Acute Hemodynamic Effects of Nifedipine in Patients with Ischemic Heart Disease

PIRZADA A. MAJID, M.B.B.S., PH.D., AND JAAP DE JONG, M.D.

SUMMARY We studied the acute hemodynamic effects of nifedipine in 20 patients with angiographically proved coronary artery disease. Eight patients were studied during exercise-induced pain. There was an expected abnormal increase in pulmonary wedge pressure (28 ± 8 mm Hg, mean ± SD) accompanying chest pain (onset 179 seconds, duration 334 seconds) and ST-segment depression (2.2 ± 0.9 mm) on the ECG. Pacing stress was used in six patients and increased left ventricular (LV) end-diastolic pressure (from 16 ± 6 to 26 ± 6 mm Hg), volumes (end-diastolic 63 ± 20 to 81 ± 22 ml/m², end-systolic 26 ± 15 to 47 ± 16 ml/m²) and impaired ejection fraction (0.60 ± 0.15 to 0.44 ± 0.11) compared with control values. In both groups, nifedipine, 20 mg sublingually, significantly shortened duration of pain, reduced ST depression on the ECG (p < 0.001) and reversed all hemodynamic abnormalities. In another group of six patients with recent (less than 4 months) acute myocardial infarction and moderately severe LV dysfunction at rest, nifedipine reduced LV end-diastolic pressure from 21 ± 6 to 12 ± 5 mm Hg and volumes (end-diastolic from 109 ± 35 to 95 ± 32 ml/m², end-systolic from 41 ± 15 to 31 ± 7 ml/m²), while the ejection fraction improved significantly, from 0.43 ± 0.08 to 0.58 ± 0.11.

Thus, the antianginal effect of nifedipine is associated with improved systolic emptying and reduced diastolic filling of the heart. Nifedipine appears to have no discernible adverse effects in patients with depressed LV function.

NIFEDIPINE, a dihydropyridine derivative, blocks excitation-contraction coupling in the muscle cell by inhibiting movement of calcium ions through the so-called slow-membrane channels.1,2 The calcium antagonistic activity of the drug results in the relaxation of smooth muscle in regional vascular beds and depressed contractility in isolated papillary muscle.1 Because of its distinctive coronary vasodilator properties, nifedipine is becoming popular in the treatment of patients with suspected or proved coronary arterial spasm.3-4 Preliminary clinical studies suggest that nifedipine is equally effective in relieving exercise-induced angina.5-6 In the present study, we examined the acute hemodynamic effects of nifedipine in patients with coronary artery disease during pain induced by exercise or pacing.5,10 The study was extended to assess the effect of nifedipine in patients with moderately depressed left ventricular function at rest after an acute myocardial infarction.

Patients and Methods

The patients gave informed consent. The studies were performed during routine hemodynamic investigations before angiographic studies.

Study 1

Eight men, mean age 52 years (range 41–61 years), with uncomplicated, stable, exercise-induced angina pectoris of 6 months' to 6 years' duration were studied. All were being considered for coronary artery bypass surgery. All patients had at least 1 mm of ST-segment depression on the ECG, accompanied by typical chest pain during exercise on a treadmill conducted according to the protocol described by Bruce and Hornsten.11

X-ray films of the chest showed normal heart size in every patient. Left ventricular angiography revealed an ejection fraction greater than 50% in all the patients and left ventricular end-diastolic pressure averaged 9 mm Hg (range 6–12 mm Hg). Selective coronary arteriography revealed three-vessel disease in four patients, two-vessel disease in three patients and one-vessel disease in one patient. The coronary lesions were considered significant if 75% or more luminal diameter was stenotic.

The patients were trained to exercise in the supine position on a bicycle ergometer. The level of exercise chosen consistently induced pain between the second and fourth minute of a 6-minute period. The time of onset and total duration of pain was recorded by a stopwatch. On the day of investigation, patients exercised for approximately 4 minutes after the catheters were inserted. This was designated as a warm-up period. The studies started 15 minutes later with a 6-minute period of exercise at the predetermined load, followed by a 15-minute period of recovery. Cardiac output was determined in triplicate by thermodilution (Edwards) during the fourth and six minute of exercise and the final 4 minutes of the recovery period. The coefficient of variation between three cardiac output measurements was 7.0 ± 3.5% (mean ± SD) between 4.9 and 14.5 l/min. The ECG (V₅ position) and intravascular pressures were monitored continuously.

