Diastolic Vibration Improves Systolic Function in Cases of Incomplete Relaxation

Takehiko Takagi, MD; Yoshiro Koiwa, MD; Jun-ichi Kikuchi, MD; Hideyuki Honda, MD; Nobuo Hoshi, MD; James P. Butler, PhD; and Tamotsu Takishima, MD

Background. Incomplete relaxation of the left ventricle (LV) affects LV filling, but the subsequent effect on LV systolic function remains unclear. We attempted to improve relaxation by applying oscillatory mechanical perturbation during diastole (diastolic vibration) and examined the extent to which systolic function improved.

Methods and Results. Using 10 open-chest canine preparations, pacing tachycardia and administration of propranolol were imposed to induce various levels of incomplete relaxation. Myocardial length perturbation was induced with an oscillator attached to the LV surface (50 Hz, 1-mm amplitude) and was restricted to the period from the beginning of isovolumic relaxation to end diastole. At resting heart rates, diastolic vibration caused an immediate decrease in the time constant (T) of LV pressure fall without any influence on heart rate, LV peak systolic pressure (peak LVP), stroke volume (SV), LV peak positive dP/dt, and total systemic vascular resistance. With pacing tachycardia, diastolic vibration increased both peak LVP and SV at 160 beats per minute (before) and 120 beats per minute (after propranolol), simultaneously decreasing both T and LV diastolic pressures and increasing end-diastolic segment length. The increase in peak LVP and SV caused by diastolic vibration correlated with the T/diastolic interval (r=0.82), the assumed index of severity of incomplete relaxation.

Conclusions. These results suggest that diastolic vibration accelerates the LV relaxation rate and that this increased relaxation improves systolic function through the Frank-Starling mechanism. (Circulation 1992;86:1955–1964)

KEY WORDS • load-dependent relaxation • time constant • diastolic function • length perturbation

Impairment of left ventricular (LV) relaxation has been observed in patients with congestive heart failure such as ischemic heart disease, hypertrophic cardiomyopathy, and hypertensive heart disease1–3 and is considered to be one of the important factors contributing to the pathophysiology of congestive heart failure.4,5 Several investigators have demonstrated that a transient change in LV filling can occur under the condition in which the LV pressure continues falling even at end diastole (incomplete relaxation).6–8 It may be possible that incomplete relaxation affects subsequent LV systolic function through the Frank-Starling mechanism. However, this has been difficult to demonstrate because previous interventions affecting LV relaxation also influenced other factors involved in the regulation of LV systolic function such as peripheral vascular resistance and LV contractility.

On the other hand, several investigators have reported that an abrupt change in myofibril length or mechanical oscillation induces a decline of tension development by deactivating or detaching active cross-bridges.9,10 In particular, Brutsaert et al.11 reported that an abrupt change in muscle length induces a more rapid relaxation (load-dependent relaxation). Based on these observations, we hypothesized that if we could restrict the timing of oscillatory length perturbations to the period of diastole and if length perturbations promote load-dependent relaxation, then incomplete relaxation might be relieved and lead to an improvement of LV systolic function by increasing ventricular filling.

The aims of the present study were therefore twofold. One was to investigate the effects of length perturbation applied during diastole (diastolic vibration) on LV relaxation and the other was to examine how the associated changes in LV relaxation quantitatively affect systolic function.

Methods

Animal Preparation

Ten mongrel dogs weighing 14–22 kg were anesthetized with 25 mg/kg sodium pentobarbital and ventilated with room air. A fluid-filled catheter was introduced into the ascending aorta via the right common carotid artery and was connected to a pressure transducer (P23XL, NEC-Sanei Instruments Co., Ltd., Tokyo) to monitor aortic pressure (AoP). After bilateral thoracotomy, the pericardium was opened, and a pericardial cradle was constructed to suspend the heart.
Puncturing the left atrial appendage and the LV apex, two sheaths were advanced into the respective chambers and secured in place. To measure LV pressure (LVP), a catheter-tipped micromanometer (TCP2RN136F30, Tonokura Instrument Co., Ltd., Tokyo) was inserted into the sheath positioned at the LV apex. The same type of catheter-tipped micromanometer was inserted into the other sheath to measure left atrial pressure (LAP). Each sheath was connected to a fluid-filled pressure transducer to calibrate the micromanometer. All pressures were taken relative to atmospheric pressure (equivalent to midepicardiac pressure in the open chest). An electromagnetic flow probe (MF-46, Nihon Kohden Co., Ltd., Tokyo) was placed around the ascending aorta near its origin to measure stroke volume (SV) by integration. In eight dogs, a pair of 5-MHz piezoelectric crystals (2-mm diameter) was implanted into the subendocardium of the LV wall to measure segmental length (4105, NEC-Sanei Instruments Co., Ltd.). These crystals were positioned approximately in the minor equatorial plane and adjacent to the contralateral posterior wall at a predetermined input site. Two metal electrodes were affixed to the right atrium and paced with a cardiac stimulator (3F61, NEC-Sanei Instruments Co., Ltd.). After completion of surgical procedures, the disc-shaped tip of an oscillator (type 4809, Brual Kajar Co., Ltd., Denmark) was attached to the LV anterior wall with the shaft motion perpendicular to its surface. All studies were approved by the Institutional Care and Use Committee.

