Acute Hemodynamic Responses to Sublingual Nifedipine: Dependence on Left Ventricular Function

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SUMMARY To characterize the acute effects of nifedipine on left ventricular (LV) systolic and diastolic function, we studied 32 patients stratified with respect to baseline LV function before and 30 minutes after nifedipine (20 mg sublingually) with a randomized, single-blind protocol. Nineteen patients received nifedipine and 13 received placebo. No change occurred in any variable after placebo. Nifedipine lowered left ventricular afterload, reflected by significant decreases in systolic, mean and diastolic arterial pressures of 13%, 10% and 17%, respectively. LV systolic pressure fell by 13%, ejection fraction, mean Vcf, mean normalized systolic ejection rate (MNSER), and the end-diastolic pressure/volume (P-V) ratio increased by 14%, 41%, 25% and 19%, respectively, and cardiac index rose by 16% (p < 0.05 for each). Overall, diastolic LV function did not change; diastolic pressures, early diastolic relaxation, diastolic exponential P-V and P-V elasticity relations and end-diastolic stiffness remained constant. However, among patients stratified according to baseline LV function (group 1: end-diastolic volume ≤ 90 ml/m², end-diastolic pressure ≤ 20 mm Hg; group 2: end-diastolic volume > 90 ml/m², end-diastolic pressure > 20 mm Hg) striking differences were evident. In group 2 patients, nifedipine decreased LV systolic and end-diastolic pressures, while LV end-diastolic and systolic volumes, and systemic and pulmonary vascular resistance all declined significantly, by 13%, 27%, 41% and 52%, respectively. Enhancement of ejection fraction (34%), Vcf (46%) and MNSER (41%) in group 2 patients was substantially more prominent than that in patients with normal baseline LV function (9%, 35% and 15%, respectively). Relaxation and diastolic stiffness properties were insignificantly changed in both groups, but the diastolic exponential P-V relation was displaced downward by nifedipine in patients with impaired baseline ventricular function, and cardiac output was increased by 25%, compared with a negligible change (3%) in group 1 patients.

These results show that nifedipine has significant, clinically favorable effects due predominantly to reduction of LV afterload in patients with impaired baseline LV function. Nifedipine reduced myocardial oxygen requirements, enhanced diastolic performance and consequently improved systemic and pulmonary hemodynamics, LV ejection function and cardiac output.

NIFEDIPINE appears to relieve variant
diastolic angina pectoris,
thought its mechanisms have not been
completely defined. Nifedipine and other calcium
antagonists modify the movement of calcium ions across
cell membranes — particularly in myocardium and
vascular smooth muscle — by inhibiting the slow in-
ward calcium channel. In cardiac muscle, calcium
activates ATPase of the contractile proteins. Thus,
calcium antagonists inhibit excitation-contraction
coupling, favoring relaxation of the muscle and induc-
ing a negative inotropic effect. Similarly, in vascular
smooth muscle, calcium antagonists diminish smooth
muscle contractility, which results in vasodilatation.
Although net consequences vary, combinations of
these two effects appear to underlie the therapeutic
efficacy of nifedipine in patients with angina due to
coronary vasospasm, fixed obstruction, or both, and
may facilitate myocardial preservation. In addition,
inhibition of calcium transport by nifedipine may
modify the rate of relaxation of cardiac muscle, though to depend on cytosolic concentrations of cal-
cium, thereby altering the diastolic properties of the
myocardium.

Hagemann et al. attributed the beneficial effects of the
drug in vivo to its ability to reduce left ventricular
(LV) preload and afterload. Conversely, Wolf et al. concluded that the antianginal effects of the drug do
not result from nitrate-like reduction of left ventricu-
lar filling pressure, while others have claimed that
nifedipine's antianginal effects depend on its ability to
augment cardiac output by increasing (sic) venous
return.

The present study was designed to characterize
the acute hemodynamic effects of nifedipine on car-
diovascular performance in patients stratified with
respect to baseline LV function. Because diastolic per-
formance is a sensitive indicator of early LV func-
tional impairment, we examined nifedipine's influence
on systolic and diastolic properties of the ventricle, as
well as its influence on the relationships between right
ventricular and LV mechanics.

