Effects of nifedipine on intrinsic myocardial stiffness in man*

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ABSTRACT To determine whether alteration of intrinsic myocardial stiffness is responsible for the reduction of left ventricular filling pressure and volume by nifedipine in patients with impaired baseline ventricular function, we evaluated the hemodynamic responses in 32 patients undergoing diagnostic cardiac catheterization. Micromanometric pressure and ventriculographic dimensional data were acquired before and 30 min after randomly assigned administration of nifedipine (20 mg sublingual) or placebo. A mathematical model requiring no assumptions about the stress-radius relationship or direct measurement of strain was used. No hemodynamic variables were changed after placebo. Left ventricular end-diastolic volume and pressure declined and cardiac output increased after nifedipine, particularly in subjects with impaired ventricular performance. Despite these salutary effects, intrinsic myocardial stiffness, elastic stiffness at a common level of stress, chamber stiffness, and rate of isovolumic relaxation were unchanged after nifedipine, even in patients with abnormal baseline ventricular function. The potent peripheral arteriolar dilator effect of nifedipine, rather than any direct myocardial or ventricular effects, appears to be responsible for the improved systolic and diastolic performance.


THE calcium channel-blocking agents, particularly nifedipine, have been claimed to influence diastolic relaxation and stiffness in patients with hypertrophic cardiomyopathy and in those with coronary artery disease.

We have previously shown that nifedipine lowers diastolic pressures and volumes in ventricles with impaired function in patients with coronary disease but not in those with normal function.¹ These changes occurred without alteration of chamber stiffness (kₚ) or time constant of relaxation (τ). Altered myocardial stiffness (kₜ) has not been evaluated as a potential determinant of these changes. Others have suggested that an increase in stiffness² and an impairment of relaxation²,³ occur in response to nifedipine in the presence of coronary disease. In patients with hypertrophic cardiomyopathy, both nifedipine⁴ and verapamil⁵ exert beneficial effects on relaxation and filling properties.

Nifedipine relieves myocardial ischemia at least in part by alteration of ventricular loading conditions. It is important to determine whether improvement in intrinsic myocardial stiffness contributes to this beneficial effect. Assessment of intrinsic myocardial stiffness in man has been constrained by methodologic difficulties, particularly with respect to the accurate measurement of variables included in specific quantitative models. Thus the current investigation also included refinements of the methods required for evaluation of myocardial stiffness.

Methods

Patient selection. Subjects were selected from those undergoing scheduled diagnostic cardiac catheterization for evaluation of chest pain. Entry criteria included the presence of normal sinus rhythm and the absence of acute myocardial infarction (within the preceding 3 months), valvular heart disease, peripheral vascular disease, or the need for uninterrupted therapy with long-acting nitrates or β-blocking or calcium antagonist agents.

All cardioactive medications were tapered gradually and withdrawn completely at least 24 hr before each study. The protocol was approved by the Washington University School of Medicine Institutional Review Board, and written informed consent was obtained from all patients before their inclusion.
 Patients were assigned to receive either nifedipine or an identical-appearing placebo by random number code.

**Cardiac catheterization and experimental protocol.** Cardiac catheterization was performed via the percutaneous femoral approach. All subjects were in the fasting state and had been premedicated with 0.75 mg/kg im hydroxyzine hydrochloride 1 hr before the procedure. In each patient right and left heart hemodynamics and cardiac output (Fick or indicator-dilution technique) were measured first. A No. 6F micromanometer catheter (Millar Instruments PC360) was advanced to the left ventricle via the left femoral artery with the use of an arterial introducer equipped with a side port through which arterial pressure was measured continuously. Micromanometer pressure was matched to the fluid-filled lumen pressure. A No. 7F angiographic pigtail catheter was advanced to the left ventricle via the right femoral artery. Catheters were positioned carefully to avoid trabecular entrapment of the micromanometer tip and to avoid stimulation of ventricular ectopic beats. Left ventriculography was performed in the right anterior oblique projection at 60 frames/sec, patients being instructed to retain a submaximal inspiration and to avoid the Valsalva maneuver. Contrast injection was performed with the use of a triggered injector (Medrad Mark 4); 40 ml of sodium and meglumine iothalamate (Vascoray) was injected at a rate of 12 ml/sec. Left ventricular high-fidelity pressure, as well as right ventricular and arterial pressures, and timing signals were recorded simultaneously during left ventriculography, providing for assessment of simultaneous pressure and volume changes as described previously.1,6

