Mechanism of Altered Patterns of Left Ventricular Filling During the Development of Congestive Heart Failure

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Background  The mechanism of the alterations in the pattern of left ventricular (LV) filling during the development of congestive heart failure (CHF) is not fully understood.

Methods and Results  We studied six conscious dogs instrumented to measure LV and left atrial (LA) pressures and LV volume as CHF was induced by rapid pacing. Diastolic filling dynamics were serially measured over 4 weeks during normal sinus rhythm. Four days after we initiated pacing, the peak early diastolic filling rate decreased from 108±24 to 88±27 mL/s (P<.05) as the maximal early diastolic LA-LV pressure gradient decreased associated with a slowing of the rate of LV relaxation. Subsequently, the peak early filling rate progressively increased, returning to control at 1 week, and by the fourth week, it had increased to 168±39 mL/s (P<.05). These changes in early filling rates occurred as the maximal early diastolic LA-LV pressure gradient increased in association with a progressive increase in LA pressure despite further progressive slowing of the rate of LV relaxation. Throughout the development of CHF, peak early filling rate and the maximal LA-LV pressure gradient correlated (r=.99, P<.001). The early filling deceleration rate increased and deceleration time progressively decreased over the 4 weeks as LV stiffness and net LA plus LV stiffness increased (P<.05). As predicted by a theoretical analysis, the deceleration time was linearly related to the reciprocal of the square root of LV stiffness (r=.94, P<.01).

Conclusions  Early in CHF, slowing of LV relaxation reduces the maximal early diastolic LA-LV pressure gradient, decreasing the peak early filling rate. As CHF progresses, this is overcome by an increase in LA pressure that augments the early diastolic LA-LV pressure gradient, increasing peak early filling rate. Increasing LV stiffness during the development of CHF progressively shortens the early filling deceleration time and augments the early filling deceleration rate. These observations suggest that the early filling deceleration time reflects LV stiffness. (Circulation. 1994;89:2241-2250.)

Key Words  heart failure • diastole • valves

The pattern of left ventricular (LV) filling determined by Doppler echocardiography or radionuclide angiography is used to noninvasively evaluate LV diastolic performance. Interpretation of these observations requires an understanding of the mechanism of both the normal and the abnormal patterns of LV filling.

The LV fills in diastole in response to the pressure gradient from the left atrium (LA) to the LV.1-5 This occurs at two times during the cardiac cycle: early in diastole after mitral valve opening and late in diastole during atrial systole. Normally, the majority of filling occurs early in diastole as LV pressure falls below LA pressure. The magnitude of this early filling is influenced by the rate of relaxation and elastic recoil of the LV, the LA pressure, and the pressure-volume characteristics of the LV and the LA.2-6 Late in diastole, atrial contraction again produces a gradient to propel blood from the LA to the LV.

The normal pattern of LV filling is altered in congestive heart failure (CHF).7-11 Early in CHF, the amount and rate of early filling are reduced, and the relative importance of filling during atrial contraction is enhanced. This has been attributed to a slowing of the rate of LV relaxation.8,10 Later in the course of CHF, the rate of early filling returns to its normal level. This "pseudonormalization" has been attributed to the effect of increasing LA pressure.8,12 Even later in the course of CHF, the peak early filling rate may be higher than normal. It has been proposed that this enhanced rate of early filling seen in advanced CHF is distinguished from normal by a faster rate of deceleration of the early flow and a shortened early filling deceleration time (tdec). This more rapid deceleration of early filling in CHF has been attributed to an increase in the net stiffness of the LA and the LV.13-15 The mechanism of the altered pattern of LV filling during the development of CHF remains speculative since LA and LV pressures and LV and LA pressure-volume relations have not been determined sequentially during the development of CHF.

In the "Appendix," we present an analysis that predicts that tdec is determined by the reciprocal of the square root of LV chamber stiffness (1/√KLV). In contrast to previous theoretical analyses,13-15 we predicted that LA stiffness does not influence tdec since LA pressure remains relatively constant during early filling deceleration. If our theoretical prediction is correct, then tdec, which can be measured noninvasively in patients, should provide a measurement of LV chamber stiffness.

Accordingly, this study was undertaken to investigate the mechanism of the altered diastolic filling dynamics seen during the development of CHF produced by rapid
pacing and to evaluate the new prediction of the relation between the \( t_{\text{sec}} \) and LV stiffness.

**Methods**

**Instrumentation**

Six healthy mongrel dogs weighing between 23 and 35 kg were instrumented. Anesthesia was induced with Xylazine (2.0 mg/kg IM) and sodium pentobarbital (6 mg/kg IV) and maintained with halothane (15% to 2%). The pericardium was opened through a left thoracotomy. Micromanometer pressure transducers (Konigsberg Instruments, Pasadena, Calif) and polyvinyl catheters for transducer calibration (1.1 mm i.d.) were inserted into the LV through the LV apical stab wound and into the LA through the LA appendage. Three pairs of ultrasonic crystals (5 MHz) were implanted in the endocardium of the LV to measure the anteroposterior, septolateral, and base-apex dimensions.\(^{15}\) A pacing lead was attached to the right ventricle or right atrium and connected to a programmable pacemaker (model 8329, Medtronic Inc) implanted subcutaneously. All wires and tubing were exteriorized through the posterior neck.

