Effect of Heart Failure on the Mechanism of Exercise-Induced Augmentation of Mitral Valve Flow

Che-Ping Cheng, Toshiyuki Noda, Takashi Nozawa, and William C. Little

The exercise response of left ventricular (LV) filling dynamics may be altered by congestive heart failure (CHF). Accordingly, we studied 18 conscious dogs, instrumented to measure micromanometer LV and left atrial (LA) pressures and determine LV volume from three dimensions. CHF was produced by 4–5 weeks of right ventricular rapid pacing. Before CHF, exercise (5.5–8.5 mph for 8–15 minutes) increased the maximum rate of LV filling (dV/dt\textsubscript{max}) (197±37 versus 297±56 ml/sec [mean±SD], p<0.05) in response to an increase in the maximum early diastolic LA to LV pressure gradient (5.8±2.0 versus 9.8±1.9 mm Hg, p<0.05) produced by a fall in minimum LV pressure (1.0±0.9 versus −3.9±3.1 mm Hg, p<0.01), whereas mean LA pressure was unchanged (6.4±3.1 versus 6.4±4.2 mm Hg, p=NS). The time constant of LV relaxation was shortened (28.1±3.2 versus 21.0±4.2 msec, p<0.05). After CHF, dV/dt\textsubscript{max} (141±51 versus 200±59 ml/sec, p<0.05) and the maximum LA to LV pressure gradient (6.0±1.1 versus 11.1±2.7 mm Hg, p<0.05) continued to increase with exercise (3–5.0 mph for 4–8 minutes). However, the time constant of LV relaxation was prolonged (35.6±4.8 versus 38.9±5.5 msec, p<0.05), and minimum LV pressure (15.1±5.6 versus 17.6±5.9 mm Hg, p<0.05) and mean LA pressure increased (22.6±7.2 versus 29.1±7.3 mm Hg, p<0.05). These altered effects of exercise on LV diastolic filling dynamics persisted when heart rate and wall stress during exercise before and after CHF were matched by varying the level of exercise. We conclude that, during normal exercise, mitral valve flow is augmented by a fall of early diastolic LV pressure without a rise in LA pressure. After CHF, early diastolic LV pressure does not fall but increases during exercise. Thus, the increase in the early diastolic LA to LV pressure gradient and the rate of mitral valve flow results from an increase in LA pressure during exercise after CHF. This study suggests that the failure of the enhancement of LV relaxation and an increase in early diastolic LV pressure with exercise after CHF may contribute to exercise intolerance in CHF. (Circulation Research 1993;72:795–806)

**KEY WORDS** • left ventricular filling • diastole • exercise • heart failure

**Exercise tolerance is limited by dyspnea and fatigue in patients with congestive heart failure (CHF).** However, the correlation between objective measurements of exercise capacity and systolic left ventricular (LV) function is poor. Instead, exercise tolerance varies more closely with the level of left atrial (LA) pressure than the LV ejection fraction. Thus, changes in ventricular relaxation and filling during exercise have attracted increasing interest as potential determinants of exercise intolerance in patients with CHF.

During exercise in normals, cardiac output increases because of a marked increase in heart rate while stroke volume (SV) is maintained or increases. Since tachycardia decreases the duration of diastole, there is less time for diastolic filling of the LV. Thus, mitral valve flow increases during exercise in order to maintain or augment the SV. Mitral valve flow results from a pressure gradient across the mitral valve. Recently, we have observed that in conscious animals the LA to LV pressure gradient necessary for rapid flow across the mitral valve during exercise was generated by a fall in LV early diastolic pressure. This fall in LV early diastolic pressure, produced by enhanced LV relaxation from the adrenergic stimulation and tachycardia occurring during exercise, promoted rapid LV early diastolic filling without an increase in LA pressure. We hypothesized that this response to exercise may be altered in CHF. Accordingly, we evaluated the effect of exercise on LA and LV pressure and LV filling both before and after inducing CHF by right ventricular (RV) rapid pacing.

**Materials and Methods**

**Instrumentation**

A total of 24 healthy, adult, heart worm–negative mongrel dogs (weight, 24–35 kg) were instrumented under anesthesia after induction with xylazine (2 mg/kg i.m.) and sodium thiopental (6 mg/kg i.v.) and main-
tained with halothane (0.5–2%). They were intubated and ventilated with oxygen-enriched room air to main-
tain arterial oxygen tension greater than 100 mm Hg and 

\[ \text{pH} \text{ between 7.38 and 7.42.} \]

A sterile left lateral thoracotomy was performed, and the pericardium was widely opened. Micromanometer pressure transducers (Konigs-

\[ \text{berg Instruments, Inc., Pasadena, Calif.) and polyvinyl} \]

\[ \text{catheters for transducer calibration (1.1 mm i.d.) were} \]

\[ \text{inserted into the LV through an apical stab wound and} \]

\[ \text{into the LA via the LA appendage. Three pairs of} \]

\[ \text{ultrasonic crystals (5 MHz) were implanted in the} \]

\[ \text{endocardium of the LV to measure the anterior to posteri-} \]

\[ \text{or, septal to lateral, and base to apex (long-axis) dimen-} \]

\[ \text{sions, using the method previously described from our} \]

\[ \text{laboratory.}^{13-15} \]

\[ \text{In four animals, a 54-cm sutureless myocardial lead (model 4312, Cardiac} \]

\[ \text{Pacemakers, Inc., Minneapolis, Minn.) was implanted within the myo-} \]

\[ \text{cardium of the LA, and the lead was attached to a unipolar} \]

\[ \text{multiprogrammable pacemaker (model 8329, Medtronic} \]

\[ \text{Inc., Minneapolis, Minn.) positioned under the skin of the} \]

\[ \text{chest. The wires and tubing were tunneled subcuta-} \]

\[ \text{nously and brought out through the skin of the neck.} \]

