Effects of Nifedipine on Left Ventricular Diastolic Function in Patients With Asymptomatic or Minimally Symptomatic Hypertrophic Cardiomyopathy

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We investigated the effects of nifedipine on left ventricular diastolic function in 17 asymptomatic or minimally symptomatic patients with hypertrophic cardiomyopathy by simultaneously measuring left ventricular pressure and volume with a catheter-tipped manometer and biplane cineangiography. Studies were performed before and 20 minutes after sublingual administration of nifedipine (20 mg). Heart rates were held constant (79±12 beats/min, mean±SD) by right atrial pacing. Left ventricular volumes and instantaneous rates of left ventricular volume were derived from frame-by-frame (20-msec) analyses of left ventricular biplane angiograms. Left ventricular peak systolic pressure (from 122±21 to 108±13 mm Hg, p<0.01 vs. control) and mean aortic pressure (from 96±15 to 87±11 mm Hg, p<0.01) decreased significantly with nifedipine. With afterload reduction, left ventricular ejection fraction (from 0.69±0.12 to 0.74±0.08, p<0.01) and cardiac output (from 6.4±2.0 to 7.2±2.2 l/min, p<0.05) increased significantly. However, there was a slight but significant increase in left ventricular end-diastolic pressure (from 15±8 to 18±8 mm Hg, p<0.05). Nifedipine did not improve left ventricular relaxation as assessed by the time constants of isovolumic pressure decay (t1/2, from 39.8±6.6 to 39.4±7.7 msec, NS; t1/4, from 53.8±9.0 to 54.4±10.7 msec, NS). The peak filling rate of left ventricular volume during the rapid filling phase significantly increased with nifedipine (from 511±127 to 627±154 ml/sec, p<0.05), but when the peak filling rate was normalized for stroke volume, there was no statistically significant change (from 5.46±1.03 to 6.20±1.46 sec⁻¹, NS). The time from end systole to the peak filling rate also remained unchanged with nifedipine (from 204±36 to 196±34 msec, NS). The left ventricular diastolic pressure-volume relation was shifted downward (indicating improved left ventricular distensibility) in only one of 14 patients. We conclude that nifedipine does not improve left ventricular relaxation, diastolic filling, and distensibility in patients with hypertrophic cardiomyopathy who have minimal or no impairment of functional status. This finding suggests that abnormal left ventricular diastolic function is not necessarily associated with myocardial ischemia or intracellular calcium overload in hypertrophied myocardium in a mild form of hypertrophic cardiomyopathy. (Circulation 1990;81:593-601)

It is well known that hypertrophic cardiomyopathy is usually associated with abnormal left ventricular isovolumic relaxation1-5 and diastolic filling.1,2,5,6 Several recent studies have indicated that calcium blocking agents, especially verapamil, produce beneficial effects on diastolic dysfunction in some patients with hypertrophic cardiomyopathy.3,7-10 However, there are conflicting data on the effectiveness of nifedipine on left ventricular diastolic function in hypertrophic cardiomyopathy.11-13 Lorell et al11 and Paulus et al12 have demonstrated that nifedipine favorably modifies abnormal left ventricular diastolic properties in hypertrophic cardiomyopathy, probably by improving...
myocardial ischemia or correcting intracellular calcium overload. In contrast with these reports, Betocchi et al.\textsuperscript{13} reported that nifedipine generally does not have any effect on left ventricular systolic or diastolic function and even seems to have a detrimental effect in some patients because it increased diastolic filling pressures. Although the reasons for this discrepancy are not clear, several factors might be responsible for these results. First, these studies included some patients with left ventricular outflow obstruction, which might be modified by nifedipine-induced vaso-dilation and thus affect left ventricular diastolic function. Second, the patients in these studies had various functional impairments. Nifedipine has been shown to exert beneficial effects on ventricular filling pressure in patients with impaired left ventricular function but not in those with normal function,\textsuperscript{12} and nifedipine might also have a beneficial effect on left ventricular relaxation in heart failure.\textsuperscript{15} These factors might have affected the results of these studies.