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Methods

Patient Selection

Thirty-two patients (28 males and four females), mean age 52.3 years (range 33–71 years), were selected from those undergoing diagnostic cardiac catheterization for evaluation of chest pain. Additional criteria included the presence of sinus rhythm, the absence of acute myocardial infarction within the preceding 3 months, and the absence of valvular heart disease, peripheral vascular disease, or the need for continuing therapy with long-acting nitrates or \( \beta \)-blocking agents. All cardioactive medications were withdrawn gradually at least 24 hours before each study. All patients gave informed consent and were given either nifedipine (n = 19) or an identical appearing placebo (n = 13) with assignment made with the use of a random number code. There were no complications attributable to nifedipine or the investigational procedure.

Catheterization Procedure

Catheterization was performed with subjects in the fasting state, premedicated with 50–100 mg of i.m. hydroxyzine hydrochloride. Right- and left-heart hemodynamics and cardiac output were measured in all subjects in the basal state. A #5–7F micromanometer catheter (Millar Instruments, Inc.) was advanced to the LV percutaneously through the left femoral artery with an introducer equipped with a side channel through which arterial pressure was measured continuously. Left ventriculography was performed in the right anterior oblique projection with patients in the basal state, and again 30 minutes after administration of nifedipine or placebo; the contrast medium was injected through a #6–8F pigtail catheter. Ventriculography in the left anterior oblique projection was performed subsequently to ascertain the presence and extent of asynergy. Finally, selective coronary arteriography was performed with use of preshaped catheters.

Protocol

The techniques for measuring simultaneous LV pressure-volume (P-V) data have been described.7–12 Routine determinations of right- and left-heart hemodynamics and cardiac output were obtained initially. After careful positioning of catheters to avoid ectopic beats or erroneous pressure recordings due to myocardial entrapment of the micromanometer, intracardiac pressure measurements were repeated during held, submaximal inspiration without injection of contrast to provide a baseline for determination of hemodynamic changes attributable to the contrast injection. Left ventriculography was then performed under identical respiratory conditions with an ECG-triggered injector (Medrad Mark 4); 30–40 ml of sodium and meglumine diatrizoate (Hypaque-76) were injected over 3 seconds.

After a pause of at least 15 minutes to permit dissipation of the immediate effects of the contrast material,13–15 intracardiac pressure and cardiac output measurements were repeated. Sublingual nifedipine, 20 mg, or placebo was then administered. The subjects were instructed to retain the solution sublingually for as long as possible. After an interval of 30 minutes to allow for absorption, intracardiac pressures and cardiac output measurements were repeated and a second ventriculogram was performed under identical respiratory conditions.

Data Analysis

Comprehensive hemodynamic and volume analyses14 were performed using the first available adequately opacified sinus beat, avoiding ectopic beats and the first or second postectopic beat. In each case analysis was performed within the first three beats after onset of contrast injection when the effects of contrast upon myocardial function are negligible.13–15 Simultaneous LV pressures were measured serially from the high-fidelity pressure recording at 16.7-msec intervals corresponding to each volume determination during the interval between minimal diastolic and peak “a” wave pressures.7,9,11 LV P-V coordinates were fitted (least-squares technique) to the monoeponential function

\[
P = be^{kV}
\]

where \( P = \) LV pressure (mm Hg), \( V = \) LV volume (ml), \( b = \) data constant, \( e = \) base of the natural log, and \( k = \) rate constant of the monoeponential function, which was used as an index of LV diastolic chamber volume stiffness.7,10,11 To define the “position” of each P-V relation, P-V curves were extrapolated to the pressure (y) axis at zero volume.7,10,11 The pressure intercept at zero volume is mathematically derived and has no physiologic analog.

In addition, to permit evaluation of diastolic function in the presence of changing LV chamber dimensions induced by nifedipine, P-V relations were normalized with respect to initial LV volume at each P-V coordinate, based on the definition of volume elasticity.22,23 This normalized variable can be expressed in differentiated form:

\[
dP/dV/V = k_{\text{norm}} P + c
\]

where \( P = \) LV pressure (mm Hg), \( V = \) volume (ml), \( c = \) data constant, \( dP/dV/V = \) volume elasticity,7,23 and \( k_{\text{norm}} = \) the rate constant of the diastolic P-V elasticity relationship, used as an index for comparison of LV chamber stiffness normalized for the effects of varying chamber dimensions.

