The Effect of Acute Alterations in Left Ventricular Afterload and β-Adrenergic Tone on Indices of Early Diastolic Filling Rate

Michael R. Zile, Alvin S. Blaustein, and William H. Gaasch

The effects of an acute increase in left ventricular systolic pressure and the effects of an intravenous isoproterenol infusion on myocardial (segment) lengthening rate and chamber (minor axis dimension) filling rate were examined in 12 anesthetized dogs. Measurements of left ventricular systolic pressure (by micromanometer) and of segment length and chamber dimension transients (by ultrasonic crystals) were made in variably afterloaded beats (three-beat descending aortic cross-clamp) before and during an isoproterenol infusion that raised (+)dP/dt by 40%. During the baseline state, we found an inverse relation between the peak rate of increase in minor axis dimension [(+)dD/dt] and systolic pressure over a wide range of systolic pressures (110-160 mm Hg) and end-systolic dimensions (25-40 mm); peak (+)dD/dt and end-systolic dimension were also inversely related. During isoproterenol infusion, end-systolic dimension fell from 29.7±3.1 to 28.0±3.1 mm and (+)dD/dt increased from 79.6±8.0 to 90.1±8.7 mm/sec; however, the slope and y intercept of the relation between (+)dD/dt and end-systolic dimension were unchanged. Peak (+)dD/dt at a common end-systolic dimension of 31 mm was nearly equal during baseline and Isoproterenol states (64.2±6.3 vs. 65.1±6.6 mm/sec). Similar results were found using segment length transients. We interpret these data to indicate that (+)dD/dt is strongly influenced by changes in systolic pressure and dimension and that isoproterenol-induced changes in (+)dD/dt are mediated, at least in part, through changes in systolic pressure and dimension. (Circulation Research 1989;65:406-416)

Left ventricular (LV) filling abnormalities appear to be sensitive indicators of disease that can be present before abnormalities of systolic function develop.1-7 Thus, several relaxation indices have been used in early identification of heart disease, in following its natural history, and in assessment of the response to therapy.8-14 However, before we can fully understand the consequences of a disease process or the effects of pharmacological therapy on the cardiac relaxing system, it is necessary to define the individual mechanical and hemodynamic factors that influence the speed of relaxation and filling in the normal heart. We and others have found that short-term alterations in systolic pressure or β-adrenergic tone influence the rate of LV isovolumic pressure decline.15-18 Based on these observations, we hypothesized that an acute increase in systolic pressure would decrease LV filling rate while β-adrenergic stimulation would augment filling rate. There are difficulties in isolation of the independent effects of β-adrenergic stimulation on myocardial relaxation rate. In addition to its direct effects on the cardiac relaxing system (i.e., augmented myocardial cyclic AMP levels and increased sarcoplasmic reticulum uptake of calcium), β-adrenergic stimulation may also change loading conditions that may independently affect filling rate.19-21

The few studies that have examined the effects of adrenergic stimulation on the rate of early diastolic filling have produced conflicting results. Some investigators have reported more rapid LV filling rates during intravenous catecholamine infusion22,23 while others have not.24 It is possible that these disparate results were due to unrecognized differences in loading conditions (which themselves may be independent determinants of relaxation). Recently, in our isolated muscle laboratory, we demonstrated that over a wide range of afterloads, there was a strong inverse correlation between end-systolic fiber length and peak isotonic lengthening rate (analogous to auxotonic filling rate in the intact dog).21 We
hypothesized that in an intact working LV a similar relationship exists between peak filling rate and end-systolic dimension or length. Furthermore, we hypothesized that if the effects of enhanced β-adrenergic tone were mediated through a direct effect on the cardiac relaxing system, then the auxotonic relaxation rate (filling rate) would be faster for any given end-systolic dimension or length; in contrast, if the effects were mediated primarily through a change in loading conditions, then relaxation rate at a common end-systolic dimension or length should be unchanged. Therefore, the purpose of this study was to define the relation between indices of peak filling rate and end-systolic dimension or length over a wide range of systolic pressures and to assess the effects of isoproterenol, a β-adrenergic agonist, on this relation. An evaluation of these interrelationships will provide a better understanding of the independent effects of systolic load and β-adrenergic tone on the LV filling rate.

Materials and Methods

Twelve mongrel dogs were premedicated with morphine (2.5 mg/kg) and anesthetized with pentobarbital (15-20 mg/kg). The animals were ventilated for maintenance of an arterial oxygen partial pressure of 80-150 mm Hg. After a median sternotomy, the pericardium was opened, a unipolar electrode was affixed to the right atrium, and the sinus node was crushed.