There have been no investigations on the effects of nifedipine on left ventricular diastolic function in hypertrophic cardiomyopathy without or with only mild functional impairment. The purpose of this study was to investigate the effects of nifedipine on left ventricular diastolic function and to speculate on the role of myocardial ischemia and intracellular calcium overload in the hypertrophied myocardium in patients with asymptomatic or minimally symptomatic hypertrophic cardiomyopathy.

**Methods**

**Patient Population**

Studies were conducted in 17 patients with hypertrophic cardiomyopathy. There were 16 men and one woman whose average age was 49 years (range, 28–59 years) and who had undergone cardiac catheterization for clinical diagnosis. The diagnosis of hypertrophic cardiomyopathy was based on clinical, echocardiographic, and angiographic evaluation according to the criteria of the Study Group of Idiopathic Cardiomyopathy of Japan.\textsuperscript{16} Based on echocardiographic and angiographic classification of the site and extent of left ventricular hypertrophy, eleven patients had asymmetrical septal hypertrophy, with the septum being 15 mm or more in thickness with a septal to posterior wall ratio of 1.3:1 or more. Two patients had symmetrical concentric hypertrophy, and four patients had apical hypertrophy. The thickness of the interventricular septum and posterior free wall was 17±5 and 12±2 mm as determined from echocardiograms. All patients were in normal sinus rhythm and had received no drug treatment before cardiac catheterization. Eight were in functional class I, and nine were in functional class II according to the New York Heart Association (NYHA) criteria. Eight asymptomatic patients (functional class I) were referred to our hospital for cardiac catheterization because of electrophysiographic abnormalities. No patient had a history of heart failure and a resting left ventricular outflow tract pressure gradient. In all patients, cardiac catheterization was performed for diagnostic reasons or to guide medical therapy.

Informed consent was obtained from each patient, and no complication occurred as a result of this study.

**Study Protocol**

Cardiac catheterization was performed by the percutaneous femoral approach in the fasting state and under premedication with hydroxyzine hydrochloride injected intramuscularly (50 mg). All patients underwent routine right and left heart catheterization from which cardiac output measurements were obtained. After this procedure, left ventricular pressure measurements, biplane cineventriculograms, and cardiac output measurements were obtained before and after sublingual administration of 20 mg nifedipine. To avoid any effect of heart rates on left ventricular function, we maintained constant heart rates by right atrial pacing at 10 beats/min faster than basal heart rates before and after nifedipine administration. Left ventricular pressure was measured with an 8F pigtail angiographic micromanometer-tipped catheter (Millar Instruments, Houston, Texas), and cardiac output was measured with the thermodilution technique. After a pause of at least 15 minutes for dissipation of the effects of the contrast material in the control left ventriculogram, we confirmed that left ventricular pressure had returned to the control state value. We excluded patients in whom left ventricular peak systolic pressures and end-diastolic pressures did not return to the baseline level within 30 minutes after a first ventriculogram. We then administered 20 mg nifedipine sublingually. After 20 minutes, we obtained repeat hemodynamic measurements and a second ventriculogram with the use of an identical dose of contrast agent. After the completion of the protocol and during isoproterenol infusion or a Valsalva maneuver, we again measured the intraventricular pressure gradient in all patients. No patient showed an intraventricular pressure gradient while in the control state and while after receiving sublingual nifedipine. Two patients developed a pressure gradient on provocation. Selective coronary angiography was performed with the Judkins technique in all the patients. No patient had significant coronary artery stenosis of more than 50% in the major coronary arteries.

Simultaneous biplane cineventriculograms were obtained in the 30° right anterior oblique and 60° left anterior oblique projections by injecting 40 ml sodium and meglumine diatrizoate (Urogramin) or iopamidol (Iopamiron) at a rate of 12 ml/sec. The film speed was 50 frames/sec.

Left ventricular pressures and the first derivative of pressure (dP/dt) were recorded simultaneously during ventriculography at a paper speed of 150 mm/sec (VR-12, Electronics for Medicine, Pleasantville, New York), and an electrically triggered cineracrer marked the radiographic film and sent a
timing signal to the recorder for simultaneous measurement of pressure and volume. Central aortic pressure was recorded immediately before each ventriculogram. The micromanometer-tipped catheter was calibrated against luminal pressures with a fluid-filled system at intervals throughout the study. In seven patients, right atrial and ventricular pressures were measured with a fluid-filled system and strain-gauge transducers (model P23XL, Statham-Gould, Cleveland, Ohio) before and after nifedipine administration. The reference level for zero pressure was 5 cm below the sternal angle.