After a pause of at least 15 min to permit dissipation of the effects of the contrast material,7 intracardiac pressure and cardiac output measurements were repeated. Nifedipine (20 mg) or placebo was then administered by opening one end of the fluid-filled capsule and applying the contents beneath the subject’s tongue; the subject was instructed to retain the solution sublingually for as long as possible without swallowing. After an additional 30 min, at which time the full nifedipine effect was observed,1,8 complete hemodynamic and cardiac output determinations were repeated. Left ventriculography was then repeated under conditions identical to those extant during the recording of the initial left ventriculogram with simultaneous measurement of high-fidelity left ventricular pressures and volume. Left ventriculography in the left anterior oblique projection was then performed to ascertain the presence and extent of asynergic contractions. This was followed by selective coronary arteriography performed with the use of preshaped catheters.

**Mathematical modeling.** Stiffness analysis was based on dimensional and hemodynamic data gathered between minimum left ventricular diastolic and peak “a” wave pressure. The right anterior oblique left ventriculogram was outlined for each frame as was a segment of the epicardial border of the free wall at end-diastole and an x-ray calibration grid with the use of a sonic digitizer connected to a Hewlett Packard 5600M dedicated computer system. The area (a) and chord (c) were calculated by the computer, corrected for x-ray magnification, and smoothed over the interval of interest with the use of a fourth-order polynomial. With the model of a thick-walled prolate sphere, the semi-major axis (a = c/2), semi-minor axis (r = a/2), and chamber volume (V = π ar = ½ ac) were computed. Wall thickness (b) was measured at end-diastole and, assuming a uniform wall thickness and a myocardial specific gravity of 1.05 g/ml, wall volume and mass were calculated. Wall thickness during the remainder of diastole was then computed with assumption of a constant wall volume. Left ventricular, right ventricular, and arterial pressures as well as the electrocardiogram and electronic cine frame timing markers were recorded on an FM tape recorder. Data were replayed off-line into the dedicated computer system with the left ventricular pressure digitized 800 times/sec. Hemodynamic data were selected coincident with the appropriate cine ventriculogram with the use of 2 msec wide timing pulses.

Midwall equatorial stress (σ) was adapted from the method of Mirsky9 and calculated for each frame as:

$$\sigma = \frac{PR}{h} \left(1 - \frac{R^2}{2A^2} - \frac{h}{2R}\right)$$

where P = left ventricular intracavitary pressure, R = r + h/2, and A = a + h/2. Strain was defined as natural strain (ε) expressed as

$$\varepsilon = \ln \frac{R}{R_0},$$

where R0 is the unstressed radius. Because the unstressed radius is not generally obtainable in vivo, the need for calculation of ε per se was avoided by differentiating ε with respect to R, i.e.,

$$\varepsilon = \frac{1}{dR} \frac{dR}{R}.$$

The general assumption of an exponential σ-ε relationship was employed with

$$\sigma = C_1 + C_2 e^{C_3 \varepsilon}.$$ 

Combining constants

$$\sigma = C_1 + C_4 R^{C_3} \quad (1)$$

Thus assumption of an exponential stress-strain relationship and use of the natural strain definition implies a power function relationship between stress and radius. Since σ and R were available for each frame, C1, C3, and C4 were calculable by nonlinear best-fit methods.

Elastic myocardial stiffness (E) was expressed in the form

$$E = \frac{d\sigma}{d\varepsilon} = k_5 \sigma + d \quad (2)$$

Differentiating the σ-R relationship,

$$\frac{d\sigma}{dR} = C_7 C_4 R^{C_3 - 1} \quad (3)$$

Since

$$\frac{d\sigma}{d\varepsilon} = \frac{d\sigma}{dR} \times \frac{dR}{d\varepsilon},$$

Combining equations 2 and 3,

$$k_5 \sigma + d = C_3 C_4 R^{C_3}$$

Substituting equation 1,

$$k_5 \sigma + d = C_1 (\sigma - C_1)$$

Thus, k5 = C3 and d = -C1C3. Elastic stiffness was evaluated at σ = 30 kdyne/cm², chosen because that level of stress fell in the physiologic range for nearly all subjects.