In view of the marked changes in end-diastolic pressures in some patients given nifedipine, diastolic P-V relations were also analyzed at end-diastole in terms of the “operational” end-diastolic chamber stiffness (dP/dV at end-diastole), which represents the diastolic P-V relation at the volume at which the LV was operating at the time of each ventriculogram,24 and the asymptotic slope of the end-diastolic log pressure-log volume relationship (IV/P) [dP/dV],25 which is relatively insensitive to LV pressure and geometry at pressures greater than 10 mm Hg, but is
related to and predominantly sensitive to changes in muscle stiffness.22, 23

LV relaxation was analyzed in terms of peak negative dP/dt;27 the time course of early diastolic relaxation (T), derived from the rate constant of the exponential LV pressure decay during isovolumic relaxation subsequent to peak negative dP/dt;28 and the angiographically derived isovolumic relaxation time.29 In view of recent suggestions that isovolumic relaxation may be bieponential, T was also analyzed in terms of modified T1 and T2 indexes29 derived from the first and second halves, respectively, of isovolumic relaxation.

Analysis of LV systolic function included both isovolumic (peak positive dP/dt) and ejection phase indexes (ejection fraction, mean velocity of circumferential fiber shortening [Vcf], mean normalized systolic ejection rate [MNSER]30 and the LV end-diastolic P-V ratio31).

Comparisons between data from individual patients under the different conditions were assessed using the paired t test. Group comparisons were assessed using the t test for differences between group means.

Results

Clinical Characteristics

Among the 19 patients given nifedipine, significant coronary arterial obstruction was documented in 11; four patients had asynergic contraction involving one or two regions of the LV wall. Mitral valve prolapse was present in one patient and no cardiac abnormality was observed in the remaining seven patients. Eight of the 13 patients given placebo had significant coronary disease; four had asynergy involving one or two segments. No cardiac abnormalities were evident in the remaining five patients.

Effects of Nifedipine on Hemodynamics and LV Performance (table 1)

Placebo did not significantly change any measurement.

Nifedipine lowered systemic arterial systolic and LV systolic pressures significantly by an average of 13%, and arterial mean and diastolic pressures by 10% and 17%, respectively. However, no statistically significant change occurred in LV minimal diastolic, peak "a" wave, or end-diastolic pressures. Conversely, both systolic and diastolic right ventricular pressures fell significantly by an average of 15% and 18%, respectively, implying reduction of central venous return.

Nifedipine lowered LV end-diastolic and end-systolic volumes significantly (average 9% and 23%, respectively) and augmented LV systolic function, reflected by an average increase in ejection fraction (14%), Vcf (41%), MNSER (25%) and end-systolic P-V ratio (19%).

The coefficients of determination (r) of the exponential fit to the isovolumic pressure decay averaged 0.996, similar to those for T1 (0.994) and T2 (0.998). The absolute values of T1 and T2 did not differ significantly from T before or after nifedipine. Nifedipine did not significantly alter the rate of early diastolic relaxation, though a trend toward its attenuation was suggested by the 13% prolongation of T (NS). The decline in peak negative dP/dt is difficult to interpret clinically in view of its sensitivity to changes in load, particularly aortic peak systolic pressure and LV end-systolic volume.28

Diastolic P-V coordinates were fitted to monoexponential functions with an average coefficient of determination of 0.918. For the overall patient population, both the average rate constant "k" and the y-axis intercept of the P-V function remained statistically unchanged, implying the absence of a direct effect of nifedipine on LV chamber volume stiffness. These observations were confirmed when P-V relations were normalized to compensate for concomitant changes in LV volume: neither the rate constant (knorm) nor the y-axis intercept of the P-V elasticity relation was changed by nifedipine. In addition, end-diastolic LV stiffness remained constant.