**Vibration Control System**

The vibrator was driven by an intermittent sine wave signal, which was produced by passing a 50-Hz signal through a special on/off gate, which in turn was triggered by the R wave of the ECG as described below. The displacement of the tip was measured with a miniature acceleration sensor (Emic 540, Shin Nippon Sokki Co., Ltd., Tokyo), which was firmly attached to the shaft of the vibrator.

To avoid the effects of vibration on LV systolic function, we restricted the timing of vibration to the diastolic period from the end of ejection to the beginning of subsequent systole in this study. We defined the end of ejection to be the point at which LVP was equal to AoP at the incisure. The onset of subsequent systole was identified by the upstroke of LVP; we were careful not to apply vibration after this point. The timing of these starting and ending points was adjusted manually by monitoring the waveform of LVP and AoP on an oscilloscope (2G66, NEC-Sanei Instruments Co., Ltd.).

In the present study, the amplitude and frequency of the vibration were fixed at 1 mm and 50 Hz, respectively. Our previous studies describing the instantaneous transfer function showed a resonant frequency in the range of 40–100 Hz. In the vicinity of the resonance, the vibration was effectively transmitted throughout the entire LV.12-14 The 1-mm amplitude was near the limit of the vibrator but was sufficient to induce observable changes in the relaxation rate during diastole.

With vibration applied, vibrations propagated throughout the entire LV. The amplitude of myocardial vibration was of course maximal in regions near the area of direct excitation, but even on the contralateral surface, significant vibrations were observed. Figure 1 shows in one example the ECG, vibration signal, segment length detected at the surface of the LV contralateral to the site of excitation, and LVP. At this remote portion of the heart, the amplitude of myocardial length perturbation was 0.4±0.1% of end-diastolic segment length.

**Protocol**

To examine different levels of incomplete relaxation, we imposed pacing tachycardia and/or administration of propranolol.7 After 15 minutes of stabilization, the heart was allowed to contract at resting heart rate, and the heart rate was then raised by right atrial pacing in increments of 20 beats per minute from 120 beats per minute until it reached 200 beats per minute. At each heart rate (including resting) after 5 minutes of stabilization, vibration was applied during diastole for at least six beats. The hemodynamic and segment length data were measured before and during diastolic perturbation with the ventilator held at end expiration. After completion of the measurements at 200 beats per minute, the heart rate was returned to the resting rate. After that, we intravenously administered propranolol (0.05 mg/kg), and after 15 minutes of stabilization, the heart rate was again raised in increments of 120 beats per minute from 100 beats per minute until 200 beats per minute was reached or pulsus alternans developed. As above, measurements were taken at resting heart rates and each paced heart rate.

In four experiments, we also applied vibration during systole at the highest pacing rate (systolic vibration). In one series, vibration was applied from the onset of systole to the end of ejection. In a second series, vibration was applied only during the first half of systole. LV pressure was assessed in order to examine the possibility that vibration per se might exert a positive inotropic action on systolic function.

Pao2 and Paco2 were maintained at physiological levels by adjusting the level of ventilation and the inspired oxygen fraction. Blood loss was compensated for with doses of plasma expander as needed. No additional drugs were used that could affect left ventricular relaxation. After completion of the study, the dogs
were killed with an injection of KCl, and the hearts were removed and weighed.

**Data Analysis**

All data obtained in the experiments were recorded on an analog tape recorder (KS-616, Sony Magnescale Co., Ltd., Tokyo) and after low-pass filtering (50-Hz cutoff) on a thermal recorder (8M15, NEC-Sanei Instruments Co., Ltd.) for later analysis. The ECG, LVP, LAP, and segment length signals were simultaneously digitized at 1,000 Hz with a computer system (7T-17, NEC-Sanei Instruments Co., Ltd.). We obtained values described below from the digitized data.

Using a hand-controlled cursor of the computer system, we determined the time at which LVP equaled LAP during early and late diastole. We assumed these two times correspond to mitral valve opening and closing. Diastolic filling period (DFP) was defined as the time interval between these two times. The transmitral pressure gradient (TMPG) was obtained by integrating the pressure difference between the instantaneous LAP and instantaneous LVP during the diastolic filling period, as follows.

\[ \text{TMPG} = \int_{t_1}^{t_2} (\text{LAP}(t) - \text{LVP}(t)) \, dt \]  

where LAP(t) and LVP(t) are the instantaneous LAP and LVP at time t. Times t1 and t2 are the times of mitral valve opening and closing. The integral was approximated by trapezoidal summation.