A catheter-tipped micromanometer (Mikrotip Millar, Houston, Texas) was calibrated to mercury at 37°C and introduced into the LV from the carotid artery. In selected experiments, a second catheter was placed in the left atrium through the left atrial appendage. The descending thoracic aorta was isolated, and a mechanical occluder was placed around the aorta 2 cm distal to the left subclavian artery. In six dogs, ultrasonic segment length crystals, placed approximately 10 mm apart, were inserted to a midwall depth of the LV myocardium; the crystals were aligned perpendicular to the long axis of the LV, in the distribution of the left anterior descending coronary artery, midway between apex and base. In an additional six dogs, endocardial ultrasonic minor axis–dimension crystals (placed in an anteroposterior position) were used. All measurements were made at arrested end expiration. Segment length and minor axis–dimension measurements were made at end diastole and at end systole. Peak segment lengthening rate [(+)dL/dt, mm/sec] and the peak rate of increase in dimension [(+)dD/dt (mm/sec) were derived by electronic differentiation of the length or dimension signal. These parameters are not volumetric measurements of LV early diastolic filling rate, but were used as indices of peak filling rate. Measurements of the time constant of isovolumic pressure decline (T) and peak negative dP/dt are not reported in this study; these data have been previously published.

In each of the 12 experiments (n=6 with segment length crystals, n=6 with dimension crystals), a series of variably afterloaded contractions was used to examine the relation between indices of peak filling rate [(+)dL/dt or [(+)dD/dt] and LV systolic pressure (SP), length, or dimension (Figure 1). During diastole, the descending thoracic aorta was abruptly and completely occluded; the occlusion was maintained for three beats and was then released, resulting in a control and three progressively loaded beats. Only atrial paced beats with normal QRS duration were used, and cross-clamps resulting in electrocardiographic evidence of unstable atrioventricular conduction were excluded. During the baseline state (sinus node crush plus propranolol 0.1 mg/kg), 10 sets of three-beat aortic occlusions were performed, generating 10 control and 30 variably loaded filling rate versus afterload coordinates. Each set of cross-clamps was separated by a 2-3-minute equilibration period; all 10 sets of cross-clamps were completed in less than 30 minutes.

As a guarantee that all dogs would be paced at constant heart rate of 120 beats/min throughout baseline and isoproterenol states, a small dose of propranolol (0.1 mg/kg i.v.) was given. Since previous studies have shown that heart rate itself can influence isovolumic relaxation rate, peak filling...
rate, and other indices of relaxation rate, it was necessary that a constant heart rate be maintained in the baseline and isoproterenol states. The heart rate before the sinus node was crushed ranged from 150 to 190 beats/min. In preliminary experiments, it was demonstrated that despite an effective sinus node crush, some animals could not be paced at 120 beats/min in the baseline state; in other animals, isoproterenol produced a heart rate that exceeded the paced rate of 120 beats/min. Propranolol (0.1 mg/kg, total dose 1-3 mg) administered after the sinus node was crushed allowed every dog to be paced at 120 beats/min throughout the experiment. This dose of propranolol attenuates but does not completely block β-adrenergic tone; previous studies have shown that 1.0-1.5 mg/kg is necessary to fully block β-adrenergic tone. For further validation of this approach, the relation between the peak rate of increase in dimension [(+)]dD/dt and end-systolic dimension (ESD) before propranolol, after propranolol, and during isoproterenol administration was studied in a number of early experiments. As the example in Figure 2 illustrates, the ESD vs. (+)dD/dt relation in all three states lies along a common inverse relation. The isoproterenol state produced the smallest ESD and fastest (+)dD/dt. These data indicate that while β-adrenergic tone may have been increased before the administration of propranolol, isoproterenol (in doses given in this study) produced an increase in β-sympathetic tone that exceeded that present in the prepropranolol state. Therefore, the data presented in this study are from two states studied in all 12 animals: baseline (sinus node crush plus propranolol 0.1 mg/kg) and isoproterenol.

An infusion of isoproterenol was administered to enhance β-adrenergic tone; isoproterenol was infused at a rate sufficient to produce a 40% increase in LV peak (+)dP/dt (1,679±25 mm Hg/sec during baseline vs. 2,393±42 mm Hg/sec during isoproterenol infusion). After a steady state was achieved, 10 additional sets of aortic occlusions were performed.

