Restrictive Left Ventricular Filling Pattern Does Not Result From Increased Left Atrial Pressure Alone

Satoshi Masutani, MD; William C. Little, MD; Hiroshi Hasegawa, MD, PhD; Heng-Jie Cheng, MD, PhD; Che-Ping Cheng, MD, PhD

Background—The restrictive filling pattern seen with severe heart failure (HF) may be due to diastolic dysfunction with elevated left ventricular (LV) diastolic pressure or may merely be a manifestation of an overfilled LV as a result of increased left atrial (LA) pressure. We investigated whether the LV restrictive filling pattern is due to elevated LA pressure alone.

Methods and Results—We studied conscious dogs instrumented to measure LA pressure, LV pressure, and 3 LV diameters. LV filling dynamics were evaluated in 2 situations with similar elevations of LA pressure: in normal animals after rapid volume loading with dextran 500 mL and in animals with pacing-induced HF with restrictive filling. With HF, there was increased LV chamber stiffness and slow relaxation. Volume loading and HF had similar heart rates (129±19 versus 131±15 bpm) and LA pressure (22.1±5.8 versus 22.6±3.3 mm Hg). The peak early filling rate (E) was increased with both HF and volume loading. However, in HF, the peak mitral annular velocity (E’) was decreased and delayed, and the E deceleration time was shorter. In contrast, with volume loading, E’ was increased and not delayed.

Conclusion—The restrictive filling pattern is distinguished from overfilling of a normal ventricle by a reduced and delayed E’ and a shortened E deceleration time that reflect slow relaxation and increased LV stiffness. (Circulation. 2008;117:1550-1554.)

Key Words: diastole ■ dynamics ■ heart failure ■ physiology ■ ventricles

D iastolic function has been evaluated from the dynamics of left ventricular (LV) filling, reflected in the mitral valve flow velocity measured by Doppler echocardiography and by tissue Doppler measurement of mitral annular velocity reflecting LV long-axis lengthening.1-5 Normally, most filling occurs early in diastole, with the peak filling rate during early diastole (E) being larger than the peak filling rate during atrial contraction (A). With diastolic dysfunction, the LV filling pattern is altered. With mild diastolic dysfunction, the E wave is reduced and is smaller than the A wave. This pattern usually is associated with little or no elevation in mean left atrial (LA) pressure. With progressively increasing diastolic dysfunction and elevations in LA pressure, the mitral E wave increases, resulting in a pseudonormal and then a restrictive pattern. The restrictive pattern consists of a high peak E, increased E/A ratio, short E deceleration time, and reduced and delayed peak early mitral inflow annular velocity (E’).6 The presence of a restrictive filling pattern indicates a poor prognosis whether the patient has a normal or a reduced ejection fraction.7,8 Because the restrictive filling pattern occurs in patients with elevated LA pressure, it has been suggested that it may be merely a manifestation of an overfilled ventricle, not diastolic dysfunction.9

Clinical Perspective p 1554

We hypothesized that the restrictive filling pattern seen with heart failure (HF) is different from the filling pattern in normal subjects with similarly increased LA pressure resulting from acute volume loading. Thus, the restrictive pattern does not result from increased LA pressure alone but is related to LV diastolic dysfunction. We tested this hypothesis by evaluating LV filling determined from the time derivative of LV volume (dV/dt)10,11 and long-axis lengthening8 in chronically instrumented dogs in 2 situations with similar elevations of LA pressure: normal animals after acute volume loading and animals with severe HF with restrictive filling.

Methods

Instrumentation

This investigation was approved by the Wake Forest University Health Sciences Animal Care and Use Committee. A total of 18 healthy male mongrel dogs (32.2±5.3 kg) were instrumented. Ten animals were studied under normal control conditions and after volume loading. Ten animals were studied after HF was induced (see below). Two dogs were common between normal control/volume loading and animals with severe HF with restrictive filling.
in a previous report. Anesthesia was induced with xylazine (2.0 mg/kg IM) and sodium pentobarbital (6 mg/kg IV) and maintained with halothane (1% to 2%) or isoflurane (0.5% to 2%). The pericardium was opened through a left thoracotomy. Micromanometer pressure transducers (Koningsberg Instruments, Pasadena, Calif.) and polyvinyl catheters for transducer calibration (1.1-mm internal diameter) were inserted into the LV through the LV apical stab wound and into the LA through LA appendage. The LV transducer was placed snugly on the endocardial surface of the apex and sutured in place.