We adopted the method of Weiss et al.15 in calculation of the time constant of LVP fall (T), which we used as an index of myocardial relaxation. Briefly, the digitized LVP during isovolumic relaxation was fitted to an exponential decay by least squares.

\[ P(t) = P_0 e^{-t/T} \]  

where P(t) is instantaneous LVP at time t, and P0 and T are constants. Time zero was taken at LVP peak negative dP/dt. The end of isovolumic relaxation period was taken to be at the atroventricular pressure crossover. We emphasize that we used T only as an index of the time scale for LVP fall during diastole. There are other methods for characterizing LVP(t), including the use of a nonzero pressure asymptote,16 but these appear to have only a small effect on the estimated T17 and to have little or no effect on the directional changes in T.18,19

We choose to regard the ratio of this time constant to diastolic interval (T/DI) as a quantitative estimate of the extent of relaxation because both the time constant and the diastolic interval (DI) have been reported to affect the level of relaxation at end diastole.7,14 This form rather than its inverse8 preserves the role of T as a dependent variable, DI being a variable under approximately independent control through pacing. The diastolic interval was derived from the time interval from peak negative dP/dt to end diastole. All data are analyzed for the mean of five consecutive measurements.

**Statistical Analysis**

Values are expressed as mean±SD, bpm.  

<table>
<thead>
<tr>
<th>Vibration</th>
<th>Absent</th>
<th>Present</th>
<th>Absent</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>118±12</td>
<td>117±12</td>
<td>88±12§</td>
<td>88±11</td>
</tr>
<tr>
<td>Peak LVP (mm Hg)</td>
<td>112.7±13.3</td>
<td>112.9±12.8</td>
<td>105.0±12.9§</td>
<td>105.4±13.0</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>9.4±2.2</td>
<td>9.4±2.5</td>
<td>11.3±3.6§</td>
<td>11.1±3.7</td>
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<td>Min LVP (mm Hg)</td>
<td>7.1±2.3</td>
<td>6.8±2.5</td>
<td>8.6±3.1</td>
<td>8.7±3.3</td>
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<td>LAP (mm Hg)</td>
<td>9.5±3.5</td>
<td>9.4±3.5</td>
<td>11.2±3.5</td>
<td>11.2±3.4</td>
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<tr>
<td>SV (ml)</td>
<td>12.6±2.1</td>
<td>12.7±2.0</td>
<td>13.4±3.5</td>
<td>13.4±3.5</td>
</tr>
<tr>
<td>+dP/dt (mm Hg/sec)</td>
<td>2,020±680</td>
<td>2,030±670</td>
<td>1,390±310§</td>
<td>1,400±320</td>
</tr>
<tr>
<td>−dP/dt (mm Hg/sec)</td>
<td>−1,640±280</td>
<td>−1,810±350†</td>
<td>−1,290±330§</td>
<td>−1,480±340†</td>
</tr>
<tr>
<td>TSV (dyne sec⁻¹ cm⁻³)</td>
<td>5,370±1,460</td>
<td>5,360±1,430</td>
<td>6,390±1,390§</td>
<td>6,420±1,410</td>
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<td>T (ms)</td>
<td>40±6</td>
<td>35±6*</td>
<td>58±15§</td>
<td>51±12†</td>
</tr>
</tbody>
</table>

Values are mean±SD. bpm. Beats per minute; Peak LVP, left ventricular (LV) peak systolic pressure; LVEDP, LV end-diastolic pressure; min LVP, LV minimum pressure; LAP, mean left atrial pressure; SV, stroke volume; −dP/dt, peak negative dP/dt; +dP/dt, peak positive dP/dt; TSV, total systemic resistance; T, time constant of LV pressure fall.  

*p<0.05; †p<0.01 vs. values before vibration.  

§p<0.05; §p<0.01 vs. values before propranolol.

**Results**

**Effects of Diastolic Vibration at Resting Heart Rate**

Effects of diastolic vibration on hemodynamic variables measured before and after propranolol at resting heart rate are summarized in Table 1. The diastolic vibration did not significantly change the heart rate, LVP peak systolic pressure (peak LVP), LV end-diastolic pressure (LVEDP), LV minimum pressure, mean LAP,
or SV under resting conditions. However, T and peak negative dP/dt were significantly reduced by diastolic vibration. These decreases in both T and peak negative dP/dt were observed independent of the administration of propranolol. Total systemic resistance and peak positive dP/dt were not significantly changed by diastolic vibration at resting heart rate. The administration of propranolol significantly reduced the heart rate, peak LVP, and peak positive dP/dt, slightly increasing LVEDP, T, and peak negative dP/dt (Table 1).

Effects of Vibration at Pacing Tachycardia

Before propranolol, the heart rates at which we started atrial pacing varied because of differences in resting heart rate. The number of experiments was seven at 120 beats per minute, but all 10 dogs were successfully paced from 140 to 200 beats per minute. After propranolol, all dogs were paced from 100 beats per minute, but because of the development of pulsus alternans, none was paced above 160 beats per minute (n=6 at 160 beats per minute). The number of experiments is shown in each table and figure.