**Data Collection**

Studies were performed after full recovery from instrumentation (from 7–10 days after the original sur-

\[ \text{gery with the dogs standing and then running on a} \]

\[ \text{motorized treadmill (model 1849C, Quinton Inc., Seat-} \]

\[ \text{tle, Wash.). The LV and LA catheters were connected to} \]

\[ \text{pressure transducers (Statham P23Db, Gould, Cleve-} \]

\[ \text{land, Ohio) calibrated with a mercury manometer. The} \]

\[ \text{signal from the micromanometers was adjusted to} \]

\[ \text{match that of the catheters. The zero of the LA} \]

\[ \text{micromanometer was adjusted so that the LV and LA} \]

\[ \text{pressure were equal at the end of long periods of diastasis.}^{12} \]

\[ \text{The transit time of 5-MHz sound between the} \]

\[ \text{crystal pairs was determined and converted to} \]

\[ \text{distance by assuming a constant velocity of sound in} \]

\[ \text{blood of 1.55 m/sec. The derivatives of LV pressure} \]

\[ \text{and volume were calculated using the five-point Lagran-} \]

\[ \text{gian method.}^{16} \]

**Experimental Protocol**

In an initial set of experiments, the effect of exercise before and after CHF was assessed in 18 dogs.

**Studies during exercise.** The animals were studied after full recovery from the operation. Steady-state data were recorded during 15-second periods at rest while the animals stood on a motorized treadmill (Quinton). The animals then ran on the treadmill. The treadmill speed was gradually increased over 1–2 minutes from 2.5 mph to the maximum level tolerated for steady-state exercise (5.5–8.5 mph). The animals exercised at this level until they could no longer keep up with the treadmill. Data were collected during 15-second periods throughout the exercise protocol. We analyzed the data recorded during the last minute of exercise. The total exercise time ranged from 8 to 15 minutes. Data during normal exercise from five of these dogs have been reported in a previous study.\(^{12}\)

**Studies during the development of CHF.** After the completion of the baseline exercise studies, a trans-

\[ \text{venous pacing lead (Medtronic) was inserted into the} \]

\[ \text{jugular vein under local anesthesia. The lead was ad-} \]

\[ \text{vanced to a stable position in the RV apex under} \]

\[ \text{fluoroscopic guidance and attached to a specially pro-} \]

\[ \text{grammable pulse generator (model 5985, DG2065008H,} \]

\[ \text{Medtronic) positioned under the skin of the neck.} \]

After pacemaker implantation, the pacemaker rate was adjusted using an external magnetic control unit below the spontaneous rate. After 3 days of recovery, the pacing rate was adjusted, using the external magnetic control unit, to 220–250 beats per minute. Three times per week, the pacemaker rate was adjusted below the spontaneous rate. The animal was allowed to equilib-

\[ \text{rate for 30 minutes, and then data were collected. The} \]

\[ \text{pacing rate was returned to 220–250 beats per minute.} \]

\[ \text{After pacing for 4–5 weeks, when the LV end-diastic} \]

\[ \text{pressure during the nonpaced period had increased by} \]

\[ \text{more than 20 mm Hg over the prepacemaker control level,} \]

\[ \text{CHF data were obtained. This level of CHF was chosen} \]

\[ \text{because the animals had begun to show clinical evidence} \]

\[ \text{of CHF (anorexia, mild ascites, and pulmonary congestion) but} \]

\[ \text{were still able to run.} \]

**Studies during exercise after the onset of CHF.** The pacemaker was turned off, and the animal was allowed to stabilize for at least 30 minutes. Data were collected with the animal standing at rest. Then, the animal ran on the treadmill as the speed was slowly increased and adjusted to the maximum tolerated steady-state level, and data were collected while the animal was running. After CHF, the exercise level was reduced to 3–5.0 mph.

In additional sets of experiments, the effects of β-adrenergic blockade, loading conditions, and heart rate were assessed.

**Studies on the effect of β-adrenergic blockade.** To assess the role of β-adrenergic stimulation on LV filling during exercise before and after CHF, the exercise protocol was repeated after administering β-adrenergic blockade (0.5 mg/kg i.v. metoprolol) in six animals before CHF. The response to exercise after CHF in these animals was compared with the effect of exercise after β-adrenergic blockade before CHF.

