Effects of sublingual nifedipine on hemodynamics and systolic and diastolic function in patients with hypertrophic cardiomyopathy

SANDRO BETOCCHI, M.D., RICHARD O. CANNON III, M.D., RITA M. WATSON, M.D., ROBERT O. BONOW, M.D., HAROLD G. OSTROW, M.S., STEPHEN E. EPSTEIN, M.D., AND DOUGLAS R. ROSING, M.D.

ABSTRACT The hemodynamic effects of sublingual nifedipine were examined in 36 patients with hypertrophic cardiomyopathy. Twenty-one patients were initially given 20 mg and 15 patients were given 10 mg of the drug; 30 min after this first dose 26 patients received 10 mg and one patient 20 mg as a second dose. Hemodynamic findings in patients who received different doses of the drug were similar. Peak effects included an increase in heart rate from 79 ± 12 to 91 ± 14 (mean ± 1 SD) beats/min (p < .01), and a decrease in mean blood pressure from 89 ± 12 to 77 ± 10 mm Hg (p < .01). Cardiac index increased after nifedipine (2.8 ± 0.6 to 3.3 ± 0.8 liters/min/m²; p < .01); stroke volume index, however, did not change (36 ± 7 to 36 ± 8 ml/beat/m²; NS). Peripherical vascular resistance index fell significantly from 822 ± 261 to 610 ± 197 dynes-sec-cm⁻² (p < .01). Overall, left ventricular outflow tract gradient (LVOTG) did not change in patients with significant (≥30 mm Hg) basal LVOTG (75 ± 22 to 83 ± 22 mm Hg; NS), but it increased significantly in those six patients in whom peripheral vascular resistance fell by 25% or more (73 ± 28 to 99 ± 22 mm Hg; p < .05). Pulmonary arterial wedge pressure increased significantly in patients with normal (≤15 mm Hg) basal values (9 ± 3 to 14 ± 7 mm Hg; p < .01) and in patients with significant basal LVOTG (15 ± 8 to 20 ± 10 mm Hg; p < .01). In 10 patients, systolic and diastolic function were studied simultaneously by a nonimaging scintillation probe. No changes in systolic or diastolic function were detected when determinations obtained at the time of the peak nifedipine effect were compared with control values recorded at similar heart rates obtained by atrial pacing. The pattern of change in the pressure-counts loops after administration of nifedipine was not consistent; in only three of 10 patients was an improvement in the diastolic pressure-volume relationship observed. These results indicate that in patients with hypertrophic cardiomyopathy sublingual nifedipine induces a marked reduction in afterload without demonstrating any beneficial effects on LVOT obstruction and diastolic function. Moreover, in patients with normal pulmonary arterial wedge pressures and/or significant LVOTGs, nifedipine seems to be detrimental because it increases filling pressures, with these changes being exaggerated in patients with more marked falls in peripheral vascular resistance.

_Circulation 72, No. 5, 1001–1007, 1985._

SEVERAL STUDIES have demonstrated that verapamil, the prototype calcium channel–blocking drug, is an effective therapeutic agent for patients with hypertrophic cardiomyopathy. The administration of verapamil to these patients reduces left ventricular outflow tract (LVOT) obstruction, enhances diastolic function, and increases exercise capacity and reduces symptoms when given either over the short or long term.

Approximately one-third of patients who have been started on verapamil treatment, however, do not find this drug beneficial either because of its inability to reduce symptoms or because of adverse drug effects. Therefore, since the calcium channel-blocking drugs differ in their molecular structures, electrophysiologic properties, and hemodynamic effects, it seemed reasonable to examine the effects of another one of this category of drugs in patients with hypertrophic cardiomyopathy.
Although some reports indicate that administration of nifedipine to patients with hypertrophic cardiomyopathy has beneficial hemodynamic effects,13 the relatively small number of such patients treated with this drug, as well as some conflicting data,14, 15 make its clinical usefulness in the treatment of hypertrophic cardiomyopathy still unclear. Nifedipine, however, has the potential advantage over verapamil that it does not produce atioventricular conduction disturbances or sinus node depression, which are the most frequent side effects encountered during verapamil therapy.12, 16 In the present study we examined the hemodynamic effects of nifedipine in a large number of patients with hypertrophic cardiomyopathy, with and without LVOT obstruction.