Figure 2 shows the effect of systolic vibration on LV function before, during, and after systolic vibration. The left and right panels show the effect when vibration was applied throughout the entire systolic period and during the first half of systole, respectively. In both cases, peak LVP decreased immediately with the application of systolic vibration and recovered immediately to previbrational level with cessation of vibration. Peak LVP significantly decreased with systolic vibration (before propranolol, 100.0±4.2 versus 98.0±5.3 mm Hg, p<0.05; after propranolol, 96.5±3.1 versus 91.5±3.1 mm Hg, p<0.01). Both before and after propranolol, peak LVP obtained immediately after the cessation of systolic vibration showed no significant change compared with LVP before vibration.

Figure 3 shows raw tracings of LVP obtained at 100 beats per minute (upper panel) and at 160 beats per minute (lower panel) after propranolol. From top to bottom, tracings of ECG, vibration signal, and LVP are shown in each panel. No significant change in peak LVP is seen at 100 beats per minute. However, as shown in the lower panel, an abrupt increase in peak LVP was observed at 160 beats per minute immediately after the application of vibration. Moreover, peak LVP returned to the previbrational level concurrent with the cessation of vibration. Note also that LV minimum pressure was slightly reduced.

For simplicity, we present the hemodynamic variables obtained at both the lowest and highest pacing rates in Table 2; other hemodynamic variables at each pacing stage are graphically presented in Figure 4. All data were matched according to heart rate. The left panel summarizes the effects of vibration on peak LVP (upper part) and SV (lower part) obtained before (circles) and after propranolol (squares). With diastolic vibration, significant increases in peak LVP were observed at heart rates ≥160 beats per minute (before) and ≥120 beats per minute (after propranolol). In a similar fashion, diastolic vibration increased SV at heart rates ≥160 beats per minute (before) and ≥120 beats per minute (after propranolol). These increases in peak LVP and SV became greater as the heart rate became more rapid (before propranolol: Δpeak LVP, 2.5±1.5 versus 5.3±1.5 mm Hg, p<0.01; ΔSV, 1.0±0.7 versus 1.3±0.6 ml, p<0.01; values at 160 beats per minute versus 200 beats per minute). These increases were greater after propranolol than before when compared at correspond-
TABLE 2. Effects of Diastolic Vibration on Hemodynamic Values at Right Atrial Pacing

<table>
<thead>
<tr>
<th>HR (bpm)</th>
<th>Vibration</th>
<th>Peak LVP (mm Hg)</th>
<th>Min LVP (mm Hg)</th>
<th>LAP (mm Hg)</th>
<th>SV (ml)</th>
<th>TSR (dyne⋅sec⁻¹⋅cm⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before propranolol</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120 (n=7)</td>
<td>Absent</td>
<td>111.2±14.3</td>
<td>7.1±2.5</td>
<td>9.8±2.0</td>
<td>11.7±2.3</td>
<td>5,610±1,250</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>111.6±14.1</td>
<td>6.9±2.4</td>
<td>9.7±2.0</td>
<td>11.9±2.4</td>
<td>5,620±1,270</td>
</tr>
<tr>
<td>200 (n=10)</td>
<td>Absent</td>
<td>94.7±15.8</td>
<td>11.7±2.9†</td>
<td>14.0±5.8†</td>
<td>7.7±1.3‡</td>
<td>4,410±1,160</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>100.0±15.6*</td>
<td>10.4±2.9*</td>
<td>13.6±5.7</td>
<td>9.0±1.4*</td>
<td>4,400±1,150</td>
</tr>
<tr>
<td>After propranolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 (n=10)</td>
<td>Absent</td>
<td>105.4±11.7</td>
<td>8.4±2.9</td>
<td>10.3±3.7</td>
<td>12.1±2.4</td>
<td>5,470±1,770</td>
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<tr>
<td></td>
<td>Present</td>
<td>106.2±11.7</td>
<td>8.2±3.2</td>
<td>10.2±3.6</td>
<td>12.3±2.0</td>
<td>5,460±1,780</td>
</tr>
<tr>
<td>160 (n=6)</td>
<td>Absent</td>
<td>91.4±15.0</td>
<td>11.8±5.1</td>
<td>13.6±4.9</td>
<td>7.5±1.6‡</td>
<td>5,720±1,960</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>96.1±15.4*</td>
<td>10.4±4.7*</td>
<td>13.2±4.9</td>
<td>8.7±2.0*</td>
<td>5,720±1,970</td>
</tr>
</tbody>
</table>

Values are mean±SD. HR, heart rate; bpm, beats per minute; peak LVP, left ventricular (LV) peak systolic pressure; min LVP, LV minimum pressure; LAP, mean left atrial pressure; SV, stroke volume; TSR, total systemic resistance.

*p<0.01 vs. values before vibration.
†p<0.05; ‡p<0.01 vs. values at 120 beats per minute (before propranolol) or 100 beats per minute (after propranolol).