Data Analysis

To assess the effect of nifedipine on left ventricular relaxation, we calculated two indexes: the isovolumic relaxation time and the time constant of isovolumic pressure decay. The isovolumic relaxation time was defined as the period from the point of end-systolic volume (the smallest left ventricular cavity volume) to 20 msec before the first frame showing the entry of unopacified blood into the left ventricular cavity. To calculate the time constants of pressure decay, left ventricular pressure was measured every 5.0 msec from the point of minimal dP/dt to a level 5 mm Hg above the end-diastolic pressure of the next beat. Left ventricular pressure and time during this interval were fit by an exponential method with a variable asymptote to the following equation: P(t) = ae^{−bt} + c, where P is left ventricular pressure (mm Hg), t is time (msec), c is the asymptote of pressure fall (mm Hg), and a, b are constants. From this equation, two time constants were calculated and were defined as the times required for the left ventricular pressure to decay to 1/e (t1/2) and half (t1/2) of its value at left ventricular peak negative dP/dt according to the method of Mirsky.17 The mean correlation coefficients of the exponential fits with a variable asymptote were 0.998 (range, 0.996–0.999). There was no significant change of the correlation coefficients at control and after nifedipine administration.

To assess the effects of nifedipine on left ventricular diastolic volume dynamics, we analyzed biplane left ventricular silhouettes by digitizing frame by frame (50 frames/sec) and calculated left ventricular volumes by the biplane area-length method.18 All beats were analyzed during right atrial pacing, and postextrasystolic beats were excluded. Biplane cineangiograms of 14 patients could be satisfactorily digitized frame by frame for an entire cardiac cycle before and after nifedipine administration. To describe left ventricular early diastolic filling, we measured the peak diastolic filling rate (PFR) of volumes and the time from the end-systolic frame to the PFR (TPFR). Because a curve derived from left ventricular volume plotted against time may contain some scatter, the volume-time curve was smoothed with a polynomial approximation technique. The third-degree polynomial was fit to each set of five consecutive points with the method of least squares. After digitizing and filtering, the volumes were differentiated, and the PFR and the TPFR were calcu-
Table I. Hemodynamic Data Before and After Sublingual Nifedipine Administration in 17 Patients With Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>LVPSP (mm Hg)</th>
<th>LVESP (mm Hg)</th>
<th>Mean AoP (mm Hg)</th>
<th>Peak (+)dP/dt (mm Hg/sec)</th>
<th>Peak (-)dP/dt (mm Hg/sec)</th>
<th>LVEDP (mm Hg)</th>
<th>RVEDP (mm Hg)</th>
<th>Mean RAP (mm Hg)</th>
<th>MVOP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>79±12</td>
<td>122±21</td>
<td>115±20</td>
<td>96±15</td>
<td>1,510±246</td>
<td>1,369±262</td>
<td>15±7</td>
<td>7±2</td>
<td>3±1</td>
<td>17±14</td>
</tr>
<tr>
<td>Nifedipine (20 mg)</td>
<td>79±12</td>
<td>108±13†</td>
<td>98±14†</td>
<td>87±11†</td>
<td>1,454±194*</td>
<td>1,204±225†</td>
<td>18±8†</td>
<td>7±3</td>
<td>3±2</td>
<td>25±10*</td>
</tr>
</tbody>
</table>

Data are mean±SD. HR, heart rate; LVPSP, left ventricular peak systolic pressure; LVESP, left ventricular end-systolic pressure; AoP, aortic pressure; LVEDP, left ventricular end-diastolic pressure; RVEDP, right ventricular end-diastolic pressure; RAP, right atrial pressure; MVOP, mitral valve opening pressure; CI, cardiac index; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; EF, ejection fraction; IRT, isovolumic relaxation time; \(t_1/2\), time constant of isovolumic pressure decay; PFR, peak filling rate; SV, stroke volume; TPFR, time to the peak filling rate; MVOP, mitral valve opening pressure.