Myocardial stiffness was therefore derived from clinically

Vol. 74, No. 1, July 1986

127
available variables without the need for estimation of ventricular dimensions at zero stress and without explicit constraints or assumptions regarding the stress–radius relationship. The derivation was performed as directly as possible to minimize reliance on curve-fitting.

The chamber stiffness constant ($k_p$) was derived from the pressure-volume data over the same interval of interest in the form $P = B_p e^{k_p V} + B_p$, since we found this to provide a considerably better fit to the observed data than the simpler $P = B_p e^{k_p V}$.

The time constant of ventricular relaxation ($T_r$) was calculated by a best-fit technique in the form used by Thompson et al.,$^{10}$ $P(t) = P_0 e^{-t/T_r} + P_0$, over the interval from the time of minimum $dP/dt$ until the time when $P$ fell to the level of end-diastolic pressure. $P_0$ is the pressure asymptote at $t = \infty$, $P_A + P_B$ is the pressure at the time of minimum $dP/dt (t = 0)$, and $T_r$ is the time needed for $P(t) - P_0$ to decrease to $1/e$ of its initial value. In addition, since Mirsky$^{11}$ has pointed out that $T_r$ often occurs at a time outside of the isovolumic relaxation period, $T$, according to the formula employed by Weiss et al.,$^{12}$ which assumes a pressure asymptote of 0, was also computed. $T$ calculated by this method was less than the duration of isovolumic relaxation in all but one subject, for relaxation defined as the period from minimum $dP/dt$ until the time when $P$ declined to the level of end-diastolic pressure.

**Statistical analysis.** Changes in hemodynamic variables after the intervention were evaluated with use of the paired $t$ test. Intergroup differences with respect to baseline values and differences in responses to the intervention between patients with normal and those with abnormal left ventricular function were assessed with Student’s $t$ test.

**Results**

**Clinical characteristics.** Thirty-two patients (30 men and two women) with an average age of 54.8 years (range 36 to 70) were studied. This is an entirely separate group of patients from those previously examined in our laboratory.$^1$ Twenty-one received nifedipine and 11 placebo. Five patients who received nifedipine were excluded from the randomization protocol for medical reasons at the insistence of the referring physician. No complications were associated with the administration of nifedipine or placebo or with the catheterization procedure.

Patients were categorized into two groups with the use of previously established criteria.$^1$ Group 1 had normal left ventricular function and group 2 had abnormal function as determined by the presence of at least one of the following: aneurysm, marked segmental hypokinesis or more severe wall motion abnormality, ejection fraction less than 45%, end-diastolic volume index greater than 90 ml/m$^2$, or end-diastolic pressure greater than 20 mm Hg. Among the 21 patients receiving nifedipine, left ventricular function was normal in five (group 1) and abnormal in 16 (group 2). In the patients receiving placebo, left ventricular function was normal in three and abnormal in eight. Patients with normal and abnormal ventricular function were distributed comparably in the treated and untreated groups. Among the 24 patients with abnormal left ventricular function, significant wall motion abnormalities were present in 21, ejection fraction was less than 45% in 12, end-diastolic pressure was 20 mm Hg or more in 12, end-diastolic volume index was 90 ml/m$^2$ or more in seven, and aneurysms were present in five. Average number of criteria met in the abnormal function group was 2.38. A comparison of baseline hemodynamic characteristics of patients with normal and abnormal left ventricular function is presented in table 1. Among the patients with coronary artery disease, nine had triple-vessel disease, 10 had double-vessel disease (including one with a 50% left main narrowing), and eight had single-vessel disease. Five patients had no significant coronary obstruction.

**Effects of nifedipine on hemodynamic and stiffness variables (table 2).** No significant changes occurred after administration of placebo.

The stress-radius relationship over the interval of interest is illustrated in figure 1 for a single patient, before and after drug administration. The best-fitting power functions are shown.

For the entire group, left ventricular end-diastolic pressure decreased by 11% ($p = .035$) and end-diastolic volume by 4% ($p = .036$). This was accompanied by an 11% decrease in mean systemic arterial pressure ($p < .0005$) but by no alteration of right ventricular pressures. Left ventricular ejection fraction increased by 4% ($p = .046$) and cardiac output by 9% ($p = .0023$), while heart rate remained unchanged.