**Data Collection**

Studies were begun after full recovery from instrumentation (10 days to 2 weeks after surgery). The LV and LA catheters were connected to pressure transducers (Statham p23Db, Gould) calibrated with a mercury manometer. The signal from the micromanometer was adjusted to match that of the catheter. The LA micromanometer was adjusted to match LA and LV pressures at the end of long periods of diastasis.

The analog signals were recorded on an eight-channel oscillograph (AstroMed), digitized with an on-line analog-to-digital converter (Data Translation Devices) at 200 Hz, and stored on a floppy disk memory system by use of a 386 computer system. Each data-acquisition period lasted for 12 seconds, spanning several respiratory cycles.

**Experimental Protocol**

Data were recorded with unsedated animals lying quietly in a sling. Control data were acquired after full recovery from the surgical instrumentation before initiating pacing. Pacing was then started at 200 to 230 beats per minute to produce CHF.\(^{17}\) To record data, we turned off the pacemaker transiently during the first week of pacing (4±2 days) and then after approximately 1, 2, 3, and 4 weeks of pacing. Before we acquired data, each animal was allowed to stabilize for 30 minutes with the pacers turned off. After the data were recorded, the pacers were reinitiated.

**Effect of Heart Rate**

To investigate the effect of the heart rate changes during the development of CHF on LV filling dynamics, we studied six additional animals without CHF with similar instrumentation. Data were acquired at rest, and then the heart rate was increased by atrial pacing to approximately 140 beats per minute. The animals were allowed to equilibrate for approximately 5 minutes, and the data were acquired.

**Postmortem Evaluation**

At the conclusion of the studies, the animals were killed with an overdose of pentobarbital, and the hearts were examined to confirm the proper positioning of the instrumentation.

**Data Processing and Analysis**

The stored digitized data were analyzed by a computer algorithm developed in our laboratory. Hemodynamic values in each dog were obtained by averaging the data obtained during the steady-state recording spanning several respiratory cycles. End diastole was defined as the relative minimal LV pressure following the A wave. (If this was not clearly apparent, the peak of the R wave of the surface ECG was used to indicate end diastole.) End ejection was defined as the time of minimal dP/dt. The LV volume was calculated as a general ellipsoid using the equation:

\[
V_{LV} = \frac{(S/6)}{D_{AP} \cdot D_{BL} \cdot D_{LA}}
\]

where \( D_{AP} \), \( D_{BL} \), and \( D_{LA} \) are the anteroposterior, septolateral, and long-axis dimensions. This method of volume calculation gives a consistent measure of LV volume (r>97, SEE<2 mL), despite changes in LV loading conditions, chamber configuration.\(^{16,18-20}\)

**Ventricular filling patterns were measured using the time derivative of LV volume (dV/dt).**\(^{3,17}\) The characteristics of these patterns were evaluated by determining the maximal rates of early diastolic LV filling (peak E) and atrial filling (peak A). The deceleration time of early diastolic LV filling \( (t_{\text{dec}}) \) was defined as the time interval between the maximal rate of early diastolic LV filling and the zero intercept of the deceleration slope (Fig 1). After atrial filling occurred before early diastolic LV filling decelerated to zero line, the slope was linearly extrapolated to the zero line to obtain \( t_{\text{dec}} \). The deceleration rate of early diastolic LV filling \( (E_{DR}) \) was calculated as peak E divided by \( t_{\text{dec}} \) (Fig 1).

The average LV chamber stiffness \( (K_{LV}) \) during diastole was obtained by dividing the change of the pressure from the time of minimal LV pressure to end-diastolic pressure \( (\Delta P_{LV}) \) by the change of the volume during this period. Although there is pulmonary venous flow into the LA during this period,\(^{21,22}\) this change in volume was used to approximate the change in LA volume \( (\Delta V_{LA}) \) (see Fig 1). LA stiffness \( (K_{LA}) \) was obtained by dividing the change of the pressure from the time of mitral valve opening to minimal LA pressure \( (\Delta P_{LA}) \) by the change of the LV volume during this period \( (\Delta V_{LV}) \) (Fig 1).

The time constant of the isovolumic decrease in LV pressure was determined by fitting the steady-state data from end ejection to mitral valve opening to the equation:

\[
P = P_{e} e^{-t/T} + P_{b}
\]

where \( t \) is the time from end ejection, \( T \) is the exponential time constant of relaxation, and \( P_{e} \) and \( P_{b} \) were constants determined by the data. The time constant was also calculated without an asymptote \( (P_{b}) \). The time derivatives of LV pressure and volume were calculated using the five-point Gaussian technique.\(^{23}\)

The LV isovolumic relaxation time (IVRT) was measured as the time interval from aortic valve closure, indicated by peak negative dP/dt, to mitral valve opening.