*p<0.05, †p<0.01.

The PFR seems to be affected by total left ventricular stroke volume, the normalized PFR corrected for stroke volume (PFR/SV) was also calculated.

The left atrial pressure plays a role in left ventricular diastolic filling. Because we could not measure left atrial pressure, we recorded the pressure at the end of the frame of the isovolumic relaxation period described above. This pressure was defined as the opening pressure (driving pressure) and is an index of the left atrial pressure at the time of mitral valve opening.

The left ventricular pressure-volume curves were constructed before and after nifedipine administration (Figure 1). To assess the alterations in left ventricular diastolic chamber compliance, we plotted diastolic pressure-volume relations in all 14 patients from the point of minimal left ventricular pressure to the top of the atrial pressure waveform.

To define the baseline left ventricular function in this study population, we compared the data of these patients with those of 27 normal subjects who underwent diagnostic cardiac catheterization but who were found to have normal cardiac anatomy and function.

Statistical Analysis

The variables obtained at control and after nifedipine administration were analyzed with the paired \(t\) test. An intergroup comparison was performed with an unpaired \(t\) test. A significant difference was indicated by a \(p\) value less than 0.05 in paired and unpaired \(t\) tests. Values are expressed as the mean±SD.

Results

Baseline Left Ventricular Systolic and Diastolic Functions

All patients had normal left ventricular systolic pump function. The cardiac index, ejection fraction, and peak positive dP/dt were not significantly different from the normal values of 3.5±0.6 l/min/m², 0.68±0.05 and 1,364±208 mm Hg/sec, respectively (Table 1). Left ventricular relaxation, diastolic filling, and compliance, however, were abnormal with prolonged isovolumic pressure decay, increased TPFR, and an upward shift of the diastolic pressure-volume relation. The time constant of pressure decay (\(t_1/2\)) was significantly prolonged compared with that of normal subjects (38±5 msec, \(p<0.01\)). The TPFR was significantly greater than that of normal subjects (162±25 msec, \(p<0.01\)). This prolongation of the TPFR, in part, was a result of prolonged isovolumic relaxation time (normal subjects, 92±13 msec, \(p<0.01\)). Time from mitral valve opening to the PFR could be adequately measured in nine of the 14 patients. For this subgroup, there was no significant difference in this value compared with that from the normal control group (the nine patients, 82±30 msec; normal subjects, 70±21 msec; NS). For the five other patients, a distinct moment of the PFR could not be identified within the interval from mitral valve opening to the onset of atrial contraction. This suggests continuous slow filling throughout diastole in these five patients. The PFR and normalized PFR identified from mitral valve opening to the onset of atrial contraction in nine patients were not significantly different from those in normal subjects (502±160 ml/sec and 5.5±1.2 sec⁻¹). The value of left ventricular end-diastolic pressure of the patients was greater than that of the normal subjects (9±3 mm Hg, \(p<0.05\)). The left ventricular diastolic pressure-volume relations of the patients, as a whole, shifted upward compared with those of normal subjects. These findings demonstrate that our patients had abnormal left ventricular diastolic function as suggested by impaired relaxation, delayed early diastolic filling, and decreased diastolic compliance.
which are all characteristics of hypertrophic cardiomyopathy as previously reported. \(^1,^6,^22\)

**Hemodynamics and Left Ventricular Volumes**

Sublingual nifedipine significantly reduced mean arterial pressure \((p<0.01)\), left ventricular peak systolic pressure \((p<0.01)\), and left ventricular end-systolic pressure \((p<0.01)\) (Table 1). There was a slight but significant increase in left ventricular end-diastolic pressure \((p<0.05)\) (Figure 2). Cardiac output increased significantly \((p<0.01)\), and a concomitant and significant increase occurred in stroke volume after nifedipine administration. With a reduction in left ventricular end-systolic volume \((p<0.05)\), the ejection fraction significantly increased from a mean value of 0.69 to 0.74 \((p<0.01)\). The end-systolic pressure-volume relation shifted leftward and downward, suggesting no clear depressant effect of 20 mg sublingual nifedipine on left ventricular contractility.