Three pairs of crystals (5 MHz) were implanted in the endocardium of the LV to measure the anteroposterior, septolateral, and long-axis diameter (D)12. The crystals used to measure D were placed at the apex and on the septal side of the mitral annulus. Pacing leads were attached to the right ventricle and right atrium and were connected to programmable pacemakers (model 8329, Medtronic Inc, Minneapolis, Minn) that were implanted subcutaneously. All wires and tubing were exteriorized through the posterior neck.

Data Collection
Studies were begun after full recovery from instrumentation (14 to 16 days after surgery). The LV and LA catheters were connected to pressure transducers (Statham p23Db, Gould, Valley View, Ohio) calibrated with a mercury monometer. The signal from the microanometer 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.

Experimental Protocol
Data were recorded with conscious, unsedated animals standing quietly in the sling after full recovery from surgical instrumentation. Control data were collected after autonomic blockade with hexamethonium (5 mg/kg IV) or metoprolol (0.5 mg/kg IV) and atropine (0.1 mg/kg IV) to minimize reflex changes.13,14 Our previous study demonstrated that this does not alter contraction or relaxation in normal conscious animals at rest.13,15 Volume loading data were subsequently collected after 10% dextran (500 mL) (Baxter, Deerfield, Ill) was infused intravenously over 10 minutes. HF was induced by rapid ventricular pacing at 200 to 220 bpm for 4 weeks. Before we acquired HF data, the animals were allowed to stabilize for 30 minutes with the pacers turned off. HF data were then collected.

Data Processing and Analysis
These data were digitized at 200 Hz and numerically filtered at 50 Hz. As previously described,16 LV volume was calculated as a modified general ellipsoid by 3 LV diameters. The rate of LV relaxation was analyzed by the time constant of LV relaxation (\(\tau\)), with the following equation: \(P = P_0 \exp(-t/\tau) + P_B\), as described previously.12 The mean LV operating chamber stiffness during diastole \(K_{LV}\) was obtained by dividing the change in pressure from the time of minimal pressure to end-diastolic pressure by the change in volume during this period.10,11

The evaluation of the LV filling pattern was assessed from \(dV/dt\) and the time derivative of \(D_{LV}\) (\(dD_{LV}/dt\)) calculated with the 5-point centered method.16 The characteristics of LV early filling patterns were evaluated by determining \(E\) as the maximal rate of \(dV/dt\) and \(dD_{LV}/dt\) during early diastole, respectively.6 Similarly, peak A was determined as peak \(dV/dt\) during atrial contraction. Because the position of the LV apex remains relatively constant during the cardiac cycle, \(dD_{LV}/dt\) reflects the velocity of the mitral annulus. We have previously found that \(E\) determined from \(dD_{LV}/dt\) was similar to \(E\) determined by tissue Doppler imaging of the mitral annulus.6 The time delay of \(E\) relative to \(E\) also was measured.8 The deceleration time of early diastolic LV filling \(t_{dec}\) was defined as the time interval between the maximal rate of the early diastolic LV filling decelerated to the zero line. The slope was linearly extrapolated to the zero line to obtain \(t_{dec}\).8 The \(E\) deceleration rate was calculated as \(E/dt_{dec}\). We previously found that \(t_{dec}\) measured from \(dV/dt\) provides a consistent measure of \(t_{dec}\) measured with mitral