**Statistical Analysis**

Changes in the variables during the development of CHF were assessed using repeated-measures ANOVA. If significant differences were present, paired comparisons between values at control and values after pacing were performed using the Student-Newman-Keuls test. A probability level of \( P<.05 \) was accepted as significant. Values are expressed as mean±SD.

**Results**

**Hemodynamics**

Consistent with our previous study,\(^2\) 4 weeks of pacing produced severe CHF with clinical evidence of pulmonary congestion and ascites. LV end-diastolic pressure progressively increased from 9.8±4.6 mm Hg at control to 34.3±7.7 mm Hg at 4 weeks \( (P<.05) \) (Table 1). Minimal LV pressure and mean LA pressure increased progressively from \(-1.1±3.0\) mm Hg at control to \(11.8±4.8\) mm Hg at 4 weeks \( (P<.05) \) and from \(4.9±3.2\) mm Hg to \(25.3±6.1\) mm Hg \( (P<.05) \), respectively, whereas LV end-diastolic and end-systolic volumes increased gradually from \(35.5±10.0\) mL to \(42.8±13.7\) mL.
(P < .05) and from 23.2±7.6 mL to 33.7±11.8 mL (P < .05), respectively. The ejection fraction decreased from 36±4% at control to 22±4% (P < .05) at 4 weeks.

LV Diastolic Filling Dynamics

A typical example of LV and LA pressures and dV/dt during the development of CHF is shown in Fig 2, and the group data for the filling dynamics are summarized in Table 2. Peak E decreased from 108±24 mL/s at control to 88±27 mL/s at 4 days (P < .05). In contrast, peak A increased significantly between control and 4 days (81±19 versus 89±18 mL/s, P < .05). Thereafter, peak E returned to control at 1 week and continued to increase progressively, reaching 168±39 mL/s at 4 weeks (P < .05), whereas peak A decreased significantly to 55±12 mL/s at 4 weeks. The t\text{dec} shortened progressively from 88±10 milliseconds at control to 51±9 milliseconds at 4 weeks (P < .05). The early filling deceleration rate (EDR) remained almost unchanged between control and 4 days (1.1±0.4 versus 1.2±0.6 L/s\textsuperscript{2}) and increased progressively to 3.6±1.8 L/s\textsuperscript{2} at 4 weeks (P < .05).

During the development of CHF, the rate of LV relaxation slowed as indicated by a progressive increase in the time constant of isovolumic LV pressure decrease, from 28±4 milliseconds to 44±5 milliseconds (P < .05). The maximal early diastolic LA-LV pressure gradient decreased from 5.5±1.1 mm Hg at control to 4.4±0.3 mm Hg at 4 days (P < .05) and increased gradually to 9.6±2.7 mm Hg at 4 weeks (P < .05). These changes in the maximal early diastolic pressure gradient closely correlated with the peak E (r = .99, P < .001) (Fig 3).