Methods

Patient population. Thirty-six patients, 20 men and 16 women from 14 to 68 years old (mean 46), had echocardiographic evidence of hypertrophic cardiomyopathy (a nondilated hypertrophied left ventricle in the absence of other congenital or acquired heart diseases that produce left ventricular hypertrophy). Twenty-three patients (64%) had no evidence of mitral insufficiency on their left ventriculograms, whereas five patients (14%) had mild and eight (22%) had moderate-to-severe mitral regurgitation. No patient had 50% or more narrowing of the coronary artery luminal diameter. All agreed to participate in the study according to a protocol approved by the Institutional Clinical Research Subpanel of the National Heart, Lung, and Blood Institute. Cardiac catheterizations were performed for diagnostic reasons and/or to guide therapy. No patient underwent an invasive procedure solely for the purpose of determining effects of nifedipine.

At admission, only one patient (3%) was asymptomatic (NYHA functional class I), 15 (42%) patients were functional class II, 18 (50%) were functional class III, and two (6%) were functional class IV. Only three patients (8%) were free of chest pain; 21 (59%) had a history of mild chest pain and 12 (33%) had moderate-to-severe chest pain, compatible with angina. Propranolol had been administered to 33 patients. Cardiac medications were discontinued at least five drug half-lives before catheterization. Each patient received 10 mg of oral diazepam 1 hr before study and had been in a fasting state for at least 8 hr before coming to the catheterization laboratory.

Hemodynamic measurements. Left ventricular pressure was obtained through a pig-tail catheter (end-hole only, no side holes) in 25 patients and through a micromanometer-tipped catheter (Millar Instruments, Inc., Houston) in 11. Catheters were placed at the apex of the left ventricle by the retrograde femoral technique. Catheter entrapment18 was excluded by the guidelines proposed by Wigle et al.19 Pulmonary arterial wedge pressure was determined with a Swan–Ganz catheter placed by the antegrade femoral technique. Cardiac output was measured with the right heart catheter by the thermodilution technique with a cardiac output computer (Edwards Laboratories, Inc., Santa Ana, CA) and by averaging at least three replicate determinations. Left ventricular stroke volume was calculated from the cardiac output. Systemic blood pressure was measured by means of a No. 20 4 inch Teflon brachial artery catheter. Left ventricular outflow tract gradient was defined as the difference between the peak left ventricular and peak systemic systolic pressures. In 18 patients, measurements of LVOT gradient (LVOTG) were repeated during a Valsalva maneuver, amyl nitrite inhalation, or isoproterenol infusion. Systemic resistances were measured in units of dynes·sec·cm⁻⁵.

In the 11 patients studied with micromanometer catheters, left ventricular relaxation was assessed by digitizing the left ventricular pressure curve and computing the time constant (T) of the fall in left ventricular pressure.20 In patients in whom a single exponential equation did not adequately fit the actual points of the digitized left ventricular pressure curve, a biexponential fitting was used and two time constants were calculated. The first constant (T1) described the behavior of the left ventricular pressure curve during the first 40 msec after peak negative dp/dt and second one (T2) described that during the following 40 msec.21

Radionuclide measurements. In 10 patients studied with micromanometer catheters, left ventricular time-activity curves and pressure-counts loops were obtained by use of a nonimaging scintillation probe, the characteristics of which have been described in detail elsewhere.10, 22 At the beginning of right heart catheterization, red blood cells were labeled in vivo with 15 to 20 mCi²⁰¹ TC. After 10 min, systemic antiocoagulation with heparin (5000 units iv) was instituted and left heart catheterization was begun.

The probe was positioned over the patient's chest in a 35 degree left anterior oblique projection with a 15 degree caudal tilt, and adjusted over the precordium to maximize the background-uncorrected ejection fraction. Electrocardiographically gated equilibrium scintillation data and digitized left ventricular pressure values were collected for the first 140 cardiac cycles falling within a preset range of cycle lengths.