Data Analysis

Peak (+)dL/dt values were measured in millimeters per second and normalized by division of their maximum value by end-systolic length (ESL) or ESD; they were then expressed as (+)dL/dt/L (sec⁻¹) and (+)dD/dt/D (sec⁻¹), respectively. ESL and ESD were measured in millimeters and were also expressed as normalized values with the control value of ESL or ESD during the baseline state equal to 100%. We plotted (+)dD/dt and (+)dD/dt against SP and ESL or ESD for the control beat (the beat that immediately preceded cross-clamp) and three progressively afterloaded beats. An example of this analytic method from one experiment that used dimension crystals is shown in Figures 3 and 4. In Figure 3 (left panel) all 40 (+)dD/dt versus SP coordinates obtained during the baseline state were plotted. On the same panel, 40 (+)dD/dt versus SP coordinates from the isoproterenol state were also plotted. Visual inspection of these coordinates revealed an inverse relation between (+)dD/dt and SP during the baseline state and the isoproterenol infusion. To model this relationship, all data points for a given state (baseline or isoproterenol) were fit either to linear, exponential, or polynomial equations by use of the PROPHET systems (a national computer resource sponsored by the Division of
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Research Resources, National Institutes of Health, Grant RR-01032). The relation was fit most closely by a linear function, which allowed comparison of the slopes and intercepts of the filling rate versus SP or ESD relation obtained during the baseline state with that obtained during isoproterenol by use of an analysis of covariance (PROPHET). In each experiment, an analysis of covariance was used to compare the filling rate versus SP or ESD relation obtained during the baseline state with that obtained during isoproterenol infusion (Tables 2 and 4). In each experiment, the analysis of curve fit, slope, and intercept was done using all 40 coordinates for each state.

The data from six experiments were summarized by use of a second method for data analysis (Figure 3, right panel). In each experiment, the data from 10 cross-clamps done during a given state were grouped into four subsets: the control beats and the first, second, and third cross-clamped beats. For each measured parameter, the mean ± SD of the 10 samples in each of four data subsets (control and three cross-clamped beats) was calculated in the baseline state and during the isoproterenol infusion. These mean values from each of six animals were then pooled to yield a mean ± SEM for the control and each of the three cross-clamped beats. For each state, values of SP, end-diastolic pressure (EDP), end-diastolic dimension (EDD), ESD, and (+)dD/dt obtained during the control beat were compared with those obtained during the first, second, and third cross-clamped beats using a one-way analysis of variance (PROPHET). The same method was used for analysis of the normalized data.

**Figure 3.** Example of analytic method used to quantify the relation between peak rate of increase in minor axis dimension [(+)dD/dt] and systolic pressure (SP). Data are from a single experiment. Left panel: Plot of all 40 (+)dD/dt vs. SP coordinates obtained from 10 sets of cross-clamps performed in baseline state and all 40 (+)dD/dt vs. SP coordinates obtained from 10 sets of cross-clamps performed during isoproterenol infusion. Inverse relation between (+)dD/dt and SP approached linearity during baseline and isoproterenol infusion (see Table 2, Experiment 1 for slope, intercept, and correlation coefficient). Right panel: Plot of data expressed as mean ± SD of all control (C) coordinates and coordinates from first (1), second (2), and third (3) beats after application of descending aortic cross-clamp. Data indicate that for a given SP, (+)dD/dt was faster during isoproterenol infusion. LV, left ventricular.

**Figure 4.** Example of analytic method used to quantify the relation between peak rate of increase in minor axis dimension [(+)dD/dt] and end-systolic dimension (ESD). Data are from a single experiment. Left panel: Plot of all 40 (+)dD/dt vs. ESD coordinates obtained from 10 sets of cross-clamps performed in baseline state and all 40 (+)dD/dt vs. ESD coordinates obtained from 10 sets of cross-clamps performed during isoproterenol infusion. Inverse relation between (+)dD/dt and ESD approached linearity during baseline and isoproterenol infusion (see Table 2, Experiment 1 for slope, intercept, and correlation coefficient). Right panel: Plot of data expressed as mean ± SD of all control (C) coordinates and coordinates from first (1), second (2), and third (3) beats after application of descending aortic cross-clamp. Data indicate that for a given ESD, (+)dD/dt was unchanged during isoproterenol infusion.
### Results

The data from six experiments that used dimension crystals are listed in Tables 1 and 2 and are presented in graphic form in Figures 3-6. The results from six experiments with segment length crystals are listed in Tables 3 and 4 and are presented graphically in Figure 7.

The changes in pressure and dimension that follow the application of a descending aortic cross-clamp are shown in Table 1. The EDD and EDP of the first cross-clamped beat did not change. However, SP and ESD increased while (+)dD/dt decreased. There were progressive increases in EDD, EDP, SP, and ESD and progressive reductions in (+)dD/dt in the second and third beats after aortic cross-clamp. Data from 10 sets of cross-clamps from one experiment are plotted in Figures 3 and 4. On the left panels, the individual data points from the 40 cross-clamped beats are plotted; on the right panels, the means of the 10 control beats and the first, second, and third cross-clamped beats are plotted. Analysis of the 40 coordinates of (+)dD/dt versus SP or (+)dD/dt versus ESD indicates a nearly linear inverse relation between (+)dD/dt and SP or ESD. Least-squares best-fit analysis of these 40 coordinates reveals a slope, y intercept, and correlation coefficient for the (+)dD/dt versus SP relation of -1.2±0.09, 241±12 mm/sec, and 0.90, respectively; for the (+)dD/dt versus ESD relation of -1.1±0.08, 241±12 mm/sec, and 0.90, respectively; for the (+)dD/dt versus ESD relation of -1.1±0.08, 241±12 mm/sec, and 0.90, respectively.