Peaking heart rates (p<0.01). Peak positive dP/dt was not changed by diastolic vibration ≤140 beats per minute and ≤120 beats per minute before and after propranolol, respectively (before propranolol at 120 beats per minute, 2,020±830 versus 2,070±800 mm Hg/sec, NS; after propranolol at 100 beats per minute, 1,420±150 versus 1,420±150 mm Hg/sec, NS). Peak positive dP/dt was increased by vibration only when heart rates reached maximum (1,690±690 versus 1,790±720 mm Hg/sec, p<0.05 at 200 beats per minute before propranolol; 1,360±200 versus 1,460±190 mm Hg/sec, p<0.01 at 160 beats per minute after propranolol). Total systemic resistance was not changed by vibration at any heart rate.

FIGURE 4. Graphs show effects of diastolic vibration on left ventricular (LV) peak systolic pressure, stroke volume, LV minimum pressure, and LV end-diastolic pressure corresponding to each heart rate before and after administration of propranolol. Before propranolol: n=7 at 120 beats per minute (bpm) and n=10 at other heart rates. After propranolol: n=6 at 160 bpm and n=10 at other heart rates. Points are mean±SEM. *p<0.05; **p<0.01 vs. before vibration. †p<0.05; ‡p<0.01 vs. values at 120 bpm (before propranolol) or at 100 bpm (after propranolol).
TABLE 3. Effects of Diastolic Vibration on Diastolic Indexes at Pacing Tachycardia

<table>
<thead>
<tr>
<th>HR (bpm)</th>
<th>Vibration</th>
<th>LVEDP (mm Hg)</th>
<th>Peak -dP/dt (mm Hg/sec)</th>
<th>T (msec)</th>
<th>T/DI</th>
<th>DFP (msec)</th>
<th>TMPG (mm Hg)</th>
<th>EDSL (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before propranolol</td>
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</tr>
<tr>
<td>120 (n=7)</td>
<td>Absent</td>
<td>9.8±1.9</td>
<td>-1,690±240</td>
<td>39±7</td>
<td>0.17±0.04</td>
<td>171±28</td>
<td>391±144</td>
<td>12.2±1.1</td>
</tr>
<tr>
<td>140 (n=10)</td>
<td>Present</td>
<td>9.8±1.8</td>
<td>-1,840±310*</td>
<td>35±6</td>
<td>0.15±0.03‡</td>
<td>178±28*</td>
<td>386±145</td>
<td>12.2±1.1</td>
</tr>
<tr>
<td>160 (n=10)</td>
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<td>0.22±0.04</td>
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<td>373±129</td>
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<td>36±4</td>
<td>0.20±0.04*</td>
<td>125±31*</td>
<td>378±129</td>
<td>11.7±2.2</td>
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<tr>
<td>200 (n=10)</td>
<td>Absent</td>
<td>9.4±1.8</td>
<td>-1,730±320*</td>
<td>34±4</td>
<td>0.26±0.05*</td>
<td>91±21*</td>
<td>321±131</td>
<td>11.4±1.9*</td>
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<tr>
<td>After propranolol</td>
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<tr>
<td>100 (n=10)</td>
<td>Present</td>
<td>10.5±3.7</td>
<td>-1,230±280</td>
<td>58±16</td>
<td>0.20±0.06</td>
<td>201±42</td>
<td>308±102</td>
<td>12.3±2.3</td>
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<td>Absent</td>
<td>10.6±3.3</td>
<td>-1,200±270</td>
<td>57±14</td>
<td>0.28±0.09</td>
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<td>11.7±1.8</td>
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<td>Present</td>
<td>10.3±3.3</td>
<td>-1,450±260†</td>
<td>50±11‡</td>
<td>0.25±0.08*</td>
<td>145±41‡</td>
<td>267±113</td>
<td>11.9±1.9‡</td>
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<td>160 (n=6)</td>
<td>Absent</td>
<td>11.8±4.8</td>
<td>-1,120±310</td>
<td>60±17</td>
<td>0.39±0.13§</td>
<td>79±17§</td>
<td>234±102</td>
<td>11.2±1.9 §</td>
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<tr>
<td>Present</td>
<td>12.3±4.9†</td>
<td>-1,280±340‡</td>
<td>53±13‡</td>
<td>0.35±0.11‡</td>
<td>87±18‡</td>
<td>248±108</td>
<td>11.5±1.9‡</td>
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</table>

Values are mean±SD. HR, heart rate; bpm, beats per minute; LVEDP, left ventricular (LV) end-diastolic pressure; peak -dP/dt, peak negative dP/dt; T, time constant of LV pressure fall; T/DI, time constant/diastolic interval; DFP, diastolic filling period; TMPG, transmitral valve pressure gradient. For end-diastolic segment length (EDSL), n=5 at 120 beats per minute before propranolol, n=6 at 160 beats per minute after propranolol, n=8 at other heart rates.