The following measurements were made: end-diastolic volume (EDV; normalized by setting the control number of counts = 100); ejection fraction; and peak filling rate (PFR in end-diastolic volumes per second = EDV/sec) and time to PFR (TPFR), defined as the time interval from the nadir of the time-activity curve, i.e., end-systole to PFR. Instantaneous relationships between left ventricular pressure and volume were analyzed by generating high temporal resolution (25 msec) pressure-counts loops, representing the average of 140 cardiac cycles. Since it was anticipated that nifedipine would increase heart rate, control radionuclide studies were obtained during atrial pacing at heart rates 10 to 30 beats/min faster than those recorded in the initial control study to avoid any effect of heart rate on left ventricular filling.

Administration of nifedipine. Nifedipine was administered buccally with the patients breaking the capsule(s) in their mouths and chewing them until the contained liquid appeared to be absorbed or diluted; the capsule(s) were then swallowed. Hemodynamic measurements were repeated 10, 20, and 30 min after swallowing the remnants of the capsule(s), whereas radionuclide studies were performed only once after each dose: at 20 minutes in five patients and at 30 min in the remaining five patients.

Initial nifedipine dose was 20 or 10 mg, determined by the investigator performing the catheterization, and based on the control blood pressure, outflow tract obstruction, and symptomatic status of the patient. A second dose was administered 30 min after the first if systolic blood pressure remained above 99 mm Hg.

Data analysis. Peak effect of nifedipine was defined for each parameter as the maximal change from the control value. Control values were compared with peak effect values with the two-tailed Student t test for paired samples. The difference between doses was assessed by comparing the percentage changes from the control values by means of the two-tailed Student t test for unpaired samples. The chi-square test was performed to determine whether the occurrence of peak effect after the first or the second dose was affected by the total nifedipine dosage.
PATHOPHYSIOLOGY AND NATURAL HISTORY–CARDIOMYOPATHY

Results

Nifedipine dosage. Twenty-one patients received 20 mg as their first dose and the remaining 15 patients were given 10 mg. Nine patients did not receive the second dose, six because their systolic blood pressures dropped below 99 mm Hg and the remaining three for various clinical reasons. Of these nine, seven had been given a first dose of 20 mg and two a first dose of 10 mg. Twenty-six patients were given 10 mg as their second dose and one patient received 20 mg. A total nifedipine dose of 10 mg was administered to two patients (5%) and 20 patients (56%) received 20 mg; 30 mg was the total dose in 13 patients (36%) and only one patient received 40 mg. For practical purposes, in the analysis of the data this latter patient’s hemodynamic responses to the drug will be included with those of patients receiving 20 + 10 mg of nifedipine.

Dose-effect relationship. Table 1 illustrates the maximal changes after nifedipine expressed as a percentage of the control value. No significant differences were observed between patients receiving 10 mg and those receiving 20 mg as their first dose, neither during the 30 min after the first dose nor during the 30 min after the second dose.

Maximal effect on heart rate occurred more frequently after the second dose than after the first (63% vs 37%), whereas peak effect of nifedipine on mean blood pressure, pulmonary arterial wedge pressure, cardiac index, and index of peripheral vascular resistance occurred with comparable frequencies after the first and second doses of nifedipine. No significant differences in the timing of the peak effects of the drug were found when results were analyzed separately according to the first dose. Moreover, no differences in hemodynamic measurements were observed when they were analyzed according to the total dose instead of the first dose.

Hemodynamics. One patient (3%) had a basal heart rate faster than 100 beats/min (105 beats/min) and none had a rate slower than 60 beats/min. In eight patients (22%), cardiac index was less than our established lower limits of normal (2.5 liters/min/m²). Fourteen patients (39%) had pulmonary wedge pressures higher than the upper limit of normal in our laboratory (15 mm Hg) and 24 (67%) had higher than normal left ventricular end-diastolic pressures (>12 mm Hg). An LVOTG of 30 mm Hg or more in the control study was present in 17 patients (47%) (range 35 to 105 mm Hg, median 85 mm Hg). Of the remaining 19 patients, 11 developed LVOTGs of 30 mm Hg or more during provocative maneuvers (Valsalva in two patients, amyl nitrite inhalation in four, and isoproterenol infusion in five). Thus, 28 of the 36 patients (78%) met our criteria for the diagnosis of obstructive hypertrophic cardiomyopathy.