### Table 1. Effect of Altered Systolic Pressure and ß-Adrenergic Tone on Chamber Filling Rate

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<th></th>
<th>SP (mm Hg)</th>
<th>EDP (mm Hg)</th>
<th>EDD (mm)</th>
<th>ESD (mm)</th>
<th>(+)dD/dt (mm/sec)</th>
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<td>64.9±6.5†</td>
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| SP, systolic pressure; EDP, end diastolic pressure; EDD, end diastolic dimension; ESD, end systolic dimension; (+)dD/dt, peak rate of increase in minor axis dimension; C, control beat; 1, 2, 3, first, second, third beat after application of descending aortic cross-clamp.
* p<0.05 vs. control.
† p<0.05 vs. preceding value.

### Table 2. Effect of Isoproterenol on Regression Equation Relating Afterload to Indices of Chamber Filling Rate

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>(+)dD/dt (mm/sec) vs. SP (mm Hg)</th>
<th>Slope</th>
<th>Intercept</th>
<th>r</th>
<th>(+)dD/dt (mm/sec) vs. ESD (mm)</th>
<th>Slope</th>
<th>Intercept</th>
<th>r</th>
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<td>0.92±0.01</td>
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<td>-0.66±0.1</td>
<td>187±20*</td>
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<td>(+)dD/dt (mm/sec) vs. ESD (mm)</td>
<td>-11.1±0.08</td>
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<td>0.89±0.02</td>
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* r, linear correlation coefficient; (+)dD/dt, peak rate of increase in minor axis dimension; SP, peak left ventricular systolic pressure; ESD, end systolic dimension.
* p<0.01 vs. baseline.
versus ESD relation the slope, intercept, and correlation coefficient values were $-11.1\pm0.08$, $440\pm39$ mm/sec, and $0.90$, respectively. Each of the six experiments analyzed in this way are listed in Table 2. The average slope, intercept, and correlation coefficient of all six experiments were $-0.7\pm0.1$, $152\pm18$ mm/sec, and $0.92\pm0.01$, respectively, for $(+dD/dt)$ versus SP and $-11.1\pm0.3$, $410\pm14$ mm/sec, and $0.93\pm0.01$, respectively, for $(+dD/dt)$ versus ESD.

When data were grouped into four subsets for a given experiment (Figures 3 and 4, right panels), the inverse relation between $(+dD/dt)$ and SP or ESD appeared somewhat curvilinear. Since the shape of this curve may have been the consequence of the method of subgrouping coordinates, no curve fit was performed on data analyzed in this fashion. Nonetheless, these data (listed in Table 1 and plotted in Figure 5) confirm that over a wide range of SP (110–160 mm Hg) and ESD (25–40 mm), the $(+dD/dt)$ versus SP and $(+dD/dt)$ versus ESD relations were inverse. Thus, both analyses indicate that the indices of chamber filling rate are slowed by an acute increase in systolic pressure and dimension.

Isoproterenol infusion caused an increase in peak $(+dP/dt)$ from $1,679\pm25$ mm Hg/sec during baseline state to $2,393\pm42$ mm Hg/sec; SP and EDP were not significantly changed, but EDD and ESD fell significantly, and $(+dD/dt)$ increased significantly. Mean left atrial pressure was unchanged by the isoproterenol infusion ($6.2\pm2.1$ during baseline versus $6.3\pm1.8$ during isoproterenol). To examine whether this isoproterenol effect on filling rate was mediated through changes in the active state or through systolic loading conditions, the $(+dD/dt)$ versus SP or ESD relations during isoproterenol infusion were compared with those obtained during baseline state. The results from a single experiment (Figures 3 and 4) and from each of six experiments (Table 2) indicate that isoproterenol did not alter the inverse and nearly linear relation between $(+dD/dt)$ vs. SP or $(+dD/dt)$ vs. ESD. The coordinates of the $(+dD/dt)$ versus SP relation were shifted upward to a new line, that is, in each experiment the $y$ intercept increased during isoproterenol ($p<0.001$).