*p<0.05; †p<0.01 vs. before vibration.

‡p<0.05; §p<0.01 vs. at 120 beats per minute (before propranolol) or at 100 beats per minute (after propranolol).

The right panel of Figure 4 shows the effects of diastolic vibration on LV minimum pressure (upper part) and LVEDP (lower part). The values of LVEDP at each heart rate are also shown in Table 3. In contrast to the effects on systolic performance, these pressures were significantly reduced by diastolic vibration when heart rates were relatively higher. For LV minimum pressure, significant decreases were observed at heart rates ≥180 beats per minute and ≥140 beats per minute before and after propranolol, respectively. Diastolic vibration reduced LVEDP at heart rates ≥180 beats per minute (before propranolol) and ≥140 beats per minute (after propranolol). The changes in LVEDP and LV minimum pressure became more rapid (after propranolol: ΔLVEDP, 1.2±0.8 versus 1.8±0.7 mm Hg, p<0.01; ΔLV minimum pressure, 0.9±0.3 versus 1.4±0.7 mm Hg, p<0.01; values at 120 beats per minute versus 160 beats per minute). Also, these decreases were greater after propranolol than before when compared at corresponding heart rates (p<0.01).

We summarize the effects of diastolic vibration on hemodynamic indexes during diastole in Table 3. When diastolic vibration was applied, there were significant decreases in both T and peak negative dP/dt independent of the heart rate or the administration of propranolol. These changes in both T and peak negative dP/dt did not significantly differ among heart rates (p<0.01). The previbration values of T/DI (our quantitative relaxation index) ranged from 0.17±0.01 to 0.39±0.03 (before propranolol) and from 0.20±0.02 to 0.37±0.04 (after propranolol) and increased in a parallel fashion with heart rate. These values of T/DI were significantly reduced by diastolic vibration at each heart rate (Table 3).

Previbration values of both DFP and TMPG significantly decreased as heart rate increased (Table 3). With diastolic vibration, DFP was slightly but significantly prolonged at each heart rate. Significant increases in TMPG were observed only when heart rates were high.

![Figure 5](http://circ.ahajournals.org/)

**Figure 5.** Superposed tracings of left ventricular pressure (LVP) and left atrial pressure (LAP) without vibration (dashed lines) and at the first application of diastolic vibration (solid lines). Diastolic vibration accelerated left ventricular relaxation (point a) and induced a premature onset of mitral valve opening (point b) and a decrease in LV minimum pressure (point c). Marked increase in systolic LVP after the first application of diastolic vibration is easily seen (point d).
Figure 5 shows a superposition of raw tracings of LVP and LAP obtained before vibration (dashed line) and the first beat after diastolic vibration (solid line). With diastolic vibration, the LV relaxed faster (point a). Moreover, diastolic vibration caused an earlier onset of mitral valve opening, a decrease in LV minimum pressure (points b and c), and in consequence, a prolonged DFP. In the right part of Figure 5, the effect of diastolic vibration on peak LVP can be clearly seen (point d). These changes during early diastole made TMPG greater.

End-diastolic segment length (EDSL) was used as an index of LV end-diastolic volume. Before vibration, EDSL decreased as the heart rate increased (Table 3). When diastolic vibration was applied, EDSL was significantly increased at heart rates ≥160 beats per minute (before) and ≥120 beats per minute (after propranolol). As for end-systolic segment length, no significant change was observed with diastolic vibration at any heart rate (before propranolol at 200 beats per minute: 9.3±1.6 versus 9.3±1.7 mm, NS; after propranolol at 160 beats per minute: 9.8±1.8 versus 9.7±1.8 mm, NS).

Figure 6 shows representative LV diastolic pressure–segment length curves obtained at 100 beats per minute (left panel) and at 160 beats per minute (right panel), both after propranolol. At 100 beats per minute, although diastolic vibration slightly shifted the curve downward at early diastole (in left panel, from dashed line to solid line), it did not change the curve at late diastole. At 160 beats per minute, the curve shifted downward and EDSL was lengthened.

In the top panel of Figure 7, we plotted LVEDP versus the relaxation index T/DI obtained before and during diastolic vibration (open and closed symbols, respectively). Before vibration, the values of LVEDP increased as T/DI increased. With diastolic vibration, both T/DI and LVEDP decreased. These vibration-induced changes in LVEDP were greater at higher values of T/DI.

Finally, we related the increases in systolic function to the severity of incomplete relaxation by plotting (bottom panel of Figure 7) the increases in peak LVP against the previbration relaxation index T/DI. Circles and squares represent data obtained before and after administration of propranolol, respectively. The statistically significant increases in peak LVP were observed when T/DI was >0.28 (see Table 1 and Table 3), and the increases in peak LVP became larger as T/DI increased. When we compared the increments in individual peak LVP with T/DI, a linear relation was observed between increments in peak LVP and T/DI (ΔLVP=14.9×T/DI−1.6; r=0.82, p<0.01). The increments of SV were also correlated with T/DI (ΔSV=2.5×T/DI+0.04; r=0.44, p<0.05), but the correlation was not so strong.