Nifedipine-induced afterload reduction did not induce left ventricular outflow obstruction in any patient.

**Left Ventricular Relaxation and Diastolic Filling**

Peak negative dP/dt fell significantly with nifedipine \((p<0.01)\) (Table 1). The isovolumic relaxation time shortened slightly but significantly \((p<0.05)\). There was no significant improvement in left ventricular relaxation as assessed by the time constants of isovolumic pressure decay. (Figure 3)

The PFR of left ventricular volume during the rapid filling phase was measured in nine patients, in each of whom the diastolic phase of rapid filling, slow filling (diastasis), and atrial contraction could be identified on the time-volume curves. There was a significant increase in the PFR of left ventricular volume after the administration of nifedipine \((p<0.05)\). The mean normalized PFR also increased but not significantly. The TPFR of left ventricular volume was not significantly changed after nifedipine administration. The mitral valve opening pressure increased significantly \((p<0.05)\).

To test the hypothesis that the patients did not respond to nifedipine because of very localized left ventricular hypertrophy in which most of the left ventricular wall was made up of normal myocardium, we examined left ventricular isovolumic relaxation and diastolic filling in 13 patients, excluding those with apical hypertrophy. In the subgroup of 13 patients with asymmetrical septal hypertrophy and concentric hypertrophy, there was no significant improvement in the time constant of left ventricular isovolumic pressure decay, the normalized PFR, and the TPFR (Table 2).

**Left Ventricular Diastolic Compliance**

The response of the left ventricular diastolic pressure-volume relation to nifedipine was variable.
There was a downward shift in the diastolic pressure-volume relation (increased chamber compliance) in only one of 14 patients after nifedipine administration. Seven patients showed no changes, and six patients showed upward shifts of the diastolic pressure-volume curves. The improvement in diastolic distensibility in one patient, however, was associated with a reduction in left ventricular diastolic volume. In seven patients, right atrial and ventricular pressure recordings were available before and after nifedipine administration. There was no significant change in either right atrial or ventricular pressures, which are potential determinants of the left ventricular diastolic pressure-volume relation.

### Discussion

In this study, we investigated the effects of sublingual nifedipine on left ventricular function in asymptomatic or minimally symptomatic patients with hypertrophic cardiomyopathy by directly measuring pressure and volume with a catheter-tipped micromanometer and biplane cineangiography. The left ventricular systolic pump function was augmented by nifedipine, probably by afterload reduction resulting from its potent peripheral artery vasodilation. However, we recognized little or no beneficial effects of nifedipine on diastolic function in hypertrophic cardiomyopathy. The time constant of left ventricular isovolumic pressure fall was unaltered, and in only one of 14 patients, the left ventricular diastolic pressure-volume relation shifted downward with nifedipine, which indicates an improvement in overall left ventricular distensibility. Lorell et al. observed a rightward and downward shift of the left ventricular diastolic pressure-volume relation on nifedipine in some patients with hypertrophic cardiomyopathy. In our study, although one patient exhibited a leftward and downward shift, a rightward and downward shift was not observed in the left ventricular diastolic pressure-volume relation.

Several studies have reported that verapamil often improved clinical symptoms in patients with hypertrophic cardiomyopathy. Improved left ventricular relaxation, normalization of left ventricular filling, and increased left ventricular diastolic compliance have been suggested as being the main mechanisms of relief of symptoms in patients with hypertrophic cardiomyopathy after verapamil administration. Similar beneficial effects of nifedipine have been suggested in hypertrophic cardiomyopathy. Lorell et al. and Paulus et al. using combined M-mode echocardiography and a catheter-tipped micromanometer, reported that sublingual nifedipine (10 mg) significantly reduced the time constant of left ventricular isovolumic pressure decay, increased peak lengthening rate of left ventricular internal dimension, and improved left ventricular distensibility assessed by the pressure-dimension relation. Paulus et al. also demonstrated that nifedipine caused more improvement of left ventricular relaxation, diastolic filling, and distensibility in hypertrophic nonobstructive cardiomyopathy compared with nitroprusside. They suggested that the beneficial effects of nifedipine on diastolic mechanics in hypertrophic cardiomyopathy results not only from systemic vasodilation but also from improved cardiac muscle inactivation associated with the relief of subendocardial ischemia or the correction of an intracellular calcium overload or both.