Despite this improvement of left ventricular performance and the diminution of filling pressure and volume, left ventricular stiffness variables were unchanged by the administration of nifedipine. The index of myocardial stiffness ($k_s$) was not altered for the entire set of patients receiving nifedipine (figure 2), nor was elastic stiffness ($E$) (evaluated at a common stress level of 30 kdyne/cm$^2$) (figure 3). As we have previously reported, the index of chamber stiffness ($k_p$) was also unchanged (figure 4). Since impaired relaxation in patients with coronary artery disease may be manifested as incomplete relaxation persisting into the filling phase of diastole and influencing diastolic stiffness variables, the time constants $T$ and $T_r$ of isovolumic relaxation were calculated. Neither variable was changed after nifedipine (figure 5). Changes in the mean values of chamber and myocardial stiffness appeared to be relatively large but did not approach statistical significance because of the accompanying large standard deviations. Elastic stiffness, an index that allows comparison of patients at a common stress level, demonstrated the absence of change more clearly.
TABLE 1
Baseline hemodynamic and stiffness characteristics of patients with normal (group 1) and abnormal (group 2) left ventricular function (mean ± SEM)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal LV function</th>
<th>Abnormal LV function</th>
<th>p value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arterial systolic pressure (mm Hg)</td>
<td>128.4 ± 4.8</td>
<td>134.7 ± 6.8</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic arterial diastolic pressure (mm Hg)</td>
<td>69.8 ± 2.9</td>
<td>78.2 ± 3.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>89.3 ± 3.2</td>
<td>97.1 ± 4.4</td>
<td>NS</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>15.7 ± 1.8</td>
<td>23.3 ± 1.9</td>
<td>.024</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>123.2 ± 5.0</td>
<td>129.9 ± 6.8</td>
<td>NS</td>
</tr>
<tr>
<td>RV end-diastolic pressure (mm Hg)</td>
<td>10.3 ± 1.5</td>
<td>13.5 ± 0.7</td>
<td>.025</td>
</tr>
<tr>
<td>RV systolic pressure (mm Hg)</td>
<td>29.0 ± 2.9</td>
<td>36.8 ± 1.9</td>
<td>.027</td>
</tr>
<tr>
<td>LV end-diastolic volume (ml)</td>
<td>138 ± 8</td>
<td>210 ± 26</td>
<td>.008</td>
</tr>
<tr>
<td>LV end-systolic volume (ml)</td>
<td>57 ± 5</td>
<td>127 ± 20</td>
<td>.0015</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.58 ± 0.03</td>
<td>0.42 ± 0.02</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RR interval (sec)</td>
<td>0.939 ± 0.11</td>
<td>0.850 ± 0.045</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area (m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>1.93 ± 0.18</td>
<td>1.99 ± 0.15</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>169 ± 11</td>
<td>266 ± 22</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Volume/mass ratio (ml/g)</td>
<td>0.83 ± 0.06</td>
<td>0.78 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Mean circumferential fiber shortening rate (sec&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>1.15 ± 0.12</td>
<td>0.76 ± 0.08</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Mean normalized systolic ejection rate (sec&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>1.86 ± 0.15</td>
<td>1.45 ± 0.07</td>
<td>&lt;.005</td>
</tr>
</tbody>
</table>

<sup>a</sup>By t test.

LV = left ventricular; RV = right ventricular.

**Differential effects of nifedipine on hemodynamics in subjects with normal compared with impaired left ventricular function (tables 1 and 3).** Hemodynamic variables in nifedipine-treated patients stratified according to normal or abnormal basal left ventricular function are tabulated in table 2. The importance of segregating patients by basal left ventricular function has been demonstrated in our previous studies,<sup>1, 8</sup> which showed