### Table. Filling Dynamics of Normal Control, Normal Acute Volume Loading, and HF

<table>
<thead>
<tr>
<th></th>
<th>Before HF</th>
<th>Volume Loading</th>
<th>After HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>115±20</td>
<td>129±19*</td>
<td>131±15</td>
</tr>
<tr>
<td>LV end-systolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pressure, mm Hg</td>
<td>92.7±7.8</td>
<td>97.7±13.9</td>
<td>93.4±14.0</td>
</tr>
<tr>
<td>Minimum LV pressure, mm Hg</td>
<td>2.6±2.5</td>
<td>9.6±2.5*</td>
<td>12.8±4.7†</td>
</tr>
<tr>
<td>Mean LA pressure, mm Hg</td>
<td>7.1±2.2</td>
<td>22.1±5.8*</td>
<td>22.6±3.3‡</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>14.9±2.8</td>
<td>18.7±3.1*</td>
<td>11.3±2.3‡</td>
</tr>
<tr>
<td>Peak E, mL/s</td>
<td>98±39</td>
<td>183±41*</td>
<td>140±29†</td>
</tr>
<tr>
<td>Peak A, mL/s</td>
<td>70±9</td>
<td>58±23</td>
<td>46±9†</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.6±0.5</td>
<td>3.4±1.8</td>
<td>3.1±0.8</td>
</tr>
<tr>
<td>Peak E’, mm/s</td>
<td>36.3±8.2</td>
<td>48.4±11.9*</td>
<td>25.8±7.1†</td>
</tr>
<tr>
<td>E’/E ratio, cm²</td>
<td>30±12</td>
<td>42±15*</td>
<td>58±19†</td>
</tr>
<tr>
<td>E’ delay relative to E, ms</td>
<td>-8.9±8.6</td>
<td>-4.8±11.2</td>
<td>29.0±12.4‡</td>
</tr>
<tr>
<td>τ, ms</td>
<td>30.8±3.1</td>
<td>32.1±2.1</td>
<td>41.9±3.6‖</td>
</tr>
<tr>
<td>E deceleration rate, LV/s²</td>
<td>1.5±0.8</td>
<td>3.0±1.0*</td>
<td>2.9±0.8†</td>
</tr>
<tr>
<td>E deceleration time, ms</td>
<td>81±17</td>
<td>68±9*</td>
<td>50±8†</td>
</tr>
<tr>
<td>LV chamber</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stiffness, mm Hg/mL</td>
<td>0.80±0.43</td>
<td>1.39±0.64*</td>
<td>2.65±1.0†‡</td>
</tr>
<tr>
<td>Late E area, mL</td>
<td>4.6±2.8</td>
<td>6.7±2.2*</td>
<td>3.5±0.8‡</td>
</tr>
</tbody>
</table>

Late E area indicates the area under early rapid deceleration line after peak E. Values are mean±SD. *P<0.05, HF vs control; †P<0.05, HF vs control; ‡P<0.05, HF vs volume loading.

Doppler.10 Specifically, we found that \(t_{dec}\) measured from \(dV/dt\) correlated with \(t_{dec}\) measured by Doppler \((r=0.87; SE=0.009 second; P<0.001). The slope was 1.0, but there was a 20-ms offset.10 Thus, \(t_{dec}\), as measured in this study, should be accurate to detect changes in \(t_{dec}\) with volume loading and HF but will underestimate the absolute value determined by Doppler by ~20 ms. Three stable beats during expiration were used to calculate mean values of the LV filling parameters.

Statistical Analysis
The effects of volume loading in normal dogs were assessed with paired t tests. The comparisons between HF, volume loading, and control were performed with ANOVA. When a significant difference was detected, comparisons were performed with Tukey’s multiple-comparison test. To avoid statistical complexity resulting from overlap of conditions within animals, the 2 animals that had baseline, volume loading, and HF observations were not included in the HF group for the statistical evaluation of the comparisons of HF, volume loading, and control. A value of P<0.05 was accepted as significant. Data are expressed as the mean±SD. The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Comparison of Hemodynamic Status Between Normal Acute Volume Loading and HF
The Table summarizes the LV filling dynamics of normal control, normal acute volume loading, and HF. The LA pressure and heart rate were similar after normal volume loading and after HF.

Representative recordings of LV filling patterns of both groups are shown in Figure 1. The A wave was not observed
Early LV filling patterns of normal acute volume loading and HF had common characteristics: Peak E was higher than normal control; the E/A ratio was similarly elevated; and the E deceleration slope as calculated by the E deceleration rate was similarly steep (the Table and Figure 1). However, as shown in the Table, volume loading and HF differed in several ways. The tdec was shorter in HF than normal acute volume loading. E'/H11032 responded in opposite directions to volume loading and HF, increasing with volume loading and decreasing with HF. Furthermore, after HF, E' occurred after E. In contrast, under normal conditions, in both control and volume loading, E'/H11032 occurred coincidentally with or before peak E (the Table and Figure 1). Despite similar mean LA measures, E/E' increased more with HF than after volume loading.