**Studies on the effect of heart rate and loading condi-

\[ \text{tions.} \]

\[ \text{To assess the influence of the less marked exercise} \]

\[ \text{tachycardia, a third protocol was performed in four} \]

\[ \text{animals that had atrial pacemakers. Data were initially} \]

\[ \text{recorded with the animal standing at rest on the tread-} \]

\[ \text{mill, and then the exercise protocol was repeated. After} \]

\[ \text{CHF, the same protocol was repeated while the heart} \]

\[ \text{was paced to the rate (170–210 beats per minute) pre-} \]

\[ \text{viously achieved during normal exercise.} \]

\[ \text{By analyzing data acquired at varying exercise levels} \]

\[ \text{before and after CHF, we were able to match heart rate} \]

\[ \text{and wall stress at end systole (WSS)} \]

\[ \text{during exercise before and after CHF in five animals.} \]

**Data processing and analysis.** Data were digitized using an on-line analog-to-digital converter (Data Translations Devices) at 200 Hz during each 15-second collection period. The LV volume (\(V_{LV}\)) was calculated as a modified general ellipsoid using the following equation:

\[ \text{\(V_{LV}=(\pi/6)D_{AP} \cdot D_{SL} \cdot D_{LA}\)} \]

where \(D_{AP}\) is the anterior to posterior LV diameter, \(D_{SL}\) is the septal to lateral LV diameter, and \(D_{LA}\) is the long-axis LV diameter. We have previously demonstrated that this method gives a consistent measure of
V_{LV} (r>0.97; SEE, <2 ml) despite changes in LV loading conditions, configurations, and heart rate.\textsuperscript{13,17-20}

To account for respiratory changes in intrathoracic pressure, steady-state measurements were averaged over the 15-second recording period that spanned multiple respiratory cycles.\textsuperscript{21} End diastole was defined as the relative minimum of LV pressure occurring after the A wave. If this was not clearly apparent, the peak of the R wave of the surface electrocardiogram was used to indicate end diastole. End systole was defined as the upper left corner of the LV pressure-volume (P-V) loop. The time of mitral valve opening was defined to be when LV pressure fell below LA pressure. LV pressure and volume were measured at end diastole, end systole, mitral valve opening, and minimum LV pressure. LA pressure was measured at the time of mitral valve opening (peak W wave) and at the peak of the A wave. The mean LA pressure was also determined.

The time derivative of LV pressure (dP/dt), the maximum diastolic mitral valve pressure gradient (LA pressure−LV pressure), and the maximum rate of change of LV volume (dV/dt max) were also determined. SV was calculated as LV end-diastolic volume minus end-systolic volume. To determine the role of the atrial contraction in increasing the maximum rate of LV filling during exercise, the time from maximum mitral valve pressure gradient to the peak of the A wave was measured, and the contribution of atrial contraction to LV filling was calculated as the increase in LV volume during the last one third of diastole, expressed as a fraction of the SV.

To quantitate shifts of the diastolic portion of the P-V loop, we compared LV minimum pressure at rest to the LV pressure at the same early diastolic LV volume during exercise. We also compared end-diastolic pressure at rest with the LV pressure at the same diastolic LV volume during exercise.

The mean end-systolic circumference stress (\(W_{SE}\), \([\text{g/cm}^2]\)) of the LV was calculated by use of a thick wall spherical model\textsuperscript{22}:  

\[
W_{SE} = G \cdot P_{ES} \cdot V_{ES}^{2/3} \left[ (V_{ES} + V_m)^{2/3} - V_{ES}^{2/3} \right]^{-1}
\]

where G (1.36) is a conversion factor (changing mm Hg units to g/cm\(^2\) units), \(P_{ES}\) is LV end-systolic pressure, and \(V_{ES}\) is LV end-systolic volume. \(V_m\) is the LV wall volume (ml), which is assumed to be 5 ml/kg body wt.\textsuperscript{22} Since pacing-induced CHF has been previously demonstrated to not alter LV wall mass,\textsuperscript{23} we used the same \(V_m\) to calculate \(W_{SE}\) both before and after CHF in each animal.

The rate of LV relaxation was analyzed by determining the time constant of the isovolumic fall of LV pressure. LV pressure from the time of peak −dP/dt

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**Table 1. Effects of Exercise on Steady-State Hemodynamics Before and After Congestive Heart Failure**