TABLE 2
Hemodynamic and stiffness values before and after nifedipine (mean ± SEM)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before nifedipine</th>
<th>After nifedipine</th>
<th>% Change</th>
<th>p value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arterial systolic pressure (mm Hg)</td>
<td>133.2 ± 5.3</td>
<td>120.4 ± 4.8</td>
<td>-9.6 ± 3.4</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Systemic arterial diastolic pressure (mm Hg)</td>
<td>76.2 ± 2.9</td>
<td>67.5 ± 2.5</td>
<td>-11.4 ± 2.3</td>
<td>&lt;.00005</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>95.2 ± 3.4</td>
<td>85.1 ± 3.1</td>
<td>-10.6 ± 2.6</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>21.5 ± 1.7</td>
<td>19.2 ± 1.0</td>
<td>-11.0 ± 5.5</td>
<td>.035</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>128.3 ± 5.3</td>
<td>113.8 ± 4.2</td>
<td>-11.3 ± 3.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RV end-diastolic pressure (mm Hg)</td>
<td>12.7 ± 0.7</td>
<td>12.8 ± 0.9</td>
<td>0.3 ± 7.5</td>
<td>NS</td>
</tr>
<tr>
<td>RV systolic pressure (mm Hg)</td>
<td>35.0 ± 1.7</td>
<td>33.3 ± 1.2</td>
<td>-4.7 ± 5.2</td>
<td>NS</td>
</tr>
<tr>
<td>LV end-diastolic volume (ml)</td>
<td>193 ± 21</td>
<td>185 ± 19</td>
<td>-4.2 ± 2.2</td>
<td>.036</td>
</tr>
<tr>
<td>LV end-systolic volume (ml)</td>
<td>110 ± 16</td>
<td>102 ± 16</td>
<td>-7.3 ± 1.8</td>
<td>&lt;.00025</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.46 ± 0.03</td>
<td>0.48 ± 0.03</td>
<td>4.3 ± 2.2</td>
<td>.046</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>6.14 ± 0.33</td>
<td>6.68 ± 0.35</td>
<td>8.8 ± 2.8</td>
<td>.0023</td>
</tr>
<tr>
<td>RR interval (sec)</td>
<td>0.871 ± 0.043</td>
<td>0.858 ± 0.036</td>
<td>-1.5 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardial stiffness (k&lt;sub&gt;E&lt;/sub&gt;)</td>
<td>12.9 ± 1.8</td>
<td>18.7 ± 2.2</td>
<td>45.2 ± 27.4</td>
<td>NS</td>
</tr>
<tr>
<td>Elastic stiffness (E) (kdyne/cm&lt;sup&gt;2&lt;/sup&gt;) at σ = 30</td>
<td>287 ± 52</td>
<td>261 ± 34</td>
<td>-9.1 ± 20.9</td>
<td>NS</td>
</tr>
<tr>
<td>Chamber stiffness (k&lt;sub&gt;P&lt;/sub&gt;) (ml&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.035 ± 0.010</td>
<td>0.053 ± 0.053</td>
<td>48.6 ± 31.4</td>
<td>NS</td>
</tr>
<tr>
<td>Relaxation time constant (T&lt;sub&gt;s&lt;/sub&gt;) (msec)</td>
<td>49.6 ± 3.8</td>
<td>52.3 ± 3.4</td>
<td>5.5 ± 4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Relaxation time constant (T&lt;sub&gt;c&lt;/sub&gt;) (msec)</td>
<td>66.2 ± 3.2</td>
<td>68.0 ± 3.7</td>
<td>2.7 ± 5.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

<sup>a</sup>By paired t test.
that only those patients with impaired baseline function exhibited a diminution of left ventricular end-diastolic pressure and volume as well as an improvement of cardiac output in response to nifedipine. Our earlier studies demonstrated that neither chamber stiffness nor relaxation were altered by nifedipine even in abnormal left ventricles and thus that these factors did not mediate the improvement of ventricular function. These findings were confirmed and extended in the current investigation.

A comparison of the effects of nifedipine in patients with abnormal left ventricular function and those with normal function is listed in table 3. Significant changes are delineated separately within each of the two groups. The significance of differential effects of nifedipine between groups is tabulated as well.

In patients with normal left ventricular function, the only hemodynamic changes associated with administration of nifedipine were diminution of left ventricular end-systolic volume by 11% (p < .01) and of right ventricular end-diastolic (29%) and systolic (20%) pressures (both p < .05).

In contrast, in patients with abnormal left ventricular function, left and right heart hemodynamics were uniformly changed after nifedipine. Left ventricular end-diastolic pressure decreased by 13% (p = .03) and end-diastolic volume by 5% (p = .04). This was accompanied by a 14% decrease in mean systemic arterial pressure (p < .00005) and an 11% decrease in right ventricular systolic (p = .03) but not diastolic pressure. Left ventricular end-systolic volume decreased by 7% (p < .002) and cardiac output increased by 10% (p < .005) while heart rate remained unchanged.