Right atrial, pulmonary artery and wedge pressures were obtained through a triple-lumen #8F catheter inserted into an antecubital vein. The systemic arterial pressure was measured at the aortic root by means of percutaneous introduction of a nylon catheter (75 cm × 1.5 mm) into the brachial artery using the Seldinger technique. The common zero level for all pressures was at the midchest. The pressures were transduced through HP 1280 C strain-gauge manometers and recorded on a six-channel, direct-writing recorder (Siemens Mingograf 8 EMT). All the manometers were calibrated against an open column of saline. Two blood samples each were taken from the aorta and
pulmonary artery for oxygen content measurements at rest and during exercise. This allowed indirect estimation of total body oxygen uptake from the cardiac output measurements and the arteriovenous oxygen content difference.

After control measurements, nifedipine, 20 mg, was given sublingually. This dose has been used in most previous investigations and is used routinely in clinical practice. The peak level of the drug or its active metabolites is reached in approximately 15 minutes and is sustained for at least 6 hours. The patients rested for approximately 20 minutes after receiving the drug, after which hemodynamic measurements were repeated at rest and during exercise as described above.

Study 2

Six men, mean age of 51 years (range 41–65 years), who had stable, exercise-induced angina pectoris were studied. All had at least 1 mm of ST depressions during exercise testing on a treadmill. Left ventricular angiography revealed an ejection fraction of 50% or greater in all the patients. Coronary angiography showed three-vessel disease in four patients, two-vessel disease in one patient and one-vessel disease in one patient. In this group, we applied the technique and design of investigation used for studying the effect of drugs on the left ventricle in patients with angina pectoris.10 Single-plane (right anterior oblique, 30°) left ventricular cineangiography was performed with approximately 40 ml of contrast agent (Iosopaque-Coronar-Nygaard) injected at a speed of 12-15 ml/sec through a #7F high-fidelity microtransducer-tipped angiographic catheter (Millar Instruments). To keep the heart rate constant during serial angiography, the control left ventricular angiography was done at a paced heart rate of about 90 beats/min. We chose this rate because the increase in heart rate induced by nifedipine, 20 mg sublingually, did not exceed 90 beats/min when tested before the studies.

Approximately 20 minutes later, when hemodynamic values had returned to control levels, patients were paced from the right atrium at increasing rates until typical chest pain and ST-segment depression appeared on the ECG. Left ventricular angiography was repeated during anginal pain within the first five to 10 beats after abrupt slowing of the pacing rate to about 90 beats/min. The patients then rested for 10–15 minutes, after which nifedipine, 20 mg, was administered sublingually. Twenty minutes later, patients were again paced to the heart rate at which angina had been induced. A third left ventricular angiogram was done within five to 10 beats of abrupt slowing of the pacing rate to approximately 90 beats/min. The angiograms were filmed at 60 frames/sec with a Phillips 6-inch image-intensifier system with a rotating U arm. The volume of contrast injected, the angle rotation of the x-ray tube, and the distance from the patient were kept constant. The amplification factor was derived from a 10-cm² grid filmed at the same level as the angiogram. The ventricular volumes and ejection fraction were calculated by the area-length method.12

Study 3

Four men and two women, mean age of 51 years (range 41–57 years), were studied. All had extensive anterior wall myocardial infarctions, sustained during the previous 3 months. None had clinical evidence of congestive heart failure. However, all patients were graded New York Heart Association class II. All had ST-segment elevation of 1 mm or more (lead V₁-V₄ position) either at rest or during exercise testing on the treadmill. X-ray films of the chest showed a normal heart size in all the patients. Left ventricular angiography showed low ejection fractions (average 0.43, range 0.34–0.50) and high end-diastolic pressures (average 21 mm, range 14–29 mm) in all the patients. Coronary angiography revealed two patients with one-, two with two- and two with three-vessel disease.