Typical examples of LV pressure-volume loops during the development of CHF are shown in Fig 4. Estimated LV chamber stiffness (KLV) progressively increased from 1.08±0.34 mm Hg/mL at control to 3.21±1.30 mm Hg/mL at 4 weeks (P < .05) (Table 3). Estimated LA stiffness (KLA) increased from 0.77±0.48 mm Hg/mL to 1.35±0.59 mm Hg/mL. However, this was not statistically significant. Estimated net left atrioventricular stiffness (KLV+KLA) increased from 1.84±0.61 mm Hg/mL at control to 4.56±1.63 mm Hg/mL at 4 weeks (P < .05). Both t\text{dec} and EDR correlated with KLV and (KLV+KLA) during the development of CHF (Fig 5).
TABLE 1. Hemodynamic Variables During the Development of Pacing-Induced Congestive Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>&lt;1 Wk</th>
<th>1 Wk</th>
<th>2 Wk</th>
<th>3 Wk</th>
<th>4 Wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of pacing, d</td>
<td>4±2</td>
<td>9±4</td>
<td>17±4</td>
<td>23±3</td>
<td>30±3</td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>114±16</td>
<td>114±16</td>
<td>114±11</td>
<td>129±14</td>
<td>134±15</td>
<td>136±13*</td>
</tr>
<tr>
<td>Minimal LV pressure, mm Hg</td>
<td>-1.1±3.0</td>
<td>0.9±3.5*</td>
<td>1.6±1.7*</td>
<td>5.0±4.2*</td>
<td>9.1±4.7*</td>
<td>11.8±4.8*</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mm Hg</td>
<td>9.8±4.6</td>
<td>15.7±2.1</td>
<td>20.0±4.0*</td>
<td>24.2±3.5*</td>
<td>30.1±4.5*</td>
<td>34.3±7.7*</td>
</tr>
<tr>
<td>LV end-systolic pressure, mm Hg</td>
<td>108.6±9.5</td>
<td>101.3±13.3</td>
<td>104.4±12.5</td>
<td>105.9±15.2</td>
<td>99.0±13.1</td>
<td>102.5±9.8</td>
</tr>
<tr>
<td>LV end-diastolic volume, mL</td>
<td>35.5±10.0</td>
<td>34.2±11.1</td>
<td>38.1±12.9</td>
<td>40.0±13.4</td>
<td>42.1±14.4*</td>
<td>42.8±13.7*</td>
</tr>
<tr>
<td>LV end-systolic volume, mL</td>
<td>23.2±7.6</td>
<td>24.6±7.8</td>
<td>27.7±11.2*</td>
<td>28.6±10.8*</td>
<td>31.3±11.9*</td>
<td>33.7±11.8*</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>12.4±2.7</td>
<td>9.6±3.4</td>
<td>10.5±2.2</td>
<td>11.4±3.0</td>
<td>10.7±2.8</td>
<td>9.1±2.3*</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>35.5±4.3</td>
<td>27.9±3.1*</td>
<td>28.5±4.9*</td>
<td>29.1±3.8*</td>
<td>26.4±4.0*</td>
<td>22.0±4.2*</td>
</tr>
<tr>
<td>Mitral valve</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>opening pressure, mm Hg</td>
<td>5.9±4.8</td>
<td>8.6±5.6</td>
<td>10.3±2.6*</td>
<td>17.6±2.9*</td>
<td>21.7±4.8*</td>
<td>25.8±5.8*</td>
</tr>
<tr>
<td>Mean LA pressure, mm Hg</td>
<td>4.9±3.2</td>
<td>6.2±4.2</td>
<td>9.2±2.1*</td>
<td>15.5±3.4*</td>
<td>21.1±4.7*</td>
<td>25.3±6.1*</td>
</tr>
<tr>
<td>Maximal dp/dt, mm Hg/s</td>
<td>3022±582</td>
<td>2200±337*</td>
<td>2126±317*</td>
<td>2128±554*</td>
<td>1926±474*</td>
<td>1958±300*</td>
</tr>
<tr>
<td>Minimal dp/dt, mm Hg/s</td>
<td>-2349±294</td>
<td>-1930±266*</td>
<td>-1917±236*</td>
<td>-1986±512*</td>
<td>-1762±415*</td>
<td>-1829±215*</td>
</tr>
<tr>
<td>Maximal gradient</td>
<td>5.5±1.1</td>
<td>4.4±0.3*</td>
<td>6.0±1.7</td>
<td>8.2±2.5*</td>
<td>9.5±2.2*</td>
<td>9.6±2.7*</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; bpm, beats per minute; and LA, left atrial. Values are mean±SD. n=6.

*P<.05 from control values.

development of CHF, the time constant of LV relaxation and the isovolumic relaxation time (IVRT) lengthened; however, these changes were not significantly correlated (Fig 6).

LA pressure during early filling deceleration is an important determinant of the rate and time for the deceleration.\textsuperscript{13,14,24} Thus, we examined LA pressure during this period (Fig 7). LA pressure remained constant during the first quarters of the flow deceleration period at all stages of CHF. At the end of the period, it increased slightly but significantly. We used this observation in the theoretical analysis contained in the "Appendix." This analysis predicts that:

\[
\tau_{dc} = \sqrt{\frac{32 \cdot \rho \cdot L}{7 \cdot A \cdot \sqrt{\frac{1}{V_{LV}}}}}
\]

where \(\rho\) is the density of blood, \(L\) is the effective length, and \(A\) is the effective area of the mitral apparatus. To evaluate this prediction, we examined the relation of \(\tau_{dc}\) and \(1/(\sqrt{V_{LV}})\). This is shown in Fig 8. A linear relation was observed \((r= .94, P<.01)\). The intercept was zero, and the slope was 0.08±0.02 \((s \cdot \sqrt{\text{mm Hg/mL}})\).

**Effect of Heart Rate**

During the development of CHF, the heart rate increased from 114±10 to 136±13 beats per minute. A similar increase in heart rate produced by atrial pacing (Table 4) before development of CHF produced decreases in the time constant of LV relaxation, minimal LV pressure and mean LA pressure, but did not significantly alter the maximal early diastolic LA-LV pressure gradient, peak E, or \(\tau_{dc}\).

**Discussion**

We measured LV and LA pressures and LV volume and calculated LV and LA stiffness during the development of CHF produced by rapid pacing in awake, unsedated dogs. These observations demonstrate the mechanism of the alterations of LV filling that occur during the development of pacing-induced CHF and suggest a method to estimate LV stiffness from the early filling deceleration time.