Effects of nifedipine on chamber and myocardial stiffness in patients with normal compared with abnormal left ventricular function. The myocardial stiffness constant (figure 2), elastic stiffness at \( \sigma = 30 \) kdyne/cm\(^2\) (figure 3), the chamber stiffness constant (figure 4), and myocardial relaxation (figure 5) remained unchanged after nifedipine in patients with normal left ventricular function and in those with abnormal function. Thus although significant potentially favorable changes were observed after nifedipine in patients with initially impaired function manifest by improved systolic function and diminished filling pressures, these changes were not mediated by significant changes in myocardial or chamber stiffness or relaxation.

Discussion

In patients with impaired baseline left ventricular function, we have shown previously that nifedipine exerts beneficial effects on ventricular filling pressure...
and volume and on cardiac output. The present study was designed to determine whether this improved performance is mediated through alteration of myocardial stiffness or as a result of changes in extracardiac conditions.

Effects of nifedipine on left ventricular stiffness. Calcium antagonists improve diastolic performance in patients with hypertrophic cardiomyopathy. Lorell et al.\textsuperscript{4} investigated 15 patients with echocardiography and catheter-tip micromanometry and found improvement after nifedipine in relaxation indexes (time constant of pressure relaxation, isovolumic relaxation time) and in filling indexes (peak filling rate, end-diastolic pressure, position of pressure-dimension curve). Bonow et al.\textsuperscript{5} studied 40 patients receiving long-term verapamil with radionuclide ventriculograms and found improvement in the peak filling rate and the time to peak filling. Myocardial stiffness was not examined in these two studies.

Nifedipine improves left ventricular performance in patients with ventricular function impaired by coronary disease but not in those with normal baseline function. Ludbrook et al.\textsuperscript{1} used simultaneous pressure and contrast ventriculography to investigate a group of 32 patients before and 30 min after 20 mg of sublingual nifedipine. End-diastolic pressure and volume were decreased and cardiac output increased in patients with abnormal but not those with normal resting ventricular function. These changes were not associated with any alteration of chamber stiffness or myocardial relaxation. Furthermore, peak positive dP/dt was unchanged. Rousseau et al.\textsuperscript{3} found that 30 sec after 0.1 mg of intracoronary nifedipine peak positive dP/dt was decreased and that the time constant of pressure relaxation was increased. Amende et al.\textsuperscript{2} reported in an abstract that 7 min after 20 mg of sublingual nifedipine given to eight patients with normal left ventricular filling pressures, end-diastolic pressure and volume increased, indirect indexes of chamber and muscle stiffness increased, and relaxation as measured by minimal dP/dt slowed. In the present study we directly examined the effects of 20 mg of sublingual nifedipine

**FIGURE 3.** Elastic stiffness (evaluated at a common stress level of 30 kdyn/cm\textsuperscript{2}) before (PRE) and after (POST) nifedipine for all patients receiving nifedipine (ALL) and for the subset of patients with impaired baseline left ventricular function (GROUP 2). Brackets represent ± 1 SD. Elastic stiffness was not altered by nifedipine.

**FIGURE 4.** Chamber stiffness constant before (PRE) and after (POST) nifedipine for all patients receiving nifedipine (ALL) and for the subset of patients with impaired baseline ventricular function (GROUP 2), measured in liter\textsuperscript{-1}. Brackets represent ± 1 SD. Chamber stiffness was not altered by nifedipine.

**FIGURE 5.** Time constant of isovolumic myocardial relaxation before (PRE) and after (POST) nifedipine for all patients receiving nifedipine (ALL) and for the subset of patients with impaired baseline left ventricular function (GROUP 2). Brackets represent ± 1 SD. Relaxation was not altered by nifedipine.
on myocardial stiffness in patients with coronary artery disease, determined 30 min after administration. It was demonstrated that myocardial and chamber stiffness, myocardial relaxation, and the volume/mass ratio were unaltered by nifedipine, even in patients with baseline impairment of ventricular function.