After control left ventricular cineangiography, patients rested until all indexes of myocardial function returned to control values. Nifedipine, 20 mg, was then given sublingually and approximately 20 minutes later left ventricular angiography was repeated. Left ventricular pressures were measured simultaneously. To test the variability of left ventricular pressure and volume measurements, two left ventricular angiograms were carried out in succession in a separate group of six patients who were undergoing catheterization for evaluation of chest pain, with administration of a placebo instead of nifedipine.

Statistical Analysis

Statistical significance of differences was calculated from the paired data with a t test.

Results

Study 1 (fig. 1)

In the control study, seven of the eight patients developed typical chest pain during exercise. The average time of onset of pain after start of exercise in seven patients was 179 seconds (range 71–237 seconds). The pain lasted for an average of 334 seconds (range 165–519 seconds). Each patient had electrocardiographic ST-segment depression (mean ± SD 2.2 ± 0.9 mm) and an abnormal rise in mean pulmonary wedge pressure. After nifedipine, at a similar oxygen uptake, pain was abolished in four patients and was appreciably shorter in the other three (419 vs 176 seconds). ST-segment depression (0.8 ± 1.0 mm, p < 0.01) and mean pulmonary artery, wedge, right atrial, and systemic arterial pressures were significantly reduced. Calculated systemic vascular resistance fell at rest and during exercise (from 3025 ± 440 to 2103 ± 287 dyn-sec-cm⁻²/m² at rest, p < 0.001; from 2003 ± 235 to 1579 ± 251 dyn-sec-cm⁻²/m² during exercise, p < 0.001). Cardiac output and heart rate increased at rest and during exercise. However, the right-heart pressures and the wedge pressure were essentially unchanged at rest.

Study 2 (table 1)

Left ventricular end-diastolic pressure and end-systolic and end-diastolic volumes increased significantly from control, accompanied by a reduction in
ejection fraction during pacing-induced angina. After nifedipine, left ventricular systolic and diastolic pressures diminished, as did the volumes. Ejection fraction returned to the control value.

Study 3 (table 2)

The abnormal left ventricular function at rest in this group of patients was confirmed by increased left ventricular end-diastolic and end-systolic volumes and end-diastolic pressure. The ejection fraction was moderately impaired. After nifedipine, the left ventricular systolic and end-diastolic pressures fell. The end-systolic and end-diastolic volumes became significantly smaller. The ejection fraction improved.

Table 1. Left Ventricular Pressure and Volume Data from Six Patients with Angina Pectoris During a Control Period, Pacing-induced Angina and Angina Induced in the Presence of Nifedipine

<table>
<thead>
<tr>
<th>Index</th>
<th>Control</th>
<th>Pacing</th>
<th>Pacing and nifedipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>157 ± 23</td>
<td>151 ± 17</td>
<td>135 ± 19§</td>
</tr>
<tr>
<td>End-diastolic pressure (mm Hg)</td>
<td>16 ± 6</td>
<td>26 ± 6*</td>
<td>11 ± 5**</td>
</tr>
<tr>
<td>dP/dt (mm Hg/sec)</td>
<td>2622 ± 514</td>
<td>2415 ± 566</td>
<td>2433 ± 392</td>
</tr>
<tr>
<td>End-systolic volume (ml/m²)</td>
<td>26 ± 15</td>
<td>47 ± 16‡</td>
<td>17 ± 10**</td>
</tr>
<tr>
<td>End-diastolic volume (ml/m²)</td>
<td>63 ± 20</td>
<td>81 ± 22†</td>
<td>63 ± 23¶</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.60 ± 0.15</td>
<td>0.44 ± 0.11†</td>
<td>0.63 ± 0.17¶</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
Dosage of nifedipine was 20 mg sublingually.
Control vs pacing:
* p < 0.05.
† p < 0.01.
‡ p < 0.001.
Pacing vs pacing and nifedipine:
§ p < 0.05.
¶ p < 0.01.
** p < 0.001.