Effects of Nifedipine Among Patients with Impaired Basal LV Function (fig. 1, tables 1, 2, 3)

To stratify patients according to LV function we used conventional criteria: end-diastolic volume exceeding the normal range32 and end-diastolic pressure exceeding 20 mm Hg.32 For the overall population, LV end-diastolic volume index declined moderately though significantly (average 9%) after nifedipine. However end-diastolic volume fell significantly and more markedly (average 15%) in every patient with impaired baseline LV function and dilatation > 90 ml/m² (group 2), in contrast to the negligible change (average 0%) among patients with baseline end-diastolic volume ≤ 90 ml/m² (group 1).

LV end-diastolic pressures initially ≤ 20 mm Hg were variably and insignificantly changed in response to nifedipine. In contrast, when baseline values exceeded 20 mm Hg, end-diastolic pressures declined by an average of 18%.

Other significant differences were evident between group 1 (end-diastolic pressure ≤ 20 mm Hg and/or end-diastolic volume ≤ 90 ml/m²) and group 2 patients (end-diastolic volume > 90 ml/m² and/or end-diastolic pressure > 20 mm Hg), including peak positive and negative dP/dt, cardiac index, systemic resistance, ejection fraction, Vcf, MNSER, end-systolic P-V ratio, end-systolic volume, stroke volume, T, and the y-axis intercept of the diastolic P-V relation (table 2). No statistically significant difference was observed between the two groups with respect to other measures of LV stiffness, though knorm tended to be higher (NS), suggesting increased LV stiffness when chamber dimensions are normalized, in these patients with impaired baseline LV function.

Table 3 compares the percent changes after nifedipine in all variables in both groups. The percent decline in systemic arterial mean and LV systolic pressures was only slightly less in group 1 (average 12% each) than in group 2 (average 16% and 14%, respec-
tively). However, LV end-diastolic pressure declined significantly (18%) in group 2, in contrast to an insignificant increase (average 8%) in group 1.

The percent increase in LV ejection fraction was significantly greater in group 2 than in group 1 patients (table 3). Ejection fraction and MNSER increased significantly by averages of 34% and 41%, respectively, in group 2, compared with 9% and 15% in group 1 (p for differences in each < 0.01).

There were no significant changes in indexes of intrinsic LV diastolic function pertaining to isovolumic relaxation or stiffness properties during the filling phases and at end-diastole after nifedipine in either group. T was significantly more prolonged in patients in group 2 than in those in group 1 in the baseline state (table 2). However, nifedipine did not abbreviate relaxation in either group (table 3).