Thus it would appear that extracardiac effects of nifedipine mediate the improvement seen in left ventricular performance after nifedipine. Indeed, speaking in general about short-term interventions, Glantz and Parmley13 assert that “acute reversible muscle elasticity changes are much smaller than have been expected and are probably inadequate to explain acute shifts in the pressure-volume curve.” Using forearm plethysmography for estimation of peripheral hemodynamics in patients with coronary artery disease, Kurnik et al.8 demonstrated a direct arterial dilator effect of nifedipine that was more pronounced in patients with impaired left ventricular function. No net effect on the venous bed was evident. Thus, in concert with the results of the present study, arterial dilatation appears adequate to explain the observed improvement in cardiac hemodynamics without implication of any direct cardiac effects.

**Modeling myocardial stiffness.** Intrinsic myocardial stiffness is difficult to assess, particularly in the intact human being. The definitions used for expression of stress and strain are fundamentally important and in general not controversial. Formulations of Mirsky are employed frequently.9,14,15 The commonly used expression, natural strain \( \varepsilon = \ln R/R_0 \), includes the clinically unmeasurable quantity \( R_0 \), i.e., ventricular radius at zero stress. We avoid this dilemma by using instead the readily calculable \( d\varepsilon /dR = 1/R \) as an intermediate step in the derivation of the myocardial stiffness constant and avoid calculation of strain itself. Peterson et al.16 and Mirsky and Parmley17 have used a similar technique, but many others have made unphysiologic assumptions about \( R_0 \) to allow explicit calculation of strain.

The stress-strain relationship is generally assumed to be exponential judging from observed experimental data fits and theoretical modeling. The stress-radius relationship is often the practical curve that can be constructed from clinically obtainable data and from which the myocardial stiffness constant can be derived. This critical stress-radius relationship is generally defined to be monoexponential, without mathematical or physiologic explanation. In fact, use of an assumed exponential stress-strain relationship coupled with the definition of natural strain can be shown to require a power function relationship between stress.
and radius, as also noted by Mirsky and Rankin.18 This derivation is detailed in the Methods section in an effort to minimize assumptions and restrictions upon the observed data. As also detailed in Methods, the myocardial stiffness constant \( k_s \) is then directly available as the exponent of the stress-radius power function. No further curve fitting is required as is the case in a number of other models. This feature helps reduce assumptions and restrictions. Frequent sampling of dimensional and pressure data over the full interval of the passive portion of diastole was performed to maximize the amount of information available for analysis.

Several areas for potential refinement of this stiffness model deserve mention. Ventricular function in coronary artery disease is in general a regional rather than global property, and use of a model that allows regional assessment of stiffness may be more sensitive than the global model developed. It is possible that nifedipine has an effect on the stiffness of ischemic myocardium but not of normal or infarcted myocardium, and regional analysis might detect such a phenomenon. Regional stiffness analysis requires regional measurement of chamber dimension, wall thickness, and transmural pressure. Techniques for regional assessment of stiffness have been suggested by Mirsky,11 Mirsky and Kraynebuehl,15 Bourdillon et al.,19 and Janz.20

Utilization of transmural rather than intracavitary pressure in the calculation of wall stress may13, 18 or may not14 be helpful but is difficult in intact human beings. Viscous properties of the myocardium may be important in pressure-overload conditions such as aortic stenosis when the atrial "kick" is included,21 but the need for this was avoided in the current investigation by limiting analysis to the presumed elastic portion of diastole.13 Examination of stiffness during a state of increased stress such as rapid pacing might demonstrate a beneficial effect of pharmacologic intervention. Investigating the combined effects of nifedipine and rapid pacing, Lorell et al.22 reported that nifedipine had a beneficial effect on end-diastolic pressure, ejection fraction, and position of the pressure-volume curve. Stiffness, however, was not assessed specifically.

In conclusion, our results indicated that in patients with abnormal left ventricular function, nifedipine reduces end-diastolic pressure and volume and increases cardiac output. The beneficial effect on ventricular filling was not mediated by the alteration of chamber stiffness, myocardial isovolumic relaxation, or global myocardial stiffness derived with use of a refined mathematical model. The potent peripheral arteriodyl-

tor effect of nifedipine, rather than any direct myocardial or ventricular effects, appears to be responsible for the improved systolic and diastolic performance.

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KURNIK et al.

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