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
<th>CHF</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>116±15</td>
<td>176±23*</td>
<td>132±15†</td>
<td>164±18§</td>
</tr>
<tr>
<td>Max mitral valve pressure gradient (mm Hg)</td>
<td>5.8±2.0</td>
<td>9.8±1.9*</td>
<td>6.0±1.1</td>
<td>11.1±2.7‡</td>
</tr>
<tr>
<td>Max dV/dt (ml/sec)</td>
<td>197±37</td>
<td>297±56*</td>
<td>141±51†</td>
<td>200±59§</td>
</tr>
<tr>
<td>Mean LA pressure (mm Hg)</td>
<td>6.4±3.1</td>
<td>6.4±4.2</td>
<td>22.6±7.2†</td>
<td>29.1±7.3§</td>
</tr>
<tr>
<td>Min LV pressure (mm Hg)</td>
<td>1.0±2.9</td>
<td>−3.9±3.1*</td>
<td>15.1±5.6†</td>
<td>17.6±5.9‡</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>9.5±2.7</td>
<td>9.2±4.3</td>
<td>29.8±6.9†</td>
<td>36.9±7.6§</td>
</tr>
<tr>
<td>LV end-systolic pressure (mm Hg)</td>
<td>114±10</td>
<td>156±28*</td>
<td>109±9</td>
<td>128±17‡</td>
</tr>
<tr>
<td>LV end-systolic volume (ml)</td>
<td>40.5±14.3</td>
<td>42.3±12.5*</td>
<td>44.8±14.2†</td>
<td>47.8±14.4†</td>
</tr>
<tr>
<td>Mitral valve opening LA pressure (mm Hg)</td>
<td>10.7±5.2</td>
<td>10.3±3.9</td>
<td>22.6±8.3†</td>
<td>32.1±9.8§§</td>
</tr>
<tr>
<td>LA peak A wave (mm Hg)</td>
<td>12.7±7.3</td>
<td>14.3±4.1</td>
<td>23.9±10.2†</td>
<td>34.6±9.8§§</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>15.3±3.7</td>
<td>18.3±5.2*</td>
<td>11.2±3.7†</td>
<td>13.1±4.4†</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>37.9±7.3</td>
<td>43.8±7.2*</td>
<td>25.3±6.7†</td>
<td>27.5±6.2‡</td>
</tr>
<tr>
<td>Duration of diastole (msec)</td>
<td>265±56</td>
<td>160±41*</td>
<td>243±52†</td>
<td>168±45‡</td>
</tr>
<tr>
<td>Duration of isovolumic relaxation (msec)</td>
<td>34.6±5.9</td>
<td>29.4±6.1*</td>
<td>41.9±7.6†</td>
<td>48.3±10.1‡§</td>
</tr>
<tr>
<td>Time from PGmax to peak A wave (msec)</td>
<td>199±62</td>
<td>117±55*</td>
<td>167±51†</td>
<td>123±53§</td>
</tr>
<tr>
<td>Peak +dP/dt (mm Hg/sec)</td>
<td>2,839±577</td>
<td>3,796±1,032*</td>
<td>1,942±557†</td>
<td>2,595±5.1§§</td>
</tr>
<tr>
<td>Peak −dP/dt (mm Hg/sec)</td>
<td>−2,303±304</td>
<td>−2,932±625*</td>
<td>−2,009±417†</td>
<td>−2,285±378§§</td>
</tr>
<tr>
<td>T(_{1/2}) (msec)</td>
<td>18.2±3.4</td>
<td>14.6±2.1*</td>
<td>25.3±3.9†</td>
<td>29.3±6.1§‡</td>
</tr>
<tr>
<td>Time constant of relaxation (msec)</td>
<td>28.1±3.2</td>
<td>21.0±4.2*</td>
<td>35.6±4.8‡</td>
<td>38.9±5.5§§</td>
</tr>
<tr>
<td>Asymptote (PB) (mm Hg)</td>
<td>−3.4±7.2</td>
<td>−14.4±9.2*</td>
<td>1.3±6.9†</td>
<td>4.9±12.6§‡</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>1,728±498</td>
<td>3,221±927*</td>
<td>1,480±461†</td>
<td>2,142±76§§</td>
</tr>
<tr>
<td>Last third filling fraction (%)</td>
<td>25±6.1</td>
<td>17±3.9*</td>
<td>25±7.2†</td>
<td>21±9.5</td>
</tr>
<tr>
<td>(W_{SE}) (g/cm(^2))</td>
<td>67.1±21.7</td>
<td>76.3±24.3*</td>
<td>71.8±20.6†</td>
<td>83.0±32.2§§</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; bpm, beats per minute; Max, maximum; LA, left atrial; Min, minimum; LV, left ventricular; PGmax, maximum early diastolic LA to LV pressure gradient; T\(_{1/2}\), time from peak −dP/dt until LV pressure fell to one half of its value at peak −dP/dt; PB, extrapolated asymptotic pressure; \(W_{SE}\), wall stress at end systole. Values are mean±SD (n=18 dogs).

*\(p<0.05\) for exercise vs. rest; †\(p<0.05\) for CHF rest vs. rest; ‡\(p<0.05\) for CHF exercise vs. CHF rest; and §\(p<0.05\) for changes in exercise vs. rest compared with changes in CHF exercise vs. CHF rest.
until mitral valve opening was fit to an exponential equation:

\[ P = P_A \exp(-t/T) + P_B \]

where \( P \) is LV pressure, \( t \) is time, and \( P_A, P_B, \) and \( T \) are constants determined by the data. Although the fall of isovolumic pressure is not exactly exponential,\(^{24} \) the time constant, derived from the exponential approximation, provides an index of the rate of LV relaxation.\(^{21,25} \) In addition, \( T_{1/2} \) was computed as the time from peak \(-dP/dt\) until LV pressure fell to one half of its value at peak \(-dP/dt.\)\(^{26} \) The duration of isovolumic relaxation was measured from peak \(-dP/dt\) until mitral valve opening.

**Statistical Analysis**

Group data were summarized as mean±SD. Multiple comparisons were made by analysis of variance. When a significant overall effect was present, intergroup comparisons were performed, using a Bonferroni correction for multiple comparisons. The level of significance was \( p<0.05. \)

**Postmortem Evaluation**

At the conclusion of the studies, the animals were euthanized by lethal injection of sodium thiopental (40 mg/kg i.v.) plus T-61 euthanasia solution (0.3 ml/kg i.v.). The hearts were examined to confirm the proper positioning of the instrumentation.

**Results**

**Effects of Exercise Before and After CHF**

A total of 24 animals were instrumented and underwent induction of CHF. Two animals were eliminated from the data analysis because of transducer failures. Another four animals died during the development of CHF. Thus, data are reported for 18 animals that had data recorded during exercise both before and after CHF.

