
<th>Propranolol (mg/day)</th>
<th>Long-acting nitrates (mg/day)</th>
</tr>
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<tbody>
<tr>
<td>Nifedipine</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>54</td>
<td>90% LAD, 75% LCX, 100% RCA</td>
<td>130/14</td>
<td>0.34</td>
<td>0.25</td>
<td>—</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>37</td>
<td>75% LAD, 90% LCX, 100% RCA</td>
<td>125/11</td>
<td>0.67</td>
<td>—</td>
<td>160</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>42</td>
<td>99% LAD, 75% RCA</td>
<td>130/13</td>
<td>0.78</td>
<td>—</td>
<td>240</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>47</td>
<td>75% LAD, 90% LCX</td>
<td>125/32</td>
<td>0.33</td>
<td>0.25</td>
<td>120</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>45</td>
<td>99% LAD, 90% LCX</td>
<td>140/12</td>
<td>0.76</td>
<td>—</td>
<td>400</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>56</td>
<td>100% LAD, 99% LCX, 100% RCA</td>
<td>90/8</td>
<td>0.38</td>
<td>—</td>
<td>120</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>49</td>
<td>90% LCX</td>
<td>130/6</td>
<td>0.85</td>
<td>—</td>
<td>320</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>48</td>
<td>99% LAD, 90% LCX, 100% RCA</td>
<td>125/5</td>
<td>0.60</td>
<td>—</td>
<td>240</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>57</td>
<td>100% LAD, 95% RCA</td>
<td>140/11</td>
<td>0.56</td>
<td>0.25</td>
<td>320</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>62</td>
<td>75% LAD, 100% RCA</td>
<td>160/8</td>
<td>0.76</td>
<td>—</td>
<td>160</td>
<td>10</td>
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<tr>
<td>Placebo</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>55</td>
<td>95% LAD, 75% LCX, 95% RCA</td>
<td>120/13</td>
<td>0.64</td>
<td>—</td>
<td>400</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>68</td>
<td>100% LAD</td>
<td>130/6</td>
<td>0.43</td>
<td>0.25</td>
<td>160</td>
<td>10</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>60</td>
<td>75% LAD, 80% LCX</td>
<td>170/8</td>
<td>0.65</td>
<td>—</td>
<td>200</td>
<td>40</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>47</td>
<td>75% LAD, 100% RCA</td>
<td>110/7</td>
<td>0.65</td>
<td>—</td>
<td>360</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>47</td>
<td>75% LAD, 100% LCX, 99% RCA</td>
<td>115/5</td>
<td>0.68</td>
<td>0.25</td>
<td>160</td>
<td>13</td>
</tr>
</tbody>
</table>

**Abbreviations:** CAD = coronary artery disease; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery; LVP = left ventricular pressures (systolic/end-diastolic); EF = left ventricular angiographic ejection fraction.

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**Table 2. Hemodynamic Responses to Control Cold Pressor Test (n = 15)**

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm Hg)</th>
<th>CSBF (ml/min)</th>
<th>CVR (mm Hg/ml/min)</th>
<th>LVDP (mm Hg)</th>
<th>ΔA-VO₂ (ml/100ml)</th>
<th>MVO₂ (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>98 ± 15</td>
<td>126 ± 27</td>
<td>0.80 ± 0.12</td>
<td>6 ± 4</td>
<td>11.5 ± 1.2</td>
<td>14.6 ± 3.9</td>
</tr>
<tr>
<td>Cold pressor test</td>
<td>117 ± 15†</td>
<td>128 ± 31</td>
<td>0.94 ± 0.20*</td>
<td>10 ± 6*</td>
<td>12.3 ± 1.2*</td>
<td>15.8 ± 4.3*</td>
</tr>
</tbody>
</table>

*\( p < 0.05 \), †\( p < 0.01 \).

**Abbreviations:** MAP = mean arterial pressure; CSBF = coronary sinus blood flow; CVR = coronary vascular resistance; LVDP = mean left ventricular diastolic pressure; ΔA-VO₂ = arterial–coronary sinus oxygen difference; MVO₂ = myocardial oxygen consumption.
Figure 1. Effects of the cold pressor test (CPT) on coronary vascular resistance in five placebo-treated patients. Coronary vascular resistance increased 16 ± 7% during the control cold pressor test and 21 ± 9% during the cold pressor test after placebo (p = 0.521).

changed. The increases in mean arterial pressure (from 95 ± 13 to 115 ± 18 mm Hg, p < 0.01), mean LVDP (from 4 ± 3 to 7 ± 3 mm Hg, p < 0.05) and arterial–coronary sinus oxygen difference (from 10.3 ± 0.6 to 11.1 ± 0.6 ml/100 ml, p < 0.05) were not significantly different from those in the same patients during the control cold pressor test. The increase in coronary vascular resistance was also reproducible (fig. 1).