After 4 days of rapid pacing, there had been little change in LV end-diastolic volume or pressure or LA pressure. Even though there was little evidence of CHF, the pattern of LV filling had been altered with a decrease in the peak early filling rate and a compensatory increase in the rate of diastolic filling during atrial contraction, similar to that seen in patients with mild diastolic dysfunction.\textsuperscript{5,7,8,12} This decreased peak rate of early filling was associated with a decreased maximal early diastolic LA-LV pressure gradient. Throughout the entire course of CHF, we found that the peak early
filling rate closely correlated with the maximal LA-LV pressure gradient, confirming the role of this pressure gradient in determining the peak early filling rate (see Fig 3). The decreased early diastolic LA-LV pressure gradient seen after 4 days of pacing was the result of increased minimal LV pressure associated with a slowed rate of LV relaxation while LA pressure was unchanged.

After 1 week of pacing, the animals had begun to show early evidence of CHF, with moderate increases in LA pressure and LV volume. The peak early diastolic filling rate had returned to the pre-CHF control level. In clinical Doppler studies, this pattern of LV filling has been called "pseudonormalization."  The return of the peak early filling rate to the normal control level was due to the restoration of the LA-LV pressure gradient to the baseline level. This resulted from an increase in LA pressure that had more than outweighed the continued slowing of the rate of LV pressure decrease and the increase in minimal LV pressure.

After 4 weeks of pacing, the animals had evidence of severe CHF with markedly increased LA and LV end-diastolic pressures and increases in LV volume. The filling pattern in these animals with severe CHF was

### Table 2. Diastolic Filling Dynamics

<table>
<thead>
<tr>
<th>Duration of pacing, d</th>
<th>Control</th>
<th>&lt;1 Wk</th>
<th>1 Wk</th>
<th>2 Wk</th>
<th>3 Wk</th>
<th>4 Wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal early rapid filling dV/dt, mL/s</td>
<td>108±24</td>
<td>88±27*</td>
<td>110±31</td>
<td>148±61</td>
<td>175±58*</td>
<td>168±39*</td>
</tr>
<tr>
<td>Early rapid filling deceleration time, ms</td>
<td>88±10</td>
<td>75±13*</td>
<td>72±6*</td>
<td>63±8*</td>
<td>56±9*</td>
<td>51±9*</td>
</tr>
<tr>
<td>Early rapid filling deceleration rate, L/s²</td>
<td>1.1±0.4</td>
<td>1.2±0.6</td>
<td>1.5±0.5*</td>
<td>2.4±1.3*</td>
<td>3.2±1.3*</td>
<td>3.6±1.8*</td>
</tr>
<tr>
<td>Early rapid filling, mL</td>
<td>8.2±3.0</td>
<td>6.3±1.8</td>
<td>7.5±2.0</td>
<td>8.6±3.1</td>
<td>8.8±2.5</td>
<td>8.4±1.5</td>
</tr>
<tr>
<td>Early rapid filling/total filling, %</td>
<td>65.0±10.0</td>
<td>55.2±4.4*</td>
<td>61.6±7.4</td>
<td>72.3±11.0</td>
<td>75.8±3.1*</td>
<td>78.1±7.3*</td>
</tr>
<tr>
<td>Maximal late atrial filling dV/dt, mL/s</td>
<td>81±19</td>
<td>89±18*</td>
<td>84±12</td>
<td>74±11</td>
<td>69±19*</td>
<td>55±12*</td>
</tr>
</tbody>
</table>

*Values are mean±SD. n=6.
*P<.05 from control values.
similar to the "restrictive" LV filling pattern recorded by Doppler echocardiography in patients with severe CHF.7,8,12 The peak early filling rate increased more than 50% above the control level. This was associated with an increase in the maximal early diastolic LA-LV pressure gradient. This increased pressure gradient was produced by the marked increase in LA pressure that more than offset the continued slowing of the rate of LV pressure decrease and increase in minimal LV pressure.

Similar to clinical observations,7,12 the pseudonormalized and restrictive patterns of LV filling that we observed in moderate and severe CHF were distinguished from the control filling pattern by a shorter early filling deceleration time (tdec) and a more rapid early filling deceleration rate. Thomas et al15,24 and Flachskampf et al12 have predicted that the rate of early flow deceleration should vary directly with atrial pressure and mitral valve area and inversely with the combined stiffness of the LA and LV (KLA+KLV). Our results are consistent with this prediction, as the early flow deceleration rate progressively increased during the development of CHF as (KLA+KLV) increased. Although KLA tended to increase during the development of CHF, the changes did not reach statistical significance, and the increase in LA+LV stiffness was predominantly due to the increase in LV stiffness. Thus, we found that the deceleration rate correlated nearly as well with LV stiffness alone as it did with the combined atrial and ventricular stiffness (Fig 5). Our finding of a slight decrease in tdec at 4 days is in contrast to the increase in tdec that has been observed in some patients with mild diastolic abnormalities.26