Our patients showed a slight but significant increase in left ventricular end-diastolic pressure. Several investigators demonstrated that nifedipine had little or no direct effect on the peripheral venous system in humans. Kurnik et al. reported that left ventricular end-diastolic pressure and volume declined after sublingual nifedipine (20 mg) only in patients with impaired left ventricular systolic function. Left ventricular preload reduction, however, was not associated with alteration of peripheral venous hemodynamics, left ventricular chamber stiffness, and the time constant of left ventricular relaxation but was secondary to the improved left ventricular systolic function in response to afterload reduction. The increase of left ventricular end-diastolic pressure in our patients was accompanied by no significant change in right atrial pressure, right ventricular pressure, and left ventricular isovolumic relaxation. Thus, we speculated that an increase of left ventricular pressure might result, in part, from an increase in coronary blood flow (an “erectile” effect) with nifedipine rather than from other factors affecting the left ventricular diastolic pressure-volume relation. The coronary “erectile” effect seemed to be more pronounced in patients with
increased ventricular stiffness such as that caused by left ventricular hypertrophy. Further studies will be needed to clarify this point.

The common findings of the effects of nifedipine on left ventricular diastolic function in our study and in the studies by Lorell et al. and Paulus et al. are a reduction in isovolumic relaxation time and an increase in the PFR of left ventricular volume during the rapid filling period. Isovolumic relaxation time is multifactorially determined by aortic pressure, left atrial pressure (mitral opening pressure), left ventricular end-systolic pressure, the time constant of left ventricular pressure decay, and heart rate. The PFR of left ventricular volume (an index of early diastolic filling) seems to be mainly determined by the isovolumic relaxation rate (the time constant of isovolumic pressure decay), the magnitude of atrioventricular pressure gradient, heart rate, and, in part, by ventricular suction. In our study, heart rate was maintained at a constant level by right atrial pacing, and the time constant remained unchanged with nifedipine. Therefore, the shortening of the isovolumic relaxation time could be due to an increase in mitral valve opening pressure and a decrease in left ventricular end-systolic pressure. Similarly, an increase in mitral valve opening pressure and ventricular suction associated with reduced left ventricular end-systolic volume might be responsible for increased PFR with nifedipine administration. In fact, when the PFR was normalized for stroke volume, an increase in the normalized PFR was still not significant. Thus, in our study, the significant changes in the isovolumic relaxation time and PFR by nifedipine can be attributed to altered left ventricular loading rather than modification of intrinsic myocardial properties as suggested by the findings of Lorell et al. and Paulus et al.