Cold Pressor Test After Nifedipine

Nifedipine (10 mg buccally) produced no significant change in any of the resting hemodynamic values (table 3). Likewise, the pressor response to the cold pressor test was also unaltered after nifedipine. Comparable increases in mean arterial pressure, mean LVDP and myocardial oxygen consumption occurred during the control and nifedipine cold pressor tests (fig. 2). The response of the coronary vasculature, however, was markedly different. Coronary sinus blood flow during the nifedipine cold pressor test increased 27 ± 12% (from 122 ± 32 to 153 ± 35 ml/min, p < 0.05), whereas coronary vascular resistance was either unchanged (two patients) or actually decreased (eight patients). The mean change in coronary vascular resistance for the group was −10 ± 6% (from 0.85 ± 0.16 to 0.76 ± 0.16, mm Hg/ml/min, p < 0.05) (fig. 3). The arterial–coronary sinus oxygen difference remained unchanged (from 12.0 ± 1.0 to 11.7 ± 0.6 ml/100 ml, p > 0.10), and neither angina nor a negative arterial–coronary sinus lactate difference developed in any patient.

Role of Left Ventricular Diastolic Pressure

The increase in coronary vascular resistance during the control cold pressor test could not be attributed solely to increased diastolic compression of intramyocardial blood vessels. Although mean LVDP increased significantly during the control cold pressor test (table 2), calculation of coronary vascular resistance as the ratio of (mean arterial pressure – mean LVDP)/coronary sinus flow, did not significantly alter the results. Coronary vascular resistance calculated by this manner increased 16 ± 5%, compared with 18 ± 6% when mean arterial pressure alone was used (table 4). Further, in the patients receiving nifedipine, mean LVDP increased to similar levels during both the control and nifedipine cold pressor tests (fig. 2), yet coronary vascular resistance increased in the former instance, but decreased in the latter (fig. 3).

Nifedipine was well tolerated by all patients. Only in patient 10, who had a long-standing history of hypertension, did resting mean arterial pressure decrease significantly (134 to 104 mm Hg) with this dose of nifedipine.

Discussion

The results of this study show that the abnormal vasoconstrictor response provoked in patients with coronary artery disease by the stimulus of the cold pressor test can be specifically blocked by the nifedipine. During the control cold pressor test, coronary vasoconstriction occurred in all 15 patients with coronary disease and exertional angina who were receiving therapy with propranolol or long-acting nitrates or both. Similar vasoconstrictor responses to a repeat cold pressor test after placebo in five of these patients confirmed the reproducibility of the response. After the administration of nifedipine in the remaining patients, coronary vascular resistance did not increase as expected during the repeat cold pressor test, but actually decreased, and coronary sinus blood flow in-

<table>
<thead>
<tr>
<th>TABLE 3. Effects of Nifedipine on Resting Hemodynamics (n = 10)</th>
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<tr>
<td></td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Nifedipine</td>
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<tr>
<td>(10 mg buccally)</td>
</tr>
</tbody>
</table>

p > 0.05 for all variables.
Abbreviations: See table 2.
increased appropriately. Because the increases in arterial pressure, LVDP and myocardial oxygen consumption in these patients were comparable during the control and nifedipine cold pressor tests, the results suggest that nifedipine exerts a selective antivasoconstrictor effect on the coronary circulation.

The apparent selectivity of nifedipine for the coronary vasculature under these circumstances may be accounted for by its calcium-blocking activity. Both the coronary and systemic vasoconstrictor responses to the cold pressor test are mediated, at least in part, by the activation of α-adrenergic receptors, and it has been shown in animals that norepinephrine-induced contractions of coronary arteries, unlike those of systemic arteries, require the influx of extracellular calcium. The ability of nifedipine to block calcium influx could thus inhibit preferentially the coronary vasoconstrictor response, leaving the systemic pressor response relatively unaffected. Such a mechanism of action may also explain the effectiveness of nifedipine in preventing the coronary vasospasm associated with Prinzmetal's angina, in which altered autonomic nervous system activity has been postulated as a causative factor in some patients.