**Effects of exercise before CHF.** As summarized in Table 1, Figure 1, and the left panel of Figure 2, the effects of exercise before CHF are similar to those in our earlier report.\(^{12} \) The heart rate increased by 60%, and both SV (15.3±3.7 versus 18.3±5.2 ml, \( p<0.05 \)) and cardiac output increased (Table 1). Peak mitral flow (dV/dt\(_{max} \)) increased from 197±37 to 297±56 ml/sec during exercise in response to an increase in the maximum mitral valve pressure gradient from 5.8±2.0 to 9.8±1.9 mm Hg (\( p<0.05 \)). The increase in the mitral valve pressure gradient was due to a downward shift of the early diastolic portion of the LV P-V loop with a decrease in minimum LV pressure from 1.0±2.9 to \(-3.9±3.1 \) mm Hg (\( p<0.01 \)) (Figures 3A and 4A), without an increase in LA pressure. During early diastole, at equal LV volume, the LV pressure was significantly lower during exercise than that at rest (3.6±2.9 versus \(-4.1±5.7 \) mm Hg, \( p<0.05 \)). During late diastole, at an equivalent LV volume, the LV pressure was similar during exercise and at rest (10.7±6.8 versus 11.6±3.6 mm Hg, \( p=NS \)) (Figure 4). The time constant of LV

**FIGURE 1.** Analog recordings at rest and during treadmill exercise before congestive heart failure. During exercise, left ventricular (LV) systolic pressure increased and left atrial pressure (LAP) were relatively unchanged, whereas early LV diastolic pressure fell. There was a decrease in LV end-systolic volume (LVV) during exercise. The maximum mitral valve flow (dV/dt) was increased during exercise.
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**Figure 2.** Analog recordings at rest and during treadmill exercise before congestive heart failure (CHF) (left panel) and after CHF (right panel). Left panel: Before CHF, the peak rate of mitral valve flow (DV/DT) occurring in early diastole increased during exercise. Mean left atrial pressure (PLA) was unchanged, and the minimum left ventricular pressure (PLV) decreased. Thus, the increased early diastolic mitral valve pressure gradient during normal exercise resulted from a fall in minimum PLV without any change in mean PLA. Right panel: In contrast, after CHF, DV/DT still increased during exercise. The stroke volume was maintained. However, in contrast to the normal response, after CHF, mean PLA increased during exercise. Furthermore, minimum PLV also increased. Thus, after CHF, the increased mitral valve pressure gradient was due to an increase in PLA.

**Figure 3.** Left ventricular (LV) pressure–volume loops at rest and during exercise before and after congestive heart failure (CHF) in one animal. Each loop was generated by averaging the data obtained during a 15-second recording, spanning several respiratory cycles. Panel A: During normal exercise, the early diastolic portion of the LV pressure–volume loop is shifted downward. Thus, the early diastolic LV pressure is lower during exercise than at rest. Panel B: In contrast, after CHF, the diastolic portion of the LV pressure–volume loop is shifted upward during exercise so that early diastolic LV pressure is higher than at rest.
the LV end-systolic pressure decreased slightly (114±10 versus 109±9 mm Hg, p=NS). LV end-diastolic pressure (from 9.5±2.7 to 29.8±6.9 mm Hg, p<0.05), minimum LV pressure (from 1.0±2.9 to 15.1±5.6 mm Hg, p<0.01), mitral valve opening pressure, mean LA pressure (from 6.4±3.1 to 22.6±7.2 mm Hg, p<0.01), and peak A wave all increased after CHF. The time constant of LV relaxation (from 28.1±3.2 to 35.6±4.8 msec, p<0.05) and T\(_{1/2}\) (from 18.2±3.4 to 25.3±3.9 msec, p<0.05) both increased. \(W_{S\text{RES}}\) increased from 67.1±21.7 to 71.8±20.6 g/cm\(^2\) (p<0.05).

Effects of exercise after CHF. After CHF, the total exercise duration was reduced from 8–15 minutes to 4–8 minutes. Heart rate, SV (from 11.2±3.7 to 13.1±4.4 ml, p<0.05), and cardiac output increased during exercise after CHF (Table 1, Figure 5). Similar to the effect of exercise before CHF, the maximum mitral valve pressure gradient increased from 6.0±1.1 to 11.1±2.7

**Figure 4.** Examples of left ventricular (LV) pressure–volume loops at rest and during exercise before congestive heart failure (CHF) (panel A) and after CHF (panel B) in the first 12 dogs studied. Panel A: There is a downward shift of the early diastolic portion of the LV pressure–volume loop during exercise in each animal before CHF. Panel B: In contrast, after CHF, the diastolic portion of the LV pressure–volume loop is shifted upward during exercise, and the early diastolic LV pressure is higher than at rest.
mm Hg (p<0.05), and dV/dt\textsubscript{max} increased from 141±51 to 200±59 ml/sec (p<0.05). In contrast to the findings during exercise before CHF, LV end-diastolic pressure (from 29.8±6.9 to 36.9±7.6 mm Hg, p<0.05), minimum LV pressure (from 15.1±5.6 to 17.6±5.9 mm Hg, p<0.05), mitral valve opening pressure, and mean LA pressure (from 22.6±7.2 to 29.1±7.3 mm Hg, p<0.05) all increased during exercise after CHF. In addition, the LV end-systolic volume increased (from 33.6±12.2 to 34.8±12.2 ml, p<0.05); and the time constant of LV relaxation (35.6±4.8 versus 38.9±5.5 msec, p<0.05), T\textsubscript{LV} and the duration of isovolumic relaxation were pro-

longed during exercise after CHF. This is in contrast to the decrease of these parameters that occurred during normal exercise. These changes were accompanied by a consistent rightward and upward shift of the early diastolic portion of the LV P-V loop during exercise after CHF (Figures 3B and 4B). During early diastole, at an equivalent LV volume, the LV pressure was significantly higher during exercise than at rest (17.3±6.2 versus 20.5±6.3 mm Hg, p<0.05). This is the opposite of the response to exercise before CHF. During late diastole, at an equivalent LV volume, the LV pressure was similar during exercise and at rest
(28.7±7.2 versus 30.2±11.3 mm Hg, p=NS). The increase in WS_{ES} during exercise was similar before (9.2±13.2 g/cm²) and after (11.2±19.7 g/cm²) CHF.