Discussion

It has been noted that incomplete relaxation affects LV end-diastolic volume and LV end-diastolic stiffness. However, it is not known how incomplete relaxation quantitatively affects systolic function per se. In the present study, we first showed that diastolic vibration immediately evoked faster relaxation at resting heart rate without any influence on systolic function, heart rate, or peripheral vascular resistance. Because these characteristics of diastolic vibration seemed to be appropriate for examining our hypothesis that incomplete relaxation has a direct influence on systolic function, we tested our hypothesis using diastolic vibration under the condition of incomplete relaxation. Our ob-
sorations showed that the application of diastolic vibration resulted in more rapid LV relaxation. Under conditions of incomplete relaxation, the application of diastolic vibration immediately decreased LV diastolic pressures and increased systolic function.

When an identical vibration was applied during systole, peak LVP immediately fell, and LV systolic function of the subsequent beat showed no improvement over the previbration state. These results suggest that the improvement in systolic function seen during diastolic vibration is not a direct effect of vibration on contractility.

**Mechanism of Modification of Relaxation Rate by Diastolic Vibration**

In our results, the faster relaxation rate observed during vibration was independent of the heart rate whether or not propranolol had been administered. This effect on the relaxation rate was common even when at lower heart rates there was little or no effect on systolic function. The primary effect of diastolic vibration is, therefore, most likely the modification of relaxation rate. Brutsaert et al.\(^2\) reported that an abrupt increase in load resulted in a premature and more rapid relaxation in isolated mammalian heart preparations (load-dependent relaxation). Recently, Ariel et al.\(^20\) and Zile and Gaasch\(^21\) clearly demonstrated the presence of load-dependent relaxation in intact canine hearts. Our results are similar to these studies in that increased relaxation is associated with rapid length perturbations. However, it should be noted that vibration is a cyclic perturbation with alternating periods of lengthening and shortening and that quantitative and specific comparisons with previous work may not be appropriate. Nevertheless, our results are certainly consistent with a load-dependent relaxation.

Among many factors that contribute to load-dependent relaxation, both the function of sarcoplasmic reticulum and load-induced cross-bridge detachment have been emphasized as fundamental mechanisms.\(^22\)–\(^24\) Because load dependence persists even with the administration of propranolol,\(^23\) we could not determine which factor is dominant in this study in which propranolol and tachycardia were used to induce incomplete relaxation. However, the following reports suggest that vibration might influence cross-bridge interaction. Using skeletal muscle preparations, Huxley and Simmons\(^9\) proposed that quick changes in the muscle length (0.1–1.5% of half sarcomere length) reduced the number of active cross-bridges (deactivation).\(^9\) This phenomenon has also been observed in papillary muscle\(^10\)–\(^23\)–\(^28\) and the isolated left ventricle.\(^29\) In a recent study, Peterson et al.\(^30\) applied mechanical impulses to detach all attached cross-bridges. In the context of the present work, these studies suggest that our mechanical oscillation induced cyclic changes in the myocardial length (see Figure 1), which in turn could promote deactivation of active cross-bridges and more rapid relaxation. We think that this is the most likely mechanism, but we cannot exclude the possibility that there is a functional enhancement of the sarcoplasmic reticulum secondary to vibration.

The amplitude of mechanical oscillation in the present study was certainly not uniform over the entire myocardium. Nevertheless, this perturbation was not localized at the site of oscillatory excitation. We have confirmed in previous studies that vibration is propagated symmetrically throughout\(^12\)–\(^14\) with a strain of 0.4±0.1% at the contralateral surface. Ghista and Rao\(^31\) anticipated this result theoretically, noting that the most likely behavior is an oscillatory mode in which the LV wall phasically distorts from an oblate to a prolate deformation from its resting state. We conclude that our results represent the effect of global vibration, although we cannot yet speculate as to the extent to which regional nonuniformities of vibratory amplitude are an important consideration.

**Mechanism of Augmentation of Systolic Function**

In applying small-amplitude, repeated, quick stretch-release to the depressed cat papillary muscle, Brutsaert et al.\(^32\) found an improved contractility. In contrast, when we imposed vibration during systole, peak LVP decreased: That is, the vibration during systole in our study did not increase contractility of subsequent systole and that consequently, diastolic vibration is unlikely to improve systolic function through a direct effect on contractility. Moreover, diastolic vibration did not affect peak LVP, SV, and peak positive dP/dt at resting heart rates or at lower heart rates. If diastolic vibration had directly affected myocardial contractility, we would have observed an augmentation of systolic function at lower heart rates. These observations imply that the effects of diastolic vibration on systolic function were not caused directly by changes in myocardial contractility but rather indirectly through the changes in the LV relaxation rate. The above observations regarding the differences between systolic and diastolic application of vibration illustrates the importance of timing. This is underscored by our previous work with continuous application of vibration, wherein vibration-induced depression of myocardial contractility was found in hearts with varying degrees of failure.\(^33\) Similar results were reported by Vukas et al.\(^34\)

LV relaxation has been reported to have a close relation with coronary circulation.\(^35\) However, modulation of systolic function by the coronary circulation, even if present, does not seem to play a principal role in our experimental design because of the rapid expression of the functional response. Such rapidity of the response cannot be explained by changes in myocardial metabolism.