At a common SP of 140 mm Hg, $(+dD/dt)$ increased from $61\pm5.6$ mm/sec during baseline to $88\pm6.5$ mm/sec during isoproterenol. Likewise, there was no change in the slope of the inverse relation between $(+dD/dt)$ and ESD, but this relationship was extended to smaller dimensions (all coordinates were on a single line with no change in intercept). The value for $(+dD/dt)$ at a common ESD of 31 mm

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure5}
\caption{Summary of six experiments that examine effect of isoproterenol on relation between peak rate of increase in chamber dimension $(+dD/dt)$ and systolic pressure (left panel) and end systolic dimension (right panel). Data presented are mean±SEM.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure6}
\caption{Effects of isoproterenol on relation between normalized peak rate of increase in minor axis dimension $(+dD/dt)$ and LV systolic pressure (SP) (left panel) and end-systolic dimension (ESD) (right panel). There was an inverse relation between $(+dD/dt)$ and SP and between $(+dD/dt)$ and ESD. Isoproterenol shifted $(+dD/dt)$ vs. SP coordinates upward; $(+dD/dt)$ at common SP=120 mm Hg increased from 2.4 sec during baseline to 3.3 sec during isoproterenol. The $(+dD/dt)$ vs. ESD coordinates fell along a common inverse relation with $(+dD/dt)$ at common ESD=100% essentially unchanged at 2.45 sec during baseline vs. 2.35 sec during isoproterenol. LV, left ventricular; O, △, control beats; O, △, afterloaded beats. Data presented are mean±SEM.}
\end{figure}
TABLE 3. Effect of Altered Systolic Pressure and β-Adrenergic Tone on Myocardial Lengthening Rate

<table>
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<th></th>
<th>SP (mm Hg)</th>
<th>EDP (mm Hg)</th>
<th>MinP (mm Hg)</th>
<th>EDL (mm)</th>
<th>ESL (mm)</th>
<th>(+)dL/dt (mm/sec)</th>
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<td>3</td>
<td>140±6†</td>
<td>6.8±1.5*</td>
<td>4.9±1.8*</td>
<td>13.6±0.9†</td>
<td>11.0±0.9*†</td>
<td>37±4*</td>
</tr>
<tr>
<td>Isoproterenol C</td>
<td>105±4</td>
<td>5.8±1.4</td>
<td>2.8±1.7</td>
<td>12.7±1.0</td>
<td>8.6±1.0</td>
<td>57±4</td>
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<tr>
<td>1</td>
<td>128±6†</td>
<td>5.8±1.4</td>
<td>3.0±1.9</td>
<td>12.7±1.0</td>
<td>9.0±1.0†</td>
<td>49±4†</td>
</tr>
<tr>
<td>2</td>
<td>146±6†</td>
<td>6.3±1.4</td>
<td>3.6±1.4</td>
<td>12.9±1.0*</td>
<td>9.4±1.1†</td>
<td>45±5†</td>
</tr>
<tr>
<td>3</td>
<td>159±7†</td>
<td>6.7±0.5*</td>
<td>4.1±1.6*</td>
<td>13.2±1.0†</td>
<td>9.8±1.1†</td>
<td>43±5†</td>
</tr>
</tbody>
</table>

SP, systolic pressure; EDP, end diastolic pressure; min P, minimum left ventricular diastolic pressure; EDL, end-systolic segment length; ESL, end-systolic myocardial segment length; (+)dL/dt, peak segment lengthening rate; C, control beat; 1, 2, 3, first, second, third beat after application of descending aortic cross-clamp.

was unchanged by isoproterenol (64.2±6.3 vs. 65.1±6.6 mm/sec). Normalized data, presented in Figure 6, show no qualitative differences compared with nonnormalized data in either the baseline state or during isoproterenol infusion.

The pressure and length data from six experiments that used myocardial segment length crystals are listed in Table 3. The relation between (+)dL/dt and SP or ESL are quantified by slope, intercept, and correlation coefficient in Table 4 and presented graphically in a normalized form in Figure 7. Data obtained by use of segment length crystals closely parallel the findings obtained with dimension crystals. During the baseline state, an inverse and nearly linear relation between (+)dL/dt versus SP and (+)dL/dt versus ESL was found. Isoproterenol infusion produced changes in segment length transients that were directionally similar to those found with dimension transients. Isoproterenol did not change the slope of the inverse relation between (+)dL/dt and SP in any of the six segment length experiments (pooled data showed that the slope was —0.26±0.02 during baseline versus —0.22±0.03 during isoproterenol). As with dimension determinations, the intercept was significantly higher (88.3±3.4 mm/sec during isoproterenol versus 70.8±2.9 mm/sec during baseline, *p<0.01 versus baseline.