**Effects of β-Adrenergic Blockade, Heart Rate, and Loading Condition**

**Comparing exercise effect before CHF with β-adrenergic blockade to CHF.** Consistent with our previous observation, the exercise-induced tachycardia and increase in systolic LV pressure were markedly reduced after β-adrenergic blockade (Table 2). There were no significant changes in the duration of exercise, LV WS_{ES} (65.2±31.9 versus 65.1±34.8 g/cm², p=NS), LV end-systolic pressure (115±10 versus 111±6 mm Hg, p=NS), end-systolic volume (29.3±13.7 versus 29.5±13.5 ml, p=NS), or the time constant of LV relaxation (29.8±2.3 versus 31.5±3.7 msec, p=NS) after β-adrenergic blockade. With exercise after β-adrenergic blockade there was an increase in peak mitral valve flow (185±53 versus 269±73 ml/sec, p<0.05), resulting from an increased maximum mitral valve pressure gradient (6.4±1.2 versus 9.8±1.8 mm Hg, p<0.05) without a significant change in minimum LV pressure. There was no significant shift of the diastolic portion of the LV P-V loop during exercise after β-adrenergic blockade. The increase in SV was due to an increase in end-diastolic volume, because end-systolic volume did not change. After CHF in these same animals, the peak mitral valve flow during exercise (153±23 versus 220±15 ml/sec, p<0.05) also increased because of a more marked increase in mean LA pressure. In contrast to the effect of exercise after β-adrenergic blockade, exercise after CHF produced a significant increase in minimum LV pressure and slowing of the rate of LV relaxation, and there were also more pronounced increases in end-systolic pressure, LV end-diastolic pressure, and WS_{ES} than occurred during β-blocked exercise before CHF. The duration of exercise was also markedly decreased (4–8 minutes).

**LV filling at similar heart rates during tachycardia induced by exercise and atrial pacing before and after CHF.** The heart rate did not increase as markedly during exercise after CHF as before CHF. Increasing the heart rate during CHF exercise by atrial pacing to the same rate achieved during normal exercise (190±6 versus 192±4 beats per minute, p=NS) did not change the altered effects of exercise after CHF. With the faster heart rate, compared with normal exercise, the rate of LV relaxation was still slowed with the time constant of LV relaxation increasing from 21.1±6.9 to 42.3±7.7 msec (p<0.05) and T_{1/2} increasing from 14.3±0.8 to 24.8±2.3 msec (p<0.05). Similarly, minimum LV pressure (1.6±5.3 versus 14.6±2.1 mm Hg, p<0.05) and mean LA pressure still increased (7.5±4.2 versus 22.4±7.1 mm Hg, p<0.01) during exercise after CHF.

**Effect of exercise before and after CHF at matched wall stress and heart rate.** As shown in Table 3, by comparing data acquired at varying levels of exercise, we were able to match the heart rate (167±6 versus 165±8 beats per minute, p=NS) and wall stress (91.2±32.7 versus 90.7±15.1 g/cm², p=NS) during exercise before and after CHF in five animals. The differences in the responses to exercise of LA pressure, minimum LV pressure, and the time constant of LV relaxation before and after CHF were not altered.

**FIGURE 5.** Analog recordings at rest and during treadmill exercise after congestive heart failure (CHF). After CHF, there were increases in both atrial pressure and minimum left ventricular (LV) pressure during exercise. The LV end-diastolic volume, end-systolic volume, and maximum mitral valve flow (dV/dt) were all significantly increased.
**TABLE 2. Comparing Effects of Exercise Before Congestive Heart Failure With β-Adrenergic Blockade to Congestive Heart Failure**