In patients with normal LV end-diastolic volume and pressure (group 1), the P-V relation was unchanged by nifedipine. In contrast, the average y-axis intercept of the diastolic P-V curve fell significantly (22%) in group 2, compared with an insignificant increase in group 1 (table 3, fig. 2). Thus, in patients with impaired baseline LV function (group 2), P-V curves were consistently translated downward and leftward (reflected by the decline in the average value of the pressure intercept of the P-V relation) without change in rate constant (table 3, fig. 3), indicative of secondary effects upon LV diastolic behavior attributable to modification of constraints to LV filling.
TABLE 2. Basal Hemodynamics, Left Ventricular Systolic and Diastolic Function in Groups 1 and 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arterial systolic pressure (mm Hg)</td>
<td>145.2 ± 13.2*</td>
<td>148.9 ± 8.5*</td>
<td>NS</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>98.5 ± 8.2</td>
<td>107.4 ± 5.8</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic arterial diastolic pressure (mm Hg)</td>
<td>75.3 ± 5.8</td>
<td>86.6 ± 4.9</td>
<td>NS</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>140.7 ± 11.5</td>
<td>142.0 ± 9.1</td>
<td>NS</td>
</tr>
<tr>
<td>LV minimal diastolic pressure (mm Hg)</td>
<td>8.9 ± 1.3</td>
<td>15.6 ± 2.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV peak “a” wave pressure (mm Hg)</td>
<td>15.2 ± 1.2</td>
<td>25.1 ± 2.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>15.7 ± 1.1</td>
<td>25.7 ± 2.4</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>LV peak positive dP/dt (mm Hg/sec)</td>
<td>1550 ± 134</td>
<td>1110 ± 102</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV peak negative dP/dt (mm Hg/sec)</td>
<td>1777 ± 183</td>
<td>1239 ± 116</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>RV systolic pressure (mm Hg)</td>
<td>36.8 ± 2.4</td>
<td>41 ± 3.5</td>
<td>NS</td>
</tr>
<tr>
<td>RV end-diastolic pressure (mm Hg)</td>
<td>12.7 ± 1.1</td>
<td>15.6 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index (ml/m²)</td>
<td>3.31 ± 0.14</td>
<td>2.72 ± 0.24</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn-sec-cm⁻⁵)</td>
<td>1120 ± 108</td>
<td>1370 ± 138</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyn-sec-cm⁻⁵)</td>
<td>95.8 ± 16.2</td>
<td>97.6 ± 35.6</td>
<td>NS</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.71 ± 0.02</td>
<td>0.49 ± 0.06</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean circumferential fiber shortening rate (circ/sec)</td>
<td>1.13 ± 0.07</td>
<td>0.69 ± 0.11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean normalized systolic ejection rate (sec⁻¹)</td>
<td>1.97 ± 0.1</td>
<td>1.26 ± 0.18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>End systolic pressure-volume ratio (ml/mm Hg)</td>
<td>2.66 ± 0.32</td>
<td>1.26 ± 0.24</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>LV end-diastolic volume index (ml/m²)</td>
<td>78.0 ± 3.4</td>
<td>113.7 ± 9.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV end-systolic volume index (ml/m²)</td>
<td>23.1 ± 2.0</td>
<td>68.6 ± 17.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>55 ± 2.9</td>
<td>49.7 ± 5.3</td>
<td>NS</td>
</tr>
<tr>
<td>Early diastolic relaxation “T” (msec)</td>
<td>45.3 ± 3.5</td>
<td>71.4 ± 6.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Isovolumic relaxation time (msec)</td>
<td>123 ± 1</td>
<td>128 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Rate constant “k” of LV P-V relation (mm Hg/sec)</td>
<td>0.008 ± 0.001</td>
<td>0.0074 ± 0.002</td>
<td>NS</td>
</tr>
<tr>
<td>Pressure intercept of LV P-V relation (mm Hg)</td>
<td>7.62 ± 2.2</td>
<td>4.92 ± 0.94</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Rate constant “k_norm” of LV P-V elasticity relation (mm Hg/unit volume)</td>
<td>1.82 ± 0.15</td>
<td>2.04 ± 0.26</td>
<td>NS</td>
</tr>
<tr>
<td>Operational end-diastolic stiffness (mm Hg/ml)</td>
<td>0.13 ± 0.01</td>
<td>0.18 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>End-diastolic stiffness ([V/P] dP/dV)</td>
<td>1.3 ± 0.16</td>
<td>1.5 ± 0.27</td>
<td>NS</td>
</tr>
<tr>
<td>RR interval (msec)</td>
<td>798 ± 46</td>
<td>925 ± 42</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Mean ± SEM.
†Group t test for difference between group means.
Abbreviations: LV = left ventricular; RV = right ventricular; P-V relation = diastolic pressure-volume relation.

particularly by the right ventricle. The P-V curves were translated downward in all patients with baseline elevation of end-diastolic pressure and volume, but in no patient in group 1.

In group 2 patients, the 13% decline in end-diastolic volume (reflecting decreased preload) and the 41% reduction of systemic vascular resistance (reflecting diminished afterload) were significantly greater than corresponding changes in group 1 patients, in whom end-diastolic volume was unchanged and systemic resistance fell by only 14%.

Of most practical therapeutic importance for patients with congestive heart failure, nifedipine increased cardiac index by 25% in group 2 patients, compared with a negligible change in group 1 patients (fig. 2).

Discussion

Despite potentially beneficial effects of nifedipine and other calcium antagonists among patients with various cardiac disorders, and despite a demonstrated negative inotropic effect in vitro, the influence of these drugs on systolic and diastolic LV performance in vivo remains controversial. In this study, LV diastolic properties were analyzed in terms of P-V relations and early diastolic relaxation, which reflect processes common to myocardial contractility and diastolic behavior. In view of observations of Noble et al. and Diamond and Forrester that diastolic LV P-V relations in intact dog hearts could be fitted to exponential functions, and the exponential nature of the length-tension curve in isolated cardiac muscle, P-V relations were analyzed in terms of a monoexponential model. Although use of exponential analysis in the clinical setting has not been unequivocally validated independently, it has been used by us and by others to quantify diastolic LV P-V relations; although such expressions do not quantify muscle stiffness per se, they do provide clinically useful descriptors of LV P-V relations in the intact ventricle, with results analogous to those based on stress-strain analysis in canine preparations.
TABLE 3. Average Percent Changes in Hemodynamics and Left Ventricular Systolic and Diastolic Function and Volumes After Nifedipine