Discussion

The first two groups of patients showed typical electrocardiographic and hemodynamic changes during chest pain induced by exercise or pacing.7–10 In the first group, significant ST-segment depression on the ECG was accompanied by an abnormal increase in pulmonary wedge pressure during exercise; in the second group, increased left ventricular end-diastolic pressure with significant impairment of ejection fraction was seen during pacing. At an identical exercise- or pacing-induced stress, sublingual nifedipine abolished or shortened the duration of pain and reduced ST-segment depression. The mean systemic arterial, mean wedge, mean right atrial left ventricu-
lar systolic and end-diastolic pressures fell. The left ventricular volumes became smaller and the ejection fraction improved. These results show that the antianginal effect of nifedipine is associated with considerable changes in the loading conditions of the left ventricle. The fall in left ventricular filling pressure, left ventricular end-diastolic volume and mean systemic arterial pressure indicate that both preload and afterload are reduced during exercise or pacing. Moreover, the decreased right atrial pressure during exercise in face of an augmented flow suggests an element of peripheral venous pooling contributing to the overall hemodynamic effects. The therapeutic efficacy of nifedipine in patients with stable angina pectoris may largely be attributed to reduced cardiac work due to peripheral vasodilator action. However, the benefits of coronary arterial dilatation cannot be excluded.

Animal experimental studies have shown that circulatory effects of nifedipine depend on its calcium-antagonistic activity. In the isolated cardiac muscle, a negative inotropic response is obtained as a direct consequence of retarded calcium ion influx into the myocardial cell. Whether this response applies to the intact heart is controversial. Results of several studies indicate that the inhibitory effect of nifedipine on myocardial contractility is modified by its peripheral vasodilator action. The reduction in mean aortic pressure is followed by activation of sympathetic nervous system through the baroreceptor reflex mechanism, leading to a compensatory increase in heart rate and cardiac output both in animals and in man. Our observations confirm that nifedipine has no deleterious effects on left ventricular function; on the contrary, salutary effects were demonstrated in three situations. In the first instance, the abnormalities of left ventricular function induced by exercise or pacing were reversed by nifedipine. Similarly, depressed myocardial function in patients with recent myocardial infarction also improved significantly.

We conclude that nifedipine offers promise as an antianginal agent. It can be given in anginal patients with depressed left ventricular function without adverse effects.

References

**Table 2. Left Ventricular Pressure and Volume Data From Six Patients with Recent Acute Myocardial Infarction During a Control Period and After Nifedipine**

<table>
<thead>
<tr>
<th>Index</th>
<th>Control period</th>
<th>Placebo</th>
<th>Control period</th>
<th>Nifedipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>132 ± 20</td>
<td>134 ± 17</td>
<td>127 ± 18</td>
<td>110 ± 18*</td>
</tr>
<tr>
<td>End-diastolic pressure (mm Hg)</td>
<td>16 ± 4</td>
<td>16 ± 4</td>
<td>21 ± 6</td>
<td>12 ± 5†</td>
</tr>
<tr>
<td>dP/dt (mm Hg/sec)</td>
<td>2623 ± 505</td>
<td>2341 ± 621</td>
<td>1908 ± 808</td>
<td>1968 ± 696</td>
</tr>
<tr>
<td>End-systolic volume (ml/m²)</td>
<td>28 ± 14</td>
<td>27 ± 18</td>
<td>41 ± 15</td>
<td>31 ± 7†</td>
</tr>
<tr>
<td>End-diastolic volume (ml/m²)</td>
<td>73 ± 31</td>
<td>76 ± 33</td>
<td>109 ± 35</td>
<td>95 ± 32†</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.58 ± 0.22</td>
<td>0.57 ± 0.24</td>
<td>0.43 ± 0.08</td>
<td>0.58 ± 0.11†</td>
</tr>
</tbody>
</table>

To test the variability of pressure and volume measurements in our laboratory, placebo was substituted for nifedipine in a separate group of six patients who underwent cardiac catheterization for evaluation of chest pain.

Dosage of nifedipine was 20 mg sublingually.

Control vs placebo: *p < 0.1.

Control vs nifedipine:

*p < 0.05.

†p < 0.01.

‡p < 0.001.


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