<table>
<thead>
<tr>
<th></th>
<th>β-Adrenergic blockade</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rest</strong></td>
<td><strong>Exercise</strong></td>
<td><strong>Rest</strong></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>115±8</td>
<td>134±14*</td>
</tr>
<tr>
<td>Max mitral valve pressure gradient (mm Hg)</td>
<td>6.4±1.2</td>
<td>9.8±1.8*</td>
</tr>
<tr>
<td>Max dV/dt (ml/sec)</td>
<td>185±53</td>
<td>269±73*</td>
</tr>
<tr>
<td>Mean LA pressure (mm Hg)</td>
<td>10.8±4.8</td>
<td>13.9±4.8*</td>
</tr>
<tr>
<td>Min LV pressure (mm Hg)</td>
<td>3.5±4.1</td>
<td>5.0±3.8</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>12.1±2.9</td>
<td>15.6±6.2*</td>
</tr>
<tr>
<td>LV end-systolic pressure (mm Hg)</td>
<td>115±10</td>
<td>111±6</td>
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<tr>
<td>LV end-diastolic volume (ml)</td>
<td>45.5±1.5</td>
<td>47.2±15.7*</td>
</tr>
<tr>
<td>LV end-systolic volume (ml)</td>
<td>29.3±13.7</td>
<td>29.5±13.5</td>
</tr>
<tr>
<td>Mitral valve opening LA pressure (mm Hg)</td>
<td>13.7±5.1</td>
<td>17.6±5.3*</td>
</tr>
<tr>
<td>LA peak A wave (mm Hg)</td>
<td>20.5±7.4</td>
<td>23.2±10.7*</td>
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<tr>
<td>Stroke volume (ml)</td>
<td>16.2±2.2</td>
<td>17.7±2.6*</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>35.9±7.4</td>
<td>37.5±6.9*</td>
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<tr>
<td>Duration of diastole (msec)</td>
<td>294±55</td>
<td>248±67*</td>
</tr>
<tr>
<td>Time from PGmax to peak A wave (msec)</td>
<td>230±27</td>
<td>249±67</td>
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<tr>
<td>Peak +dP/dt (mm Hg/sec)</td>
<td>2,685±455</td>
<td>2,731±337</td>
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<tr>
<td>Peak −dP/dt (mm Hg/sec)</td>
<td>−2,296±261</td>
<td>−2,344±275</td>
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<tr>
<td>Time constant of relaxation (msec)</td>
<td>29.8±2.3</td>
<td>31.5±3.7</td>
</tr>
<tr>
<td>Asymptote (PB) (mm Hg)</td>
<td>−7.8±1.9</td>
<td>−9.2±3.4*</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>1,863±303</td>
<td>2,372±538*</td>
</tr>
<tr>
<td>Last third filling fraction (%)</td>
<td>24±5.3</td>
<td>18.9±4.4</td>
</tr>
<tr>
<td>Ws3S (g/cm²)</td>
<td>65.2±31.9</td>
<td>65.1±34.8</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; bpm, beats per minute; Max, maximum; LA, left atrial; Min, minimum; LV, left ventricular; PGmax, maximum early diastolic LA to LV pressure gradient; PB, extrapolated asymptotic pressure; Ws3S, wall stress at end systole. Values are mean±SD (n=6 dogs).

*p<0.05 for β-blocked exercise vs. β-blocked rest; †p<0.05 for CHF rest vs. β-blocked rest; ‡p<0.05 for CHF exercise vs. CHF rest; and §p<0.05 for changes in β-blocked exercise vs. β-blocked rest compared with changes in CHF exercise vs. CHF rest.

**Discussion**

The tachycardia that accompanies exercise decreases the duration of diastole. If the SV is to be maintained or increased, the mean mitral valve flow must increase. During normal exercise, the peak mitral valve flow markedly increases in response to an increased early diastolic mitral valve pressure gradient, produced by a fall in early diastolic LV pressure without much change in LA pressure.12,21 The fall in early diastolic LV pressure during normal exercise is associated with a more rapid fall of LV pressure during isovolumic relaxation that results from the combination of the effects of the increased heart rate and the sympathetic stimulation accompanying exercise.12

We studied the dynamics of LV filling during exercise in a model of CHF produced by rapid pacing. During exercise after CHF, the heart rate, SV, peak mitral valve flow rate, and peak early diastolic mitral valve pressure gradient all showed increases similar to the effects seen during normal exercise. However, the mechanism of the increased early diastolic mitral flow during exercise after CHF was different. Instead of a fall in early diastolic LV pressure, after CHF, the early diastolic LV pressure increased during exercise. Thus, the increased early diastolic mitral valve pressure gradient entirely resulted from an increase in LA pressure (Figure 2). The rate of LV isovolumic pressure fall decreased, and the early diastolic portion of the LV P-V loop shifted upward and rightward during exercise after CHF. This response is in contrast to the more rapid relaxation and the downward shift in the early diastolic portion of the LV P-V loop seen during normal exercise (Figures 3 and 4).

Why were the effects of exercise on the rate of LV relaxation and the early diastolic LV pressure altered after CHF? One factor is the different response of the LV end-systolic volume to exercise. During normal exercise, the LV end-systolic volume decreased. This smaller volume reduces the passive portion of LV early diastolic pressure and may increase the amount of elastic recoil that contributes to the fall in early diastolic LV pressure. In contrast, after CHF, LV end-systolic volume increased during exercise. This increased end-systolic volume should be associated with higher passive pressures and lessen or abolish compression of elastic elements occurring during systole, thus decreasing the recoil during the subsequent diastole.

The upward shift in the diastolic portion of the LV P-V loop we observed during CHF exercise is similar to that reported by Miyazaki21 in exercising dogs with coronary stenoses, as well as that found in clinical studies of exercise-induced ischemia.27,28 In these studies, the decrease in LV distensibility during exercise was due to the effect of myocardial ischemia. Although our animals did not have coronary stenoses, exercise-induced ischemia may have contributed to our findings, since reduced coronary flow reserve has been recently reported in pigs with pacing-induced CHF.29 However, there was no change in the late diastolic pressures at
matched LV volume, suggesting that the passive LV P-V relation was not altered during exercise after CHF, as would be expected with ischemia.

During normal exercise, heart rate and LV systolic pressure increased more than during exercise after CHF (Tables 1 and 3). However, the less marked exercise tachycardia after CHF was not responsible for the different effects on LV relaxation and early diastolic pressure before and after CHF, since these differences persisted when the exercise heart rate after CHF was increased by atrial pacing. Although the increase in LV systolic pressure during exercise was blunted after CHF, the other determinant of wall stress, LV end-systolic volume, increased. Thus, the differences in the responses of LV relaxation and early diastolic LV pressure to exercise before and after CHF might be due to the higher wall stress produced during exercise after CHF. Consistent with this possibility, Komamura et al."^{30} recently demonstrated that resting LV diastolic dysfunction in pacing-induced CHF is due to increased systolic loading. However, in our study, the differences in the response of LV relaxation and early diastolic LV pressure during exercise before and after CHF persisted when the levels of wall stress and heart rate were matched at the same levels before and after CHF (Table 3). Thus, the altered response to exercise after CHF was not exclusively due to increased systolic wall stress. However, after CHF, the rate of LV relaxation may be more sensitive to the increases in systolic pressure and stress induced by exercise. Thus, both a higher level of systolic loading during exercise and greater load sensitivity of relaxation may contribute to the altered response we observed after CHF.