As blood leaves the LA during early diastolic filling, pressure decreases, and as LV relaxation and elastic recoil are completed, LV pressure begins to rise with the increase in LV volume.1,3 These effects decrease and then reverse the LA-LV pressure gradient. This decelerates and then stops the initial rapid flow into the ventricle. The magnitude of the decrease in LA pressure and increase in LV pressure in early diastole depend on both the volume of the blood leaving the LA and entering the LV and the stiffness of the LV and LA.13,14,24 However, during early flow deceleration, there is rapid flow into the LA from the pulmonary veins.21,22 Thus, LA pressure initially remains constant during early flow deceleration (Fig 7), and the effective LA stiffness as seen by the LV is very low. Later during flow deceleration, LA pressure increases, despite continued filling of the LV, due to pulmonary venous inflow. Our theoretical analysis (see "Appendix") predicts that the early filling deceleration time should be proportional to the inverse of the square root of the LV stiffness: 1/(√KLV). As opposed to the analysis of

![Graph](https://example.com/graph1.png)

**Fig. 3.** Plot of peak early filling rate (peak E). Throughout the development of congestive heart failure, peak E closely correlated with the maximal left atrial-to-left ventricular (LA-LV) pressure gradient in early diastole.

![Graph](https://example.com/graph2.png)

**Fig. 4.** Left ventricular (LV) pressure volume loops obtained during the development of pacing-induced congestive heart failure.

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**Table 3. Rate of Left Ventricular Relaxation and Chamber Stiffness During the Development of Congestive Heart Failure**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>&lt;1 Wk</th>
<th>1 Wk</th>
<th>2 Wk</th>
<th>3 Wk</th>
<th>4 Wk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of pacing, d</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4±2</td>
<td>9±4</td>
<td>17±4</td>
<td>23±3</td>
<td>30±3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time constant of relaxation, ms (non-zero asymptote method)</strong></td>
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<td></td>
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<tr>
<td>28±4</td>
<td>34±3*</td>
<td>35±1*</td>
<td>37±5*</td>
<td>42±5*</td>
<td>44±5*</td>
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<tr>
<td>24±4</td>
<td>30±5*</td>
<td>30±2*</td>
<td>36±5*</td>
<td>43±5*</td>
<td>45±5*</td>
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<td><strong>Isovolumic relaxation time, ms</strong></td>
<td></td>
<td></td>
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<tr>
<td>45.0±7.1</td>
<td>50.0±8.2*</td>
<td>47.5±5.2</td>
<td>38.3±8.8*</td>
<td>34.2±5.9*</td>
<td>30.8±7.4*</td>
<td></td>
</tr>
<tr>
<td><strong>LV chamber stiffness, mm Hg/mL</strong></td>
<td></td>
<td></td>
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<tr>
<td>1.08±0.34</td>
<td>1.77±0.41</td>
<td>2.08±0.77*</td>
<td>2.21±0.62*</td>
<td>2.56±0.84*</td>
<td>3.21±1.30*</td>
<td></td>
</tr>
<tr>
<td><strong>LA chamber stiffness, mm Hg/mL</strong></td>
<td></td>
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<tr>
<td>0.77±0.48</td>
<td>0.85±0.50</td>
<td>0.85±0.39</td>
<td>0.87±0.26</td>
<td>1.07±0.41</td>
<td>1.35±0.59</td>
<td></td>
</tr>
<tr>
<td><strong>Net atrioventricular stiffness, mm Hg/mL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.84±0.61</td>
<td>2.62±0.70</td>
<td>2.93±1.01*</td>
<td>3.07±0.78*</td>
<td>3.63±1.17*</td>
<td>4.56±1.63*</td>
<td></td>
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</tbody>
</table>

LV indicates left ventricular; LA, left atrial. Values are mean±SD. n=6.

*P<.05 from control values.
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Fig 5. Plots of early filling deceleration rate (EDR) closely correlated with the stiffness of the left ventricle ($K_v$) and the net atrioventricular stiffness ($K_{LV}$) during the development of pacing-induced heart failure. Similar results are also found with the time for early filling deceleration ($t_{dec}$).

Thomas et al. 13,14,24 LA stiffness does not influence $t_{dec}$ because LA pressure is relatively constant during the first three fourths of flow deceleration. Our theoretical analysis predicts the $y$-axis intercept of the $t_{dec} = [1/(\sqrt{K_v})]$ relation should be zero, which is what we observed. Furthermore, the slope should be:

Fig 6. Plot showing lack of significant relation between the time for isovolumic relaxation (IVRT) and the time constant of left ventricular relaxation during the development of congestive heart failure.

Fig 7. Plot of left atrial pressure ($P_A$). Each of the stages of development of congestive heart failure is plotted during the time of left ventricular filling deceleration ($t_{dec}$). During the first three fourths of this period, $P_A$ was unchanged at each stage. At the end of the deceleration period at each stage of congestive heart failure, $P_A$ had significantly increased.
where \( \rho \) is viscosity of blood (\(-1 \text{ g/cm}^3\)), \( L \) is the effective length, and \( A \) is the effective area of the mitral orifice. The mitral annular area in our large dogs is approximately 2.5 cm\(^2\), and the length of the mitral leaflets about 1.0 cm. If we assume that \( L/A=(1.0/2.5)=0.4 \) and add the conversion of 1 mm Hg = 1333 dyne/cm\(^2\), then our analysis predicts the slope should be 0.05 s \( \cdot \) V mm Hg/mL. This is close to our observed value of 0.08 \( \pm \) 0.02 s \( \cdot \) V mm Hg/mL (Fig 8). This suggests that early flow deceleration time may be an indicator of LV stiffness that is measurable from LV filling dynamics.