<table>
<thead>
<tr>
<th>Variable</th>
<th>% change</th>
<th>Significance*</th>
<th>% change</th>
<th>Significance*</th>
<th>Significance†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arterial systolic pressure (mm Hg)</td>
<td>-10.7</td>
<td>S</td>
<td>-13.5</td>
<td>S</td>
<td>NS</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>-11.5</td>
<td>S</td>
<td>-16.2</td>
<td>S</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic arterial diastolic pressure (mm Hg)</td>
<td>-12.6</td>
<td>S</td>
<td>-18.5</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>-12.0</td>
<td>S</td>
<td>-13.6</td>
<td>S</td>
<td>NS</td>
</tr>
<tr>
<td>LV minimal diastolic pressure (mm Hg)</td>
<td>0</td>
<td>NS</td>
<td>-12.2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LV peak &quot;a&quot; wave pressure (mm Hg)</td>
<td>-1.0</td>
<td>NS</td>
<td>-12.8</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>8.4</td>
<td>NS</td>
<td>-17.9</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>LV peak positive dP/dt (mm Hg/sec)</td>
<td>-8.0</td>
<td>NS</td>
<td>-5.6</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>LV peak negative dP/dt (mm Hg/sec)</td>
<td>-15.8</td>
<td>S</td>
<td>-14.5</td>
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<td>NS</td>
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<td>RV systolic pressure (mm Hg)</td>
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<td>NS</td>
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<td>S</td>
<td>NS</td>
</tr>
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<td>-23.7</td>
<td>S</td>
<td>NS</td>
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<td>Cardiac index (ml/m²)</td>
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<td>NS</td>
<td>25.4</td>
<td>S</td>
<td>S</td>
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<td>Systemic vascular resistance (dyn-sec-cm⁻⁵)</td>
<td>-14.21</td>
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<td>-41.2</td>
<td>S</td>
<td>S</td>
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<td>Pulmonary vascular resistance (dyn-sec-cm⁻⁵)</td>
<td>-24.4</td>
<td>NS</td>
<td>-51.6</td>
<td>S</td>
<td>NS</td>
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<tr>
<td>LV ejection fraction</td>
<td>9.4</td>
<td>S</td>
<td>33.9</td>
<td>S</td>
<td>S</td>
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<td>Mean circumferential fiber shortening rate (circ/sec)</td>
<td>34.5</td>
<td>S</td>
<td>46.4</td>
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<td>NS</td>
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<td>Mean normalized systolic ejection rate (sec⁻¹)</td>
<td>15.1</td>
<td>S</td>
<td>40.5</td>
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<td>S</td>
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<tr>
<td>End systolic pressure-volume ratio (ml/mm Hg)</td>
<td>15.4</td>
<td>NS</td>
<td>23.8</td>
<td>S</td>
<td>NS</td>
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<tr>
<td>LV end-diastolic volume index (ml/m²)</td>
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<td>NS</td>
<td>-12.6</td>
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<td>S</td>
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<td>LV end-systolic volume index (ml/m²)</td>
<td>-21.7</td>
<td>S</td>
<td>-27.0</td>
<td>S</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>2.2</td>
<td>NS</td>
<td>9</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Early diastolic relaxation “T” (msec)</td>
<td>8</td>
<td>NS</td>
<td>17.7</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Isovolumic relaxation time (msec)</td>
<td>0</td>
<td>NS</td>
<td>-2.3</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Rate constant “k” of LV P-V relation (mm Hg/sec)</td>
<td>27.3</td>
<td>NS</td>
<td>23.8</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Pressure intercept of LV P-V relation (mm Hg)</td>
<td>32.5</td>
<td>NS</td>
<td>-22.4</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Rate constant “k_m” of LV P-V elasticity relation (mm Hg/unit volume)</td>
<td>8.8</td>
<td>NS</td>
<td>12.9</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Operational end-diastolic stiffness (mm Hg/ml)</td>
<td>-9.7</td>
<td>NS</td>
<td>-10.8</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>End-diastolic stiffness ([V/P][dP/dV])</td>
<td>9.1</td>
<td>NS</td>
<td>11.2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>RR interval (msec)</td>
<td>-18</td>
<td>NS</td>
<td>-8.4</td>
<td>S</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Significance of the change (paired t test): S = statistically significant (p < 0.05); NS = not statistically significant.
†Significance of the changes in each parameter after nifedipine, between groups I and II (group t test): S = statistically significant (p < 0.05); NS = not statistically significant.