The demonstration that nifedipine can prevent abnormal coronary vasoconstriction during the cold pressor test suggests a possible therapeutic role for this agent in the management of patients with coronary artery disease.

**Table 4. Effect of Left Ventricular Diastolic Pressure on Coronary Resistance**

<table>
<thead>
<tr>
<th>Coronary vascular resistance</th>
<th>Baseline</th>
<th>Control cold pressor test</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg/ml/min)</td>
<td>0.80 ± 0.12</td>
<td>0.94 ± 0.20*</td>
</tr>
<tr>
<td>CSBF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP - LVDP (mm Hg/ml/min)</td>
<td>0.76 ± 0.15</td>
<td>0.88 ± 0.19*</td>
</tr>
<tr>
<td>CSBF</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05 compared with baseline.
Abbreviations: See table 2.

**Figure 2.** Hemodynamic responses in 10 patients during the cold pressor test (CPT) before and after nifedipine. Values (± SD) for mean arterial pressure, mean left ventricular diastolic pressure (LVDP) and myocardial oxygen consumption (\( \dot{MVO}_2 \)) are shown during the control (pretreatment) cold pressor test (solid bars) and during the cold pressor test after the administration of nifedipine (open bars).

**Figure 3.** Effects of the cold pressor test (CPT) on coronary vascular resistance in the 10 nifedipine-treated patients. After nifedipine, the coronary vascular response to the cold pressor test was normal in every subject.
pressor test in patients with coronary artery disease must be interpreted with caution, as the clinical significance of coronary vasoconstriction during other types of angina-provoking stress, such as exercise, remains to be defined. Several lines of evidence suggest, however, that activation of neurogenic vasoconstrictor mechanisms may contribute to the imbalance between myocardial oxygen supply and demand that characterizes the ischemic state in these patients. Resting \( \alpha \)-adrenergic tone is normally present in the human coronary circulation, and in experimental animals, increased \( \alpha \)-adrenergic tone during exercise and carotid sinus hypotension cause a coronary vasoconstriction that competes with metabolic vasodilatation. This competitive vasoconstriction is especially marked in animals pretreated with \( \beta \)-adrenergic blockade. In a previous study, we showed that in certain patients with coronary artery disease, angina provoked by a predominately vasoconstrictor stimulus (cold pressor test) occurs at a significantly lower rate-pressure product than angina induced in the same patient by the metabolic stimulus of rapid atrial pacing. Even coronary vasospasm has been documented during exercise in several patients with exertional, not variant, angina. Additional studies are obviously needed to clarify the role of coronary vasoconstrictor mechanisms in the pathogenesis of transient myocardial ischemia in patients with stable exertional angina. If a significant role for coronary vasoconstriction can be demonstrated in this common disorder, the newer coronary vasodilators, such as nifedipine, may be useful for its prevention.

Certain limitations of the present study should be emphasized. First, although an abnormal vasoconstrictor response to the cold pressor test was observed during treatment with conventional antianginal agents in each of the 15 patients, it cannot be determined from these data whether propranolol or long-acting nitrates can themselves favorably or unfavorably modify the vasoconstrictor response. Propranolol, by inhibiting \( \beta \)-adrenergic vasodilatory mechanisms, may theoretically potentiate the response to vasoconstrictor stimuli. Such an adverse effect of propranolol has been reported in experimental animals and in some patients with Prinzmetal's angina. Further studies comparing cold pressor responses before and after acute administration of propranolol will be necessary to determine what effect, if any, \( \beta \)-adrenergic blockade has on the vasoconstrictor response of patients with exertional angina. Second, the effects of nifedipine were studied at only one dosage level (10 mg buccally), which produced no changes in resting hemodynamics, in agreement with earlier studies, and was well-tolerated. Higher doses of this potent vasodilator, however, can result in symptomatic hypotension and reflex tachycardia. Finally, neither regional nor transmural differences in myocardial blood flow can be detected by the coronary sinus thermomemory method used in this study. It is not known, therefore, which segments of the coronary vasculature are affected by the abnormal vasoconstriction. Recent studies of \( \alpha \)-adrenergically mediated changes in coronary resistance in dogs indicate that both epicardial and intramyocardial vessels are responsive to vasoconstrictor stimuli. Additional studies to further delineate the mechanisms of this response are currently in progress.

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**References**


Prevention of nifedipine of abnormal coronary vasoconstriction in patients with coronary artery disease.
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