TABLE 4. Effect of Isoproterenol on Regression Equation Relating Afterload to Indices of Myocardial Lengthening Rate

| Experiment No. | Baseline | | | Isoproterenol | | |
|----------------|---------|---------|------|-------------|------|
|                | Slope   | Intercept | r   | Slope      | Intercept | r   |
| (+)dL/dt (mm/sec) versus SP (mm Hg) | 1       | —0.3±0.03 | 75±3 | 0.87      | —0.3±0.03 | 87±4 | 0.84 |
|                | 2       | —0.2±0.02 | 71±4 | 0.93      | —0.1±0.01 | 92±2 | 0.92 |
|                | 3       | —0.3±0.03 | 81±2 | 0.87      | —0.2±0.02 | 101±3 | 0.90 |
|                | 4       | —0.2±0.04 | 66±5 | 0.89      | —0.2±0.01 | 81±2 | 0.88 |
|                | 5       | —0.3±0.03 | 60±3 | 0.85      | —0.3±0.03 | 77±4 | 0.85 |
|                | 6       | —0.3±0.09 | 72±2 | 0.93      | —0.2±0.05 | 92±2 *| 0.92 |
| Mean±SEM      | —0.26±0.02 | 70±3 | 0.88±0.01 | —0.22±0.03 | 88±3* | 0.89±0.01 |
| (+)dL/dt (mm/sec) versus ESL (mm) | 1       | —7.7±0.2 | 173±3 | 0.80      | —8.3±0.4 | 180±4 | 0.82 |
|                | 2       | —8.0±0.9 | 113±10 | 0.89     | —8.0±0.9 | 120±11 | 0.83 |
|                | 3       | —7.3±0.4 | 157±5 | 0.93      | —8.1±0.3 | 150±6 | 0.92 |
|                | 4       | —5.4±0.5 | 68±4 | 0.80      | —4.3±0.3 | 63±2 | 0.80 |
|                | 5       | —4.5±0.8 | 51±6 | 0.79      | —5.9±0.9 | 56±9 | 0.81 |
|                | 6       | —8.5±0.3 | 145±7 | 0.90      | —8.4±0.4 | 141±8 | 0.91 |
| Mean±SEM      | —6.9±1.0 | 117±19 | 0.85±0.02 | —7.2±1.1 | 118±19 | 0.85±0.02 |

r, linear correlation coefficient; (+)dL/dt, peak rate of segment lengthening; SP, peak left ventricular systolic pressure; ESL, end-systolic myocardial segment length.

*p<0.01 versus baseline.
Neither the slope nor the intercept of the relation between (+)dL/dt and ESL was affected by isoproterenol; the slope was \(-6.9±1.0\) during baseline versus \(-7.2±1.1\) during isoproterenol, and the intercepts were \(117.8±19.8\) mm/sec during baseline versus \(118.3±19.8\) mm/sec during isoproterenol.

**Discussion**

We found that an acute increase in systolic pressure resulted in an abrupt fall in the indices of LV filling rate, and that over a wide range of systolic pressures, there was an inverse relationship between these indices of peak filling rate and end-systolic heart size. Isoproterenol infusion increased the rate of chamber filling and segment lengthening, but since isoproterenol may have both a direct \(\beta\)-stimulatory effect as well as indirect effects resulting from changes in systolic pressure and length, it was important to determine whether isoproterenol increased the filling rate primarily through its effects on loading conditions or through its direct effects on intrinsic myocardial relaxation. Therefore, we examined the effects of isoproterenol on the relationship between peak filling rate and the end-systolic heart size. Under these conditions, coordinates of the (+)dL/dt versus ESL or (+)dD/dt versus ESD relations fell along the same inverse relation as found during the baseline state; the coordinates simply moved to a smaller, faster portion of the inverse-velocity relation. We interpret these data to indicate that acute alterations in systolic pressure or \(\beta\)-adrenergic tone influence the indices of filling rate primarily through an effect on end-systolic size.

**Effects of Afterload on Relaxation Rate**

Data from our experiments in the intact heart are consonant with the results from isolated rat papillary muscle experiments in which an inverse relation between isotonic fiber lengthening rate (analogous to segment lengthening rate in the intact heart) and end-systolic muscle length was found.\(^{21,28}\) These isolated muscle studies allowed us to determine the independent effects of an acute change in afterload on relaxation rate because preload (muscle tension before stimulation) and lengthening loads (forces applied to the muscle during lengthening) were held constant. In the current study, preload could not be held constant. However, studies in isolated muscles and the intact heart indicate that preload (end-diastolic load) is not a primary determinant of relaxation rate.\(^{21,26}\)