Since no difference had been observed among patients receiving different doses of nifedipine, all results were analyzed for the group as a whole, independent of the dosage. Table 2 lists the mean hemodynamic values ± 1 SD at control and at peak effect of nifedipine. Nifedipine produced a significant increase in heart rate and a decrease in mean blood pressure. Mean pulmonary arterial wedge pressure significantly increased with nifedipine, but this was confined primarily to those patients who started out with a normal wedge pressure (figure 1). In this group, mean wedge pressure increased from 9 ± 3 to 14 ± 7 mm Hg (p < .01) while in those patients who had an elevated control wedge pressure (>15 mm Hg), it did not change significantly (23 ± 6 to 24 ± 7 mm Hg; NS). In the group that started with a normal wedge pressure, pressure became abnormal in nine (41%) after nifedipine, while the drug resulted in normalization of pressure in only two patients (14%) with initially abnormal values. Five patients developed wedge pressures equal to or greater than 30 mm Hg after receiving nifedipine.

### TABLE 1
Peak nifedipine effects, expressed as percentage change from control values, during the 30 min after each dose

<table>
<thead>
<tr>
<th></th>
<th>First dose</th>
<th>p value</th>
<th>Second dose of 10 mg</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg</td>
<td>20 mg</td>
<td>10 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Heart rate</td>
<td>14 ± 12</td>
<td>15 ± 15</td>
<td>15 ± 16</td>
<td>12 ± 16</td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td>−12 ± 7</td>
<td>−8 ± 10</td>
<td>−14 ± 11</td>
<td>−9 ± 11</td>
</tr>
<tr>
<td>Mean pulmonary artery wedge pressure</td>
<td>8 ± 42</td>
<td>47 ± 78</td>
<td>6 ± 44</td>
<td>25 ± 37</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>16 ± 26</td>
<td>15 ± 20</td>
<td>12 ± 22</td>
<td>15 ± 16</td>
</tr>
<tr>
<td>Index of peripheral vascular resistance</td>
<td>−23 ± 19</td>
<td>−20 ± 17</td>
<td>−26 ± 16</td>
<td>−23 ± 14</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
One had started out with normal pressure and one had begun with wedge pressure of 30 mm Hg that increased to 36 mm Hg.

Left ventricular end-diastolic pressure exhibited a similar pattern: it rose significantly after nifedipine for the group as a whole (table 2). In patients who initially had normal values, it rose from 10 ± 1 to 16 ± 4 mm Hg (p < .01), but it did not change in patients who had elevated pressures (>12 mm Hg) at control (23 ± 6 to 26 ± 9 mm Hg; NS). In six patients, left ventricular end-diastolic pressure rose above 30 mm Hg after nifedipine administration; none of these patients had normal left ventricular end-diastolic pressures before nifedipine.

**TABLE 2**

| Hemodynamic data recorded during the control study and at the peak effect of nifedipine |
|----------------------------------|--|--|---|
|                                   | Control | Nifedipine | p value |
| Heart rate (beats/min)           | 79 ± 12 | 91 ± 14    | <.01    |
| Mean blood pressure (mm Hg)      | 89 ± 12 | 77 ± 10    | <.01    |
| Pulmonary arterial wedge pressure (mm Hg) | 15 ± 8 | 18 ± 9    | <.05    |
| LV end-diastolic pressure (mm Hg) | 18 ± 8 | 22 ± 9    | <.01    |
| Cardiac index (l/mm²/m²)         | 2.8 ± .6 | 3.3 ± .8 | <.01    |
| Stroke volume index (m³/beat/m²) | 36 ± 7 | 36 ± 8    | NS      |
| Index of peripheral vascular resistance (dynes·sec·cm⁻¹) | 822 ± 261 | 610 ± 197 | <.01    |
| LVOTG (mm Hg)                     | 75 ± 22 | 83 ± 32    | NS      |
| Time constant of relaxation (msec)¹ | 49.1 ± 9.6 | 47.1 ± 13.7 | NS |
| T                               | 49.1 ± 9.6 | 47.1 ± 13.7 | NS |
| T1                              | 47.4 ± 11.1 | 50.6 ± 18.4 | NS |
| T2                              | 35.5 ± 11.6 | 45.9 ± 14.7 | NS |

Values are mean ± SD.