Clinically, diastolic filling patterns are assessed by measuring mitral valve flow velocity using Doppler echocardiography. In this study, we measured the rate of change of LV volume (dV/dt), which is the same as mitral valve flow. Flow velocity is equal to the flow (dV/dt) divided by the mitral valve area. Because this area remains relatively constant during diastole, the patterns of flow we observed in this study are similar to flow velocity patterns observed with Doppler echocardiography. The mitral valve area may increase during the development of CHF, altering the relation between flow velocity and flow. Importantly, \( t_{ocf} \) should be similar whether it is determined from flow or flow velocity.

The isovolumic relaxation time (IVRT), which also can be clinically measured from Doppler echocardiography, has been proposed as an index of the rate of LV relaxation. The IVRT tended to increase during the development of CHF; however, consistent with previous observations, \(^{27} \) it did not closely correlate with the rate of LV relaxation.

We determined LV stiffness from the slope of mid and late diastolic portions of the LV pressure loop, beginning at the time of minimal LV pressure, when LV relaxation is nearing completion. This period spans the time of flow deceleration. LV stiffness determined in this manner progressively increased during the development of CHF. The LV diastolic pressure-volume relation is exponential in shape, with increasing slope (ie, stiffness) with increasing volume. Thus, the increase in average stiffness (\( K_{LV} \)) was measured during the development of CHF may at least partially result from the increase in LV volume. Similarly, we estimated the relative LA stiffness from the ratio of the decrease in LA pressure to the volume leaving the LA early in diastole. During this time period, the D wave of pulmonary inflow begins. \(^{21,22} \) Thus, the change in LA volume is less than the LA stiffness change in LV volume, causing us to somewhat underestimate true left.

There are several other methodological issues to consider. First, we used endocardial diameter gauges to measure LV volume. This technique has been extensively validated in past studies and accurately reflects LV volume under a wide variety of normal and pathological conditions. We have further evaluated the effect of shape changes by assessing the constancy of calculated LV volume during isovolumic relaxation when actual LV volume is constant while LV shape changes. Because LV volume, calculated by our method, changes by only 1.6 \( \pm \) 0.4% during this period, it appears that this method is insensitive to changes in LV shape. \(^{23} \) However, the accurate measurement of LV volume using endocardial diameter gauges depends on proper alignment of the crystals, and some crystals may not be precisely placed at the endocardium, leading to errors in the estimation of absolute ventricular volume. This might explain the relatively low ejection fractions seen in our study and also have been reported in normal dogs by Rankin et al. \(^{26} \) and Miyazaki et al. \(^{27} \) Although the instrumentation may produce some LV damage, thus potentially depressing LV performance, after recovery from the operation, the animals had good exercise tolerance, and the heart rate, LV pressure, peak (+)dP/dt, and cardiac output were within the normal ranges. The accurate measurement of dV/dt requires a
higher frequency content than volumes at single points in the cardiac cycle. \(^{20}\) Our use of three LV dimensions should be accurate to detect large changes in \(dV/dt\) \(_{\text{max}}\) as occurred in this study.

Our study was performed after we opened the pericardium. At higher cardiac volumes, the pericardium substantially restrains LV filling. \(^{31}\) In addition, Hoit et al\(^{20}\) observed that pericardiomyotomy altered the pattern of right but not left ventricular filling. Because LV volume increased during exercise after CHF, it is possible that if the pericardium had been intact, there would have been a greater restraint of cardiac filling and even more marked increases in LV diastolic pressure.

We used rapid pacing to produce a model of CHF. We cannot be certain that our results apply to other causes of LV dysfunction. However, this model of CHF produces the clinical features of dilated cardiomyopathy. Furthermore, the altered patterns of LV filling we observed are similar to those occurring in CHF produced by coronary embolization in the dog\(^{2}\) and in patients with CHF.\(^{7,8,12}\)

Two other methodological points should be considered. First, the use of a single exponential function to characterize LV relaxation is an approximation since LV isovolumic pressure decay is not exactly exponential.\(^{33}\) However, the calculation of time constant, based on the assumption of monoexponential decay, is a reasonable approximation to characterize the time course of pressure decrease.\(^{34}\) Second, we measured LV pressure at the apex. Because there is intraventricular pressure gradient during diastole,\(^1\) the mitral valve pressure gradient that we measured may have been less if we had measured LV pressure just below the mitral valve.

**Conclusions**

Our study demonstrates that early in the course of pacing-induced CHF, early diastolic LV filling is reduced due to slowed LV relaxation. With more severe CHF, the peak early filling rate becomes pseudonormalized and then greater than normal as the maximal early diastolic LA-LV pressure gradient is augmented by increasing LA pressures despite continued slowing of LV relaxation. During the development of CHF, the early diastolic flow deceleration rate increases and deceleration time decreases as LV stiffness increases.