The fact that we could not find significant improvement in left ventricular relaxation and diastolic compliance clearly contrasts with observations of Lorell et al. and Paulus et al. Several factors could be responsible for the discrepancy between our data and theirs. First, there were differences in the nifedipine dose administered. We administered 20 mg nifedipine sublingually, whereas they administered 10 mg. This is unlikely to be a factor, however, because in a previous study by Betocchi et al., no significant difference in hemodynamic measurements was observed between patients with hypertrophic cardiomyopathy receiving 10 mg and those receiving 20 mg. Second, there was a difference in the changes of heart rate. Alterations in heart rate have been shown to influence the time constant of left ventricular relaxation and filling and diastolic pressure-volume relations. We maintained constant heart rates by atrial pacing before and after nifedipine administration. In the studies of Lorell et al. and Paulus et al., heart rate significantly increased by 10 and 4 beats/min, respectively. However, the average increase in heart rate in their studies was too small to explain the differences between our results. Third, to assess left ventricular diastolic filling and compliance, we calculated left ventricular volume by biplane cineventriculography, whereas they measured left ventricular regional dimension by M-mode echocardiography. Previous studies have reported that there may be wide variability in the extent and site of hypertrophy in patients with hypertrophic cardiomyopathy. Thus, the M-mode echocardiography used in their study may have some limitations in the evaluation of global left ventricular function. However, we cannot explain the differences in the indexes of diastolic function assessed by left ventricular pressure (the time constant of isovolumic pressure decay and left ventricular end-diastolic pressure). Finally, the discrepancy may have resulted from the difference in the functional impairment between their study population and ours. All patients in our study were asymptomatic or minimally symptomatic (NYHA functional class I or II), whereas patients with severe functional impairment were included in their studies. Although Betocchi et al. did not find significant improvement in left ventricular diastolic function with nifedipine as a whole, they noted that nifedipine reduced the TPFR in a subgroup of patients with moderate and severe angina in hypertrophic cardiomyopathy, implying its beneficial effects of relieving myocardial ischemia. Recently, Gwathmey et al. recorded intracellular calcium transients with aequorin in the myocardium from patients with heart failure, including hypertrophic cardiomyopathy. They demonstrated abnormal intracellular calcium handling by the sarcolemma and sarcoplasmic reticulum in the myopathic muscle; the former may cause increased calcium entry, possibly through voltage-dependent channels, and the latter may cause slowed restoration of low resting tone during diastole because of a decreased rate of calcium resequestration. Wagner et al. demonstrated that calcium-antagonist binding sites, measured as the amount of dihydropyridine bound to atrial tissue, were increased significantly in highly symptomatic patients with hypertrophic cardiomyopathy who underwent cardiac surgery compared with binding sites in patients with other cardiac disorders. The increased density of myocardial calcium channels in patients with hypertrophic cardiomyopathy may be related to an augmented calcium flux across the sarcolemma. These findings suggest that nifedipine, by improving myocardial ischemia or correcting intracellular calcium overload, could favorably alter left ventricular diastolic dysfunction in patients with severe functional impairment in hypertrophic cardiomyopathy as reported by Lorell et al. and Paulus et al. Thus, we can speculate that the discrepancies between their results and ours are mainly caused by differences in the study population rather than in the methods. Based on these considerations, we may postulate that myocardial ischemia and intracellular calcium overload does not play a major role in the pathogenesis of left ventricular diastolic dysfunction in mild forms of hypertrophic cardiomyopathy, although further
experimental and clinical studies will be needed to test this hypothesis.

Our findings on the effects of nifedipine on left ventricular diastolic function are similar to those of Betocchi et al.\textsuperscript{13} However, there are different results with respect to systolic function despite a similar reduction in mean aortic pressure with nifedipine. We noted an augmented ejection fraction associated with a significant reduction in left ventricular end-systolic volume with nifedipine, whereas they found no significant change in systolic function despite afterload reduction. This discrepancy can also be explained by the differences in study population because patients with basal outflow obstruction were included in their study. In these patients, nifedipine-induced afterload reduction might lead to an increase in left ventricular outflow obstruction, resulting in a depressed systolic performance. Thus, our data can be interpreted as meaning that the negative inotropic action of sublingual 20 mg nifedipine is minimal and is counterbalanced by afterload reduction resulting from potent peripheral artery vasodilation in hypertrophic cardiomyopathy without basal outflow obstruction.

In this study, we measured left ventricular volumes with biplane cineangiography. Although volume calculation by the biplane area-length method is valid for various cardiac diseases,\textsuperscript{18} it may have limitations in assessing absolute left ventricular volumes in hypertrophic cardiomyopathy, perhaps because of the peculiar shape of the left ventricle near end systole. To minimize data variability of left ventricular volumes and derived hemodynamic indexes, the same investigator digitized all the cineangiograms before and after nifedipine administration.

In conclusion, left ventricular systolic performance in hypertrophic cardiomyopathy was augmented by systolic unloading with short-term sublingual administration of nifedipine. However, there was no improvement of left ventricular relaxation as assessed by the time constant of left ventricular isovolumic pressure fall, and only one patient exhibited a downward shift in the left ventricular diastolic pressure-volume relation, indicating improved diastolic distensibility with nifedipine. Thus, nifedipine seems to have little or no beneficial effect on left ventricular diastolic function in patients with hypertrophic cardiomyopathy who have minimal or no impairment of functional status. These findings also suggest that left ventricular diastolic dysfunction in a mild form of hypertrophic cardiomyopathy is not necessarily associated with myocardial ischemia and intracellular calcium overload in hypertrophied myocardium.

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