Unlike preload, loads applied to the muscle during lengthening or filling (lengthening loads) have a substantial effect on measurements of relaxation rate.\(^{21,27,28}\) Lengthening loads are forces applied to or borne by the myocardium during filling and result from forces generated by left atrial pressure, the transmitral pressure gradient, and other factors that influence instantaneous LV wall stress during the filling period. An acute increase in these lengthening loads causes an accelerated relaxation rate. In the current experiment, in the first beat after application of the cross-clamp, there were no changes in preload (i.e., LV end-diastolic pressure or dimension). Therefore, the changes in peak filling rate in the first cross-clamped beat must have been related exclusively to changes in end-systolic length. In subsequent beats, however, peak filling rate may have been affected by the compound influences of an increase in end-systolic length (which would serve to decrease filling rate) and an increase in lengthening loads (which would increase filling rate). In several of our experiments, we found a tendency for the relation between end-systolic length and filling rate to be curvilinear (the coordinates from beat 3 indicated a faster rate than would be expected from a linear inverse relation). It is possible that this deviation was caused by an increase in the left atrial pressure during the second and third beats of the cross-clamp sequence. Alternatively, the inverse relation between length and filling rate may be lost at very long end-systolic muscle lengths. The current study extends the work of Bahler et al.\(^{21,29}\) who found that an increase in systolic pressure produced by a brief occlusion of the descending aorta, methoxamine infusion, or isometric handgrip exercise resulted in a decreased peak rate of increase in minor axis dimension in dogs and man.
Some studies with isolated LV papillary muscles,30 conscious dogs,21 or humans22 suggested that the absolute amount or extent of muscle shortening, not prevailing afterload or end-systolic length, was a primary determinant of the rate of early diastolic lengthening or filling. However, recent isolated muscle experiments clearly indicate that when afterload and end-systolic length are held constant while the extent of muscle shortening is varied (by change in the resting length), neither isotonic lengthening rate nor isometric tension decline is affected.21 Therefore, the extent of shortening is not an independent determinant of relaxation rate.

**Effects of β-Adrenergic Tone on Relaxation Rate**

The results of our current study on LV filling parallel previous studies that examined the effects of acute alterations in β-adrenergic tone on the rate of isovolumic pressure decline.15–18 In these studies, isoproterenol produced a shift in the relation between the rate of isovolumic pressure decline and LV systolic pressure, such that isovolumic pressure decline was faster at any given systolic pressure during isoproterenol infusion. Those experiments were not specifically designed to analyze the relationship between relaxation rate and end-systolic muscle length or dimension. The current study extends observations made on isovolumic indices by emphasizing the importance of the end-systolic size of the chamber (or length of the muscle) in determining the rates of muscle lengthening and chamber filling. We found that isoproterenol did not change the slope or the intercept of the inverse relation between end-systolic length and filling rates; this indicates that isoproterenol increased the filling rate by reducing end-systolic heart size.

These findings are consonant with previous studies of Yellin et al,33,34 who found that an isoproterenol infusion caused an increased peak mitral flow velocity, a decreased end-systolic dimension, and an increased transmural pressure gradient, but no change in left atrial pressure. From these studies, they concluded that isoproterenol augments early filling rate by increasing the restoring forces and that isoproterenol enhances ventricular filling by increasing elastic recoil without requiring an increased left atrial filling pressure. If left atrial pressure is unchanged by isoproterenol, then any change in the transmural pressure gradient must result from a decreased end-systolic volume, which causes a more rapid isovolumic pressure decline that produces a lower minimum LV pressure. Thus, the current study and those of Yellin and colleagues suggest that an increase in β-adrenergic tone increases indices of peak filling rate by increasing elastic recoil or “restoring forces” that occur as a consequence of a decrease in end-systolic heart size.

The fact that some investigators have reported more rapid LV filling rates during catecholamine infusion22,23 while others have not achieved such results24 might be explained by the fact that the effects of variations in fiber length or chamber size were not considered. For example, Bahler and Martin22 found that (+)dD/dt was increased by norepinephrine and that this increase was accompanied by a decrease in end-systolic dimension. If the two coordinates of (+)dD/dt and systolic length obtained by aortic occlusion (Bahler’s data22) are plotted together with the coordinates obtained during norepinephrine infusion, these coordinates appear to lie along a single inverse relation. In the studies of Sabbah and Stein,24 in which (+)dD/dt did not increase during an isoproterenol infusion, the average reduction in end-systolic size did not achieve statistical significance, but individual experiments indicate that those with the most substantial reduction in end-systolic size did also pronounced increases in (+)dD/dt. When analyzed in this fashion, the results of these studies22,24 are consonant with our data.