Abbreviations: LV = left ventricular; RV = right ventricular; P-V relation = diastolic pressure-volume relation.

Further, though Mirsky²², ⁴⁶ emphasized that variables of myocardial stiffness based on stress-strain analysis may be more ideal for interpatient comparisons, derivation of both stress and strain is based upon certain assumptions regarding LV geometry, some of which may not be verifiable clinically. Stress-strain analysis may be limited also by disparities due to the use of natural versus Lagrangian strain, and the difficulties of measuring net transmural pressure and LV dimensions at zero stress. Accordingly, we used exponential analysis in the present study to assess LV P-V relations in individual patients in response to nifedipine and to provide a satisfactory means for statistical comparisons of the data.

Previous studies indicated that the "position" of the P-V relation is susceptible to shift with pharmacologic or other interventions.⁷, ¹¹, ⁴⁶, ⁴⁸-⁵⁰ Although in the present study the average y-axis intercept of the diastolic P-V relations was unchanged for the overall patient population, in all patients with end-diastolic volume > 90 ml/m² the intercept declined significantly by an average of 48%, whereas in most patients with end-diastolic pressure > 20 mm Hg, the intercept declined by an average of 10%. Thus, elevated baseline end-diastolic volume appears to be a more consistent predictor of downward translation of diastolic P-V curves in response to nifedipine than does elevated end-diastolic pressure.
EFFECTS OF NIFEDIPINE ON LV FUNCTION/Ludbrook et al.

Prominent downward and leftward translation of diastolic P-V curves after nifedipine generally occurred only in patients with impaired baseline LV function. The absence of concomitant alteration of rate constants of P-V and P-V elasticity relations suggests that such downward shifts of P-V curves occurred without alteration of LV intrinsic distensile chamber or muscle properties. Although downward translation has been attributed to reduced diastolic tone, we previously observed similar changes after

FIGURE 1. Left ventricular end-diastolic volume (LVEDV) and end-diastolic pressure (LVEDP) before and after nifedipine. Average EDV declined significantly in group 2 patients, in whom baseline LVEDV exceeded 90 ml/m², but was unchanged in group 1 patients, in whom initial LVEDV was normal. Average LVEDP declined in group 2 patients, but did not change significantly in those in group 1.

FIGURE 2. Average percent change in left ventricular end-diastolic volume index (LVEDVI) pressure-axis intercept, pulmonary (PVR) and systemic vascular resistance (SVR) and cardiac index after nifedipine in group 1 (left bar) and in group 2 patients (right bar). The percent change in LVEDVI, the intercept of the diastolic pressure-volume (P-V) relation, SVR and cardiac index were each significantly more marked in group 2 patients, and the reduction of PVR appears to be substantially (though not significantly) greater.
administration of other vasodilator drugs, particularly nitroglycerin,\textsuperscript{10,11} which suggests that such shifts reflect modification of the behavior of the external constraints to LV filling attributable particularly to the right ventricle, rather than to changes in intrinsic LV distensile properties. Thus, shifts of diastolic P-V curves by nifedipine observed in the present study, particularly in patients with impaired baseline LV function, in the absence of changes in LV chamber or myocardial stiffness properties, appear to be due to modification of the influence of the extraventricular constraints to LV chamber distension, particularly those exerted by the right ventricle, since right-heart pressures declined substantially more in group 2 than in group 1 patients, despite similar changes in systemic arterial and hence coronary perfusion pressures and the "extraventricular" constraints dependent on them.\textsuperscript{11,44}