¹Measured in 17 patients with LVOTGs ≥ 30 mm Hg in the control study.

²Measured in 11 patients in whom left ventricular pressure was obtained with micromanometer-tipped catheters.

Cardiac index increased significantly after administration of nifedipine, but stroke volume index remained unchanged (table 2), even when data of patients with moderate-to-severe mitral regurgitation were excluded (36 ± 6 to 37 ± 8 ml/beat/m²; NS). The index of peripheral vascular resistance fell significantly with nifedipine.

Nifedipine had no effect on the magnitude of the LVOTG (table 2). Among 17 patients with significant basal gradients (≥ 30 mm Hg) at control, the gradient decreased below 30 mm Hg in one patient, whereas it rose to 30 mm Hg or more in two of 19 patients who started out with a nonsignificant gradient (figure 2).

Six patients who initially had LVOTGs of less than 100 mm Hg developed gradients of 100 mm Hg or more after nifedipine, including one patient whose initial gradient was 35 mm Hg. In a subgroup of six patients in whom vascular peripheral resistance decreased by 25% or more after nifedipine, the LVOTG increased from 73 ± 28 to 99 ± 22 mm Hg (p < .05; figure 3). In all six patients, both pulmonary arterial wedge pressure (figure 4) and left ventricular end-diastolic pressure increased (11 ± 4 to 20 ± 9 mm Hg [NS], and 15 ± 8 to 27 ± 12 mm Hg [p < .05], respectively). Valsalva maneuver or amyl nitrite inhalation were repeated after nifedipine in those patients in whom (1) a significant LVOTG was not present in the control study, but it developed with interventions, and (2) the drug itself did not induce a significant LVOTG. Gradients obtained with provoked were compared in seven patients before and after administration of nifedipine, and were not significantly different (63 ± 33 to 67 ± 28 mm Hg; NS).
INFLUENCE OF NIFEDIPINE ON LVOTG

Figure 3 illustrates the effects of nifedipine on pulmonary arterial wedge pressure in patients with and without significant basal LVOTGs. Pulmonary arterial wedge pressure increased in all but three patients with significant gradients and for the group rose from 15 ± 8 to 20 ± 10 mm Hg (p < .01). This change was not seen in patients without obstruction in the control study (14 ± 9 to 15 ± 7 mm Hg: NS). No further differences between patients with and without obstruction were noted with respect to nifedipine effects on the other hemodynamic parameters.

Left ventricular relaxation, as assessed by the time constants T, T1, and T2, was not affected by nifedipine (table 2).

Radionuclide data. To avoid any effect of heart rate on diastolic function measurements, we compared values obtained at the time of peak effect of nifedipine with those recorded at comparable heart rates obtained by atrial pacing in the control period. The results are presented in table 3. No changes were observed in end-diastolic volume and in ejection fraction. Rapid diastolic filling, as assessed by PFR and TPFR, was also unchanged. The analysis of responses of the diastolic pressure-counts curves showed improvement in three patients (rightward or rightward-downward shift), no modification in three patients (no changes or rightward-upward shift), and deterioration of the diastolic pressure-volume relationship in the remaining four patients (upward or leftward or upward-leftward shift) (figure 5).

Among the 10 patients who underwent radionuclide study, four had significant LVOTGs during the baseline study. Although the small number of such patients does not allow statistically meaningful analysis, no trend was observed suggesting a difference in systolic and diastolic function responses to nifedipine between

![Figure 3](image_url)

FIGURE 3. Influence of nifedipine on LVOTG in patients in whom administration of nifedipine led to a decrease in peripheral vascular resistance of less than 25% (left) or of 25% or greater (right). Open circles with vertical bars represent mean values ± 1 SD. C = control values; N = peak values after nifedipine.