These findings differ, however, from those of Weigner and Bing.25 Their isolated muscle studies, which demonstrated that isoproterenol increased the slope and y intercept of the isotonic lengthening rate versus end-systolic length relation, were performed at 28° C. This temperature is commonly chosen because it prolongs contraction-relaxation and, by slowing the process of deactivation, facilitates examination of the isometric relaxation period. We speculate that isoproterenol increased (+)dL/dt in the isolated muscle study in part because deactivation in the baseline state was prolonged by the low temperature. When the baseline temperature was higher, the effects of isoproterenol on the afterload-lengthening–rate relation were less pronounced. Based on data from the current study, we hypothesized that isoproterenol did not directly influence LV peak filling rate because baseline deactivation was normal or near normal in our open-chest anesthetized dogs. Myocardial deactivation follows the dissociation of calcium from troponin I and the sequestration of calcium by the sarcoplasmic reticulum; this process roughly parallels the rate of isovolumic pressure decline.19 Bahler and Martin22 have shown that in open-chest anesthetized dogs, during the baseline state, the time from peak (-)dP/dt to peak (+)dD/dt was greater than 3.5 times the isovolumic relaxation time constant, indicating that any residual effects of muscle activation were likely to have dissipated well before the instant at which peak (+)dD/dt occurred. Therefore, we speculated that because peak filling rate occurred after the deactivation process was essentially complete, it is unlikely that β-adrenergic stimulation had a significant direct effect on LV filling rate in the current study. However, as data from the isolated muscle studies22 suggest, when myocardial deactivation is prolonged, β-adrenergic stimulation might then have a direct effect on increased LV filling rate.

The close correlation between filling rates and end-systolic dimension can be interpreted in the context of the hypothesis advanced by Tyberg et al35
and others. These investigators believe that the process of rapid early diastolic filling is strongly influenced by myocardial restoring forces. These forces result from energy stored during systole when the LV wall is deformed during contraction. This potential energy is released in the form of elastic recoil during relaxation when the ventricle returns to its precontractile configuration. Thus, a smaller end-systolic size is associated with a more rapid relaxation; β-adrenergic tone would not be expected to influence directly these passive restoring forces.

The recent study of Slinker and Glantz has questioned the accuracy of inferring LV volume from dimension measurements. They concluded that "the ability of dimensions to represent LV volume accurately decreases as the analysis frequency that is necessary to answer the physiologic question increases." Because assessment of end-diastolic and end-systolic volume does not exceed sampling frequency of the heart rate, dimension could be used for assessment of volume during beat-to-beat changes in LV function. In contrast, however, use of derivatives of dimension or volume requires a sampling frequency well in excess of heart rate. Therefore, to compensate for this limitation, we analyzed our data according to suggestions made by Glantz (personal communication) that 1) data obtained from anteroposterior dimension crystals should be confirmed using a second pair of crystals (i.e., segment length crystals), and 2) in a given study, each animal should be used as its own control and each experiment analyzed separately.

Clinical Implications

While there are no published studies that examine the changes in LV relaxation in patients with an acute hypertensive crisis, it is likely that an increase in systolic pressure would prolong relaxation, slow filling, and elevate LV diastolic pressure; at rapid heart rates, this could lead to pulmonary venous hypertension and congestive heart failure. In such patients, an acute reduction in arterial pressure might contribute to improved relaxation and a decrease in LV diastolic pressures. Acute changes in relaxation and filling due to altered load must be distinguished from those due to chronic diseases (such as hypertension or aortic stenosis). Some studies indicate that these abnormalities of relaxation are related to increased LV mass, while others implicate abnormal loading or other processes. Fouda et al and Smith et al have shown that hypertensive patients with or without a measurable increase in LV mass exhibit decreased early diastolic filling rates and an inverse relation between filling rate and systolic wall stress. Brutsaert et al and Gaasch et al have emphasized the complex interactions of multiple factors that affect relaxation in patients with heart disease; these include dynamic factors (such as loading conditions, rate of deactivation, and asynchrony) as well as static factors (such as LV mass and composition of the LV wall). The current study supports the hypothesis that short-term changes in afterload should be considered as a mechanism that may contribute to altered relaxation rates in patients with chronic heart disease.

The observation that an acute change in systolic pressure and length affects LV relaxation and filling has implications for understanding the mechanism(s) by which pharmacological agents affect relaxation changes in patients with heart disease. For example, calcium-channel-blocking agents tend to normalize the prolonged relaxation that is so typical of hypertrophic cardiomyopathy. However, have shown that nitroprusside also increases relaxation rate in this disorder; these authors concluded that the increase in relaxation rate produced by calcium-channel blockers was at least in part due to a systolic unloading effect. The effects of isoproterenol or other pharmacological interventions may likewise depend in part on the baseline state of the muscle; in normal myocardium, β-adrenergic stimulation may augment relaxation through an indirect effect on length. In hypertrophic or failing hearts, the effects may be mediated through direct effects on the sarcoplasmic reticulum and indirect effects of systolic fiber length. If we are to completely understand the effects of any drug on LV relaxation, all loading and other determinants of relaxation rate must be considered.

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M R Zile, A S Blaustein and W H Gaasch

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