During normal exercise, any slowing of LV relaxation with increased systolic load is overcome by sympathetic stimulation and the increased heart rate that enhances the rate of LV isovolumic pressure fall."^{12} The effect of increased heart rate to speed relaxation is reduced in CHF, and the response to β-adrenergic stimulation is decreased. We have observed that the normal downward shift of the early diastolic portion of the P-V loop with normal exercise can be abolished with β-adrenergic blockade. Furthermore, during normal exercise, sympathetic stimulation of increased contractility helps sustain SV without requiring an increase in end-diastolic volume. These effects of β-adrenergic stimulation are reduced during exercise after CHF. Thus, the slowed rate of relaxation and higher early diastolic LV pressures during exercise after CHF appear to result from a failure of sympathetic stimulation and increased heart rate to offset the enhanced effect of the increased systolic pressure.
loading during exercise. However, a recent study found that LV isovolumic relaxation remains sensitive to β-adrenergic stimulation with dobutamine in patients with severe CHF at rest, although even after dobutamine the rate of LV isovolumic relaxation in these patients with CHF was slower than in normal subjects. A forceful atrial kick may compensate for impaired early diastolic LV filling in patients with impaired LV relaxation. Accordingly, we investigated the role of the LA in increasing the maximum rate of LV filling during exercise before and after the onset of CHF. During normal exercise, mean LA pressure, mitral valve opening pressure, and peak A wave LA pressure were unchanged. Thus, neither an increased LA pressure nor more vigorous atrial contraction contributed to the increased mitral valve pressure gradient and resulting increase in dV/dt max that occurred during normal exercise. After the development of CHF, the LA peak A wave was increased during exercise as well as mean LA pressure and LA pressure at the time of mitral valve opening. However, the peak mitral valve pressure gradient occurred before the A wave produced by LA contraction. Furthermore, the amount of LV filling that occurred during the last one third of diastole, representing atrial contribution to LV filling, did not increase during exercise after CHF. Thus, it does not appear that a more forceful atrial contraction contributes to the rapid early LV diastolic filling during CHF exercise.

Potential Limitations of Methods

Our study was performed after opening the pericardium. It is clear that at higher cardiac volumes the pericardium substantially restrains LV filling. In addition, Hoit et al. observed that pericardiectomy altered the pattern of RV but not LV filling. Since LV volumes 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 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 but LV shape changes. Since LV volume, calculated by our method, changes by only 1.6±0.4% during this period, it appears that this method is insensitive to changes in LV shape. 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 also reported in normal dogs by Rankin et al. and Miyazaki et al. Moreover, the instrumentation may produce some LV damage, thus potentially depressing LV performance. However, after recovery from the operation, the animals had good exercise tolerance, and the heart rate, LV pressure, peak +dP/dt, and cardiac output were all within the normal range. The accurate measurement of dV/dt requires a higher frequency content than volumes at single points in the cardiac cycle. Our use of three LV dimensions should be accurate to detect large changes in dV/dt max as occurred in this study.

The experimental evaluation of CHF has been difficult in the past because of the lack of a reliable experimental model. Although rapid pacing produces an animal model of CHF that closely mimics the clinical picture of a congestive cardiomyopathy, we cannot be certain that our results apply to CHF that is due to other causes.

Two other methodological points should be considered. First, the use of a simple exponential to characterize relaxation is an approximation, since LV isovolumetric pressure does not decay exactly exponentially. However, the calculation of the time constant of LV relaxation, based on the assumption of monoequenential decay, is a reasonable approximation to characterize the time course of pressure fall. Furthermore, the exercise-induced changes in the rate of LV pressure fall were also apparent in changes in T1/2, which is not model dependent. Second, we measured LV pressure at the apex. Since there is an intraventricular pressure gradient during diastole, the mitral valve pressure gradient that we measured may have been less if we had measured LV pressure just below the mitral valve.

Clinical Implications

Exercise tolerance is limited in patients with CHF by fatigue and dyspnea. The dyspnea may result from increases in LA pressure, producing pulmonary congestion. Exercise tolerance in patients with CHF is not well correlated with LV systolic performance. For example, some patients with near normal LV ejection fraction have marked exercise intolerance, whereas others with reduced ejection fraction have near normal exercise tolerance. On the basis of our study, we speculate that failure of the normal exercise-induced fall in early diastolic LV pressure and the increase in LA pressure may contribute to the limitation of exercise tolerance in patients with CHF. This suggests that pharmacological therapy to improve LV relaxation during exercise may be beneficial in enhancing exercise tolerance.

In conclusion, during normal exercise, mitral valve flow is augmented by a fall of early diastolic LV pressure, without a rise in LA pressure. After CHF, early diastolic LV pressure does not fall but increases during exercise. The increase in the early diastolic LA to LV pressure gradient and the rate of mitral valve flow results from an increase in LA pressure.

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