![Table 3](image_url)

TABLE 3: Effects of nifedipine on radionuclide measurements

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Nifedipine</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>88 ± 14</td>
<td>89 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>End diastolic (% of control)</td>
<td>100</td>
<td>124 ± 39</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>72 ± 14</td>
<td>70 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td>PFR (EDV/sec)</td>
<td>4.5 ± 1.7</td>
<td>4.3 ± 2.0</td>
<td>NS</td>
</tr>
<tr>
<td>TPFR (msec)</td>
<td>228 ± 72</td>
<td>203 ± 86</td>
<td>NS</td>
</tr>
</tbody>
</table>

![Figure 4](image_url)

FIGURE 4. Influence of nifedipine on pulmonary arterial wedge pressure (PWP) in patients without (left) and with (right) significant basal LVOTG obstruction. Dashed lines indicate patients in whom peripheral vascular resistance fell by 25% or more after administration of nifedipine. Open circles with vertical bars represent mean values ± 1 SD. C = control values; N = peak values after nifedipine.

![Figure 5](image_url)

FIGURE 5. Relationship between left ventricular (LV) pressure and counts (proportional to left ventricular volume) before and after administration of nifedipine to one patient. Each point represents the number of counts collected during 25 msec and the corresponding left ventricular pressure, averaged for 140 beats. Nifedipine shifts the diastolic pressure-volume relationship leftward and slightly upward as compared with that during the control study, which was recorded at a comparable heart rate obtained by atrial pacing (104 beats/min for both studies).

Vol. 72, No. 5, November 1985
patients with and those without LVOT obstruction. When data from three patients with moderate-to-severe mitral regurgitation were excluded from the analysis, a significant increase in relative end-diastolic volume was observed (100 to 136 ± 39; p < .05), whereas no changes occurred in any of the other parameters.

Discussion
The hemodynamic effects of nifedipine in patients with hypertrophic cardiomyopathy in this study were unrelated to the dose administered, as has already been shown by others in patients with coronary artery disease. In another aspect of this study, we also demonstrated no difference in nifedipine plasma concentrations over 60 min in two groups of subjects taking different sublingual doses of the drug. The hemodynamic effects of nifedipine, however, were related to plasma concentrations of the drug. Therefore, the failure to show a correlation between dose and effect appears to be the consequence of the lack of relationship between dose and plasma concentration of the drug.

As anticipated, the predominant hemodynamic response of these patients to nifedipine was the fall in blood pressure as a result of diminished peripheral vascular resistance. This finding is similar to that seen when verapamil is administered to these patients, but in contrast to the effects of verapamil, no decrease in LVOTG was observed.

The reason for this lack of beneficial effect seems to be severalfold. The administration of nifedipine had no apparent effect on systolic and diastolic function in this study. Relative end-diastolic volume was not changed by nifedipine for the group as a whole, although it did increase in patients without significant mitral insufficiency. Despite the afterload reduction and the increase in cardiac output, relaxation and filling (as assessed by the time constant of isovolumetric fall in left ventricular pressure, peak filling rate, and time to peak filling rate, respectively) were not improved after administration of nifedipine. The diastolic pressure-counts relationship was improved in only three patients in whom larger diastolic volumes were achieved at unchanged or lower diastolic pressures; in these patients, however, changes in filling parameters were not consistent in that PFR did not increase in any, and TPFR shortened in two.

These results contrast with the data in patients with hypertrophic cardiomyopathy who were studied before and after verapamil. After oral verapamil, an increase in PFR and shortening of TPFR were observed. After intravenous verapamil, the diastolic pressure-counts relationship shifted rightward and/or downward in five of 10 patients and this improvement was associated with an amelioration of filling parameters improved diastolic function after verapamil occurred in these patients despite significant negative inotropic effects. Thus, the relative lack of effect of nifedipine, which appears to contrast with the more consistent beneficial effects of verapamil, on LVOT obstruction can be explained by its pronounced vasodilative action, which was unopposed by either a tendency to enhance diastolic function or depress systolic performance.