Our observations are consistent with a theoretical analysis that predicts that the early flow deceleration time is equal to the following equation:

\[
\frac{\sqrt{\frac{22}{7} \cdot \frac{1}{A} \cdot \frac{1}{KLV}}}{m/s} 
\]

This suggests that \(t_{\text{dc}}\) can be used to judge changes in LV chamber stiffness.

**Appendix**

By Newton's second law, the deceleration rate of early diastolic filling is equal to the force (F) applied to the blood divided by the mass (M) of the blood:

\[
1 \quad \text{Deceleration Rate}=\frac{F}{M}
\]

The force producing deceleration after peak early flow is the reverse pressure gradient across the mitral valve (PLV-PLA) multiplied by the mitral valve area (A). The mass of blood is determined by density of blood (\(\rho\)) multiplied by the volume of blood in the mitral orifice, which is given by the effective area (A) multiplied by the effective length (L).\(^{13,35}\)

\[
2 \quad \text{Deceleration Rate}=\frac{(PLV-PLA) \cdot A}{\rho \cdot A \cdot L} = \frac{(PLV-PLA)}{\rho \cdot L}
\]

where \(E\) is peak early diastolic filling rate, and \(t_{\text{dec}}\) is deceleration time. \(PLA\) and \(PLV\) depend on the stiffness of the LA (\(K_L\)) and LV (\(K_L\)) and the change in the volumes (\(\Delta V\)) of the chambers from the time when the pressure equilibrates. The equilibration pressure (\(P_{\text{equil}}\)) occurs near the time of peak early diastolic flow (E) (Fig 9).\(^1\)

\[
3 \quad PLA=P_{\text{equil}}-\Delta VLA-KLA
\]

\[
4 \quad PLV=P_{\text{equil}}+\Delta VLV-KLV
\]

\[
5 \quad \Delta VLV=fdV/dt \cdot dt
\]

\[
6 \quad \Delta VLA=f \text{ Pulmonary Venous Flow} \cdot dt-\int fdV/dt \cdot dt
\]

Early during the time of flow deceleration, pulmonary venous inflow is rapid, approximating mitral flow (\(dV/dt\)); thus, \(\Delta VLA\) is small, and \(PLA\) is approximately constant (see Fig 7). Thus:

\[
7 \quad PLV-PLA=KLV-\Delta VLV
\]

We evaluated the integral at a point halfway to the midpoint of the deceleration curve. This point was chosen because the

---

**Table 4. Effect of Heart Rate on Hemodynamics**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Atrial Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>115±6</td>
<td>141±1*</td>
</tr>
<tr>
<td>Minimal LV pressure, mm Hg</td>
<td>−1.3±3.3</td>
<td>−2.9±4.2*</td>
</tr>
<tr>
<td>Mean LA pressure, mm Hg</td>
<td>4.0±3.0</td>
<td>2.6±2.7*</td>
</tr>
<tr>
<td>Time constant of relaxation (non-zero asymptote method), ms</td>
<td>27±3</td>
<td>26±4</td>
</tr>
<tr>
<td>Time constant of relaxation (zero asymptote method), ms</td>
<td>24±2</td>
<td>22±2*</td>
</tr>
<tr>
<td>Maximal gradient LA-LV pressure, mm Hg</td>
<td>5.8±1.9</td>
<td>6.7±2.2</td>
</tr>
<tr>
<td>Maximal early rapid filling dV/dt, mL/s</td>
<td>110±10</td>
<td>114±23</td>
</tr>
<tr>
<td>Early rapid filling deceleration time, ms</td>
<td>84±14</td>
<td>92±23</td>
</tr>
<tr>
<td>LV chamber stiffness, mm Hg/mL</td>
<td>1.15±0.24</td>
<td>0.94±0.20</td>
</tr>
</tbody>
</table>

\( ^* \) indicates left ventricular; bpm, beats per minute; and LA, left atrial. Values are mean±SD. \( n=6.\)
The deceleration rate has reached a plateau and PLA has not begun to increase. At this point, approximating the dV/dt curve as a straight line:

\[
\Delta V_{LV} = \frac{f dV}{dt} \cdot dt = \frac{7}{32} E \cdot t_{dec}
\]

(8)

Deceleration Rate = \(E(t_{dec} \cdot A)\)

where \(E\) is the maximal value of dV/dt.

Substituting and rearranging provides the following:

\[
t_{dec} = \sqrt{\frac{32 \cdot \rho \cdot L}{7 \cdot A \cdot KLV}}
\]

(9)

Therefore, within the accuracy of the simplifying assumptions, this analysis predicts that the time for early filling deceleration to occur is inversely related to the square root of the LV stiffness. The proportionality constant depends on the viscosity of blood (\(\rho\)) and an anatomic factor, the ratio of the effective length to the effective area of the mitral valve apparatus.

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