Weisfeldt et al.\(^7\) reported that the LV diastolic pressure–dimension relation shifts upward when the subsequent systole begins its contraction earlier than 3.5 T of the preceding relaxation. Blaustein and Gaasch\(^8\) also suggested that the prolonged relaxation induced by reoxygenation influences LV end-diastolic stiffness when relaxation is sufficiently short and/or when diastole is sufficiently short. In our results, the application of diastolic vibration significantly increased systolic function at higher heart rates (≥160 beats per minute before propranolol, ≥120 beats per minute after propranolol). At these heart rates, T/DI, which we introduced as a quantitative index of incomplete relaxation, ranged from 0.28 to 0.39. These values are equivalent to 3.6–2.6 T of Weisfeldt's index and approximately satisfy their criteria for incomplete relaxation, disregarding the differences in experimental conditions.\(^7\) These results suggest that incomplete relaxation occurred at higher heart
rates in our experiments. We observed that the LV diastolic pressure–segment relation shifted downward, and EDSL was lengthened by diastolic vibration at higher heart rates, even though it was not changed at lower heart rates. This implies that the effects of diastolic vibration on LV systolic function were mediated by an increase in end-diastolic volume. Indeed, Kikuchi et al. have shown a marked decrease in LV end-diastolic stiffness with diastolic vibration in canine isovolumic heart preparations.

We interpret our results in terms of the following hypothetical sequence of events. Diastolic vibration accelerates LV relaxation, leading to an earlier opening of the mitral valve and reduction of LV minimum pressure and LVEDP. The resulting prolongation of the diastolic filling period causes an increase in TMPG. With severe incomplete relaxation, diastolic vibration significantly increases LV filling and end-diastolic volume; an augmentation of systolic function then appears through the Frank-Starling mechanism. In short, the effects of diastolic vibration on systolic function are likely with changes in the LV filling as a result of increasing the relaxation rate.

Implications for Systolic Function and Clinical Meaning

In the present study, we created two different conditions of relaxation with the administration of propranolol. Before propranolol, the value of T was 40 ± 6 msec, almost the same as those values of normal hearts in previously reported clinical study. A previous report suggests that incomplete relaxation only occurs when the heart rate is unphysiologically high if the value of T is relatively small. This is consistent with our observations obtained before propranolol. After the administration of propranolol, T increased to 58 ± 15 msec at resting heart rate. This value of T is analogous to those measured in patients with idiopathic cardiomyopathy or ischemic heart disease. Therefore, our experimental condition mimics to some extent the clinical settings observed in patients with ischemic heart disease during exercise. During exercise, tachycardia is commonly observed, and myocardial ischemia is one of the major factors that prolongs the relaxation rate. Also, incomplete relaxation may invite a progressive deterioration of relaxation by impeding coronary perfusion. Although such harmful effects of incomplete relaxation on systolic function may not be observed clinically because of compensatory mechanisms, the present results suggest that incomplete relaxation depresses systolic function by hindering use of the Frank-Starling mechanism. In our study, a linear relation between the vibration-induced increase in peak LVP and T/ΔI was observed, suggesting that the level of incomplete relaxation is an important determinant of depressed systolic function. Furthermore, diastolic vibration may be used as a probe to investigate whether incomplete relaxation exists in various heart diseases, although further study is necessary.

Study Limitations

We investigated the effects of diastolic vibration under transient conditions of incomplete relaxation. Therefore, the present study does not address conditions arising from myocardial irreversible changes such as myocardial necrosis. Propranolol was administered to prolong the relaxation rate and the pericardium was removed in this study, which may limit comparisons of our work with the in situ heart in clinical settings. In summary, vibration (i.e., mechanical oscillation) applied during diastole accelerated LV relaxation, probably through load-dependent relaxation. Under conditions of incomplete relaxation, this faster relaxation rate induced a prolonged diastolic filling period, an increased end-diastolic volume, and most likely through the Frank-Starling mechanism, improved the LV systolic function.

Acknowledgments

We are grateful to William Grossman, MD, for his kind suggestions, and to Yasunori Yamada and Masafumi Sugi, MD, for their technical assistance. We also gratefully acknowledge the expert assistance of Yukiko Kanno.

References

Diastolic vibration improves systolic function in cases of incomplete relaxation.
T Takagi, Y Koiwa, J Kikuchi, H Honda, N Hoshi, J P Butler and T Takishima

doi: 10.1161/01.CIR.86.6.1955

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