The fact that we did not observe any improvement in diastolic function with nifedipine contrasts with findings of Lorell et al. They used M mode echocardiography to measure volumes and observed no increase in left ventricular systolic and diastolic dimension after administration of nifedipine. However, left ventricular relaxation and diastolic filling, assessed by the peak rate of changes in left ventricular dimension, were reported to be improved by sublingual administration of the drug. Several factors could account for the discrepancy between their results and ours. First, in Lorell's study, heart rate increased by 10% and diastole shortened by 27%, whereas in our radionuclide study we avoided heart rate–induced effects by using atrial pacing in the control study. Second, the M mode echocardiography used by the authors is suboptimal for the evaluation of volume changes because of the abnormalities of shape and the structural inhomogeneity of the left ventricle in patients with hypertrophic cardiomyopathy. Finally, different degrees of left ventricular hypertrophy and subendocardial ischemia in their patients and ours could be responsible for the different results. Although none of the patients in our study had angiographic evidence of coronary artery disease, most had been experiencing chest pain that was compatible with angina and the presence of myocardial ischemia. It is noteworthy that, among the patients in whom radionuclide studies were performed, nifedipine increased PFR in three of the four patients with moderate to severe angina, and reduced TPFR in all four.

In patients with basal LVOTG, pulmonary arterial wedge pressure increased significantly after nifedipine, whereas no effect was observed in patients without significant obstruction. Moreover, among patients with a significant LVOTG in the basal state in whom administration of nifedipine led to a decrease in peripheral vascular resistance of 25% or more, pulmonary arterial wedge pressure increased in all and was associated with an increase in LVOTGs in five of six patients (figures 3 and 4). Hence, the elevation in filling pressures that occurred in many patients (26/36, 72%) after
PATHOPHYSIOLOGY AND NATURAL HISTORY—CARDIOMYOPATHY

nifedipine may have been caused by the increase in LVOT obstruction (due to nifedipine-induced decreases in afterload) in addition to the lack of a consistent beneficial effect on diastolic function.

Nifedipine, like verapamil, increased pulmonary arterial wedge and end-diastolic pressures in patients with normal baseline values. Verapamil, however, tended to decrease elevated pressures, at a trend that was not observed with nifedipine. Moreover, it should be noted that although 39% of the patients started out with abnormal pulmonary wedge pressure, after nifedipine pulmonary wedge pressure was elevated in 58% of the patients, reaching a value of 30 mm Hg or more in 14%.

In conclusion, the predominant effect of short-term administration of nifedipine to patients with hypertrophic cardiomyopathy was a lowering of systemic pressure as a result of peripheral vasodilation; this was unassociated with any consistent effect on systolic or diastolic performance. In some patients with basal outflow obstruction, the drop in blood pressure produced some results that could induce hemodynamic instability, including (1) an increase in left ventricular filling pressures, and (2) an increase in LVOTG. Our data also suggest that left ventricular diastolic filling might improve after nifedipine in those patients with more severe myocardial ischemia. Verapamil exerts a similar, although less pronounced, effect on peripheral vascular resistance; however, such an effect is counterbalanced by a direct action on the systolic and diastolic performance of the myocardium. Although data obtained after sublingual, acute nifedipine administration cannot be extrapolated to the clinical results of long-term therapy, we have demonstrated that oral therapy with nifedipine does not favorably affect short-term symptomatic status and exercise tolerance.14

We acknowledge the technical assistance of Frederick Bullock, Rita Minchmeyer, Kathleen Nonnenmacher, Marjorie Rimmer, and Gail Tauscher in the acquisition of data for this manuscript.

References

Effects of sublingual nifedipine on hemodynamics and systolic and diastolic function in patients with hypertrophic cardiomyopathy.

S Betocchi, R O Cannon, 3rd, R M Watson, R O Bonow, H G Ostrow, S E Epstein and D R Rosing

_Circulation_. 1985;72:1001-1007
doi: 10.1161/01.CIR.72.5.1001

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1985 American Heart Association, Inc. All rights reserved.
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:
http://circ.ahajournals.org/content/72/5/1001