Regardless of the cause, however, operation of the left ventricle at lower diastolic pressure and volume loading conditions reflected by the downward shift of the diastolic P-V relations suggests that in patients with compromised LV performance, diastolic functional determinants of myocardial oxygen demands were favorably influenced by nifedipine. Because downward displacement of P-V curves is generally reflected by reduced pulmonary arterial and wedge pressures, the present results suggest that nifedipine may be expected to relieve symptoms and other manifestations of pulmonary congestion in patients with compromised baseline LV function.\textsuperscript{45}

In all of our patients, nifedipine reduced the systemic vascular resistance. The 13% decline in LV end-diastolic volume (reflecting diminished preload) and 41% reduction of systemic resistance (reflecting diminished afterload) in patients with impaired baseline LV function (group 2) were both significantly more pronounced than corresponding changes in patients with normal baseline LV function, in whom systemic vascular resistance fell by 14% and the decline in end-diastolic volume was negligible (fig. 2). As with other vasodilator drugs, the diminished impedance to LV ejection led to a variable augmentation of cardiac output. Accordingly, reduction of systemic arterial pressure was variable. Because ejection phase indexes of LV function are sensitive to variations in both preload and afterload, both of which were changed by nifedipine, improvement of myocardial contractility per se cannot necessarily be attributed to the drug. Although nifedipine exerts an immediate negative inotropic effect,\textsuperscript{30,44} this influence is transient and, judging from the present results, is clearly supervened in vivo by its subsequent unloading effect. Thus, in contrast to the known negative inotropic effects of verapamil,\textsuperscript{46} which occur despite concomitant reduction of LV afterload, peak positive dP/dt and the end-systolic P-V relation were not diminished by nifedipine, but in fact tended to in-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{nifedipine_dia Press_vol_curve.png}
\caption{Exponentially fitted left ventricular diastolic pressure-volume curves before and after nifedipine in three illustrative cases. In the group 1 patient with normal end-diastolic volume (EDV) and end-diastolic pressure (EDP), the pressure-volume relation was unchanged (upper left). In the group 2 patient with elevated EDV and EDP depicted (upper right), the pressure-volume curve was translated downward and leftward after nifedipine, without a change in rate constant. In particular, substantial reduction of diastolic pressures within a specific range of volume is documented after nifedipine. No change was observed in the pressure-volume relation after placebo (lower panel). Statistical analysis was by paired t test.}
\end{figure}
crease, albeit not significantly. LV function was improved most strikingly in patients with impaired baseline performance, in whom there was a significant and substantial increase in cardiac output in the presence of reduced preload. The 25% increase in cardiac output in group 2 patients further epitomizes the striking enhancement of LV performance in these patients with compromised baseline function, as compared with the negligible increase in group 1 patients. Though favorable effects on the myocardial oxygen supply-demand ratio or increased adrenergic tone stimulated by the decline in systemic arterial pressures may contribute to the augmentation of LV systolic function observed after nifedipine in the present study, the apparent augmentation of LV function appears to be attributable primarily to reduction of loading conditions.

In addition, right ventricular preload and afterload were significantly reduced after nifedipine, particularly in patients with impaired baseline LV performance. Under these circumstances, however, reduction of right ventricular loading conditions may result secondarily from decreased pulmonary vascular resistance consequent upon augmented LV systolic emptying and reduced end-diastolic volume by nifedipine, facilitating venous return from the pulmonary vascular bed, as in our patients with impaired baseline LV function. Thus, reduction of left ventricular preload and afterload in group 2 patients may be associated secondarily with reduction of right ventricular afterload and preload and thus of central venous pressure. Our findings, however, do not necessarily imply either a direct effect of nifedipine upon pulmonary vascular resistance or a “venous pooling” effect upon the systemic venous (capacitance) vascular bed.46, 47

In conclusion, conventional therapeutic doses of nifedipine exert salutary effects on systolic and diastolic determinants of myocardial oxygen requirements in vivo. Systemic and pulmonary hemodynamics, systolic LV performance, cardiac output and operational diastolic P-V relations are favorably influenced, particularly in patients with impaired baseline LV function after sublingual administration of nifedipine.

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