**Comparison of Diastolic Properties and Relation to Characteristics of LV Filling Pattern Between Normal Acute Volume Loading and HF**

Figure 2 shows KLV measured as the average slope of the diastolic pressure-volume trajectories. Compared with normal control, minimal LV pressure and diastolic pressure were increased after volume loading, and KLV was slightly elevated. After HF, there was a significantly greater increase in KLV. As summarized in the Table and displayed in Figure 3, the decrease in tdec paralleled the increase in KLV during HF. Similarly, the decrease and delay in E' during HF paralleled changes in τ.

**Discussion**

In this study, we investigated whether the restrictive filling pattern seen in severe HF can be produced by overfilling a normal LV. The LV filling dynamics with HF and normal volume loading were similar in some ways: increased E and E/A and steep E deceleration slope. However, there also were clear differences. First, HF and volume loading altered the magnitude of E'/H11032 in opposite directions. HF decreased E'/H11032 compared with normal, whereas volume loading increased E'. Second, E' occurred with a significant delay relative to E during HF, whereas E' was not delayed relative to E during control and after volume loading. Finally, the E deceleration time was shorter with HF than after volume loading. Thus, the restrictive filling pattern is differentiated from overfilling of a normal ventricle by a short E deceleration time and a reduced and delayed E'.

**Diastolic Function and LV Filling Pattern**

Consistent with previous observations,6,17 we observed that the delay and reduction in E' during HF correlated with slow relaxation indicated by an increase in τ (Figure 3). With normal relaxation, peak E' occurs coincidentally with or
before peak E and the LA-LV pressure crossover (Figure 1).\textsuperscript{6} and E' correlates with the peak pressure gradient.\textsuperscript{6,18} Consistent with this concept, in normal volume loading with no slowing of relaxation, E' continued to occur during the increased LA to LV pressure gradient, resulting in an increase in E' (Figure 1). In contrast, in HF with slow relaxation, E' occurs after the LA-LV pressure crossover as shown in Figure 1.\textsuperscript{6} As a result, E' decreased in HF despite an increase in the LA-to-LV pressure gradient. As previously observed in experimental animals\textsuperscript{10,11} and human studies,\textsuperscript{19} t\textsubscript{dec} reflects K\textsubscript{LV}. After HF, we found an increase in K\textsubscript{LV} and a decrease in t\textsubscript{dec} (Figure 3). There was a decrease in t\textsubscript{dec} and a smaller increase in K\textsubscript{LV} with volume loading as the normal LV was displaced onto a stiffer portion of its curvilinear diastolic pressure-volume relation.\textsuperscript{20} Thus, the reduced and delayed E' and short E deceleration time that distinguish restrictive filling from overfilling of a normal LV are due to diastolic dysfunction.

An increased ratio of E/E' is used as a clinical, noninvasive indicator of elevated LA pressure\textsuperscript{2} and diastolic dysfunction.\textsuperscript{21,22} Consistent with these concepts, we observed a nearly 2-fold increase in E/E' after HF. However, despite a similar increase in LA pressure with normal volume loading, E/E' did not increase as much with volume loading. This indicates that E/E' may not be useful in detecting increases in LA pressure in the setting of normal diastolic function.

**Study Limitations**

The mitral annular velocity in this study was derived from the time derivative of the D\textsubscript{LA}. Because the position of the apex remains fixed during diastole,\textsuperscript{23} the E' in this study measured as peak rate of lengthening of the D\textsubscript{LA} (dD\textsubscript{LA}/dt) is equivalent to the E' measured by tissue Doppler imaging of the velocity of the mitral annulus away from apex, as we have previously demonstrated.\textsuperscript{6} We determined E from the peak value of the dV/dt in early diastole. Because the effective mitral valve orifice area is relatively constant during diastole, the pattern of LV filling (dV/dt) we measured is similar to the pattern of diastolic filling assessed clinically by Doppler measurement of mitral valve flow velocity, as we have previously demonstrated.\textsuperscript{10} Because we measured the peak E filling rate, not E velocity, the E/E' ratio has units of centimeters squared.

The t\textsubscript{dec} in this study is smaller than that in humans as determined by Doppler\textsuperscript{19} but close to that of our previous report in conscious dogs.\textsuperscript{10,11} The smaller chamber size of dog compared with human LV, resulting in higher chamber stiffness in the dog, may explain the shortened deceleration time.\textsuperscript{11} In addition, t\textsubscript{dec} determined from dV/dt underestimates t\textsubscript{dec} determined by Doppler by \textasciitilde 20 ms.\textsuperscript{10} We did not measure ventricular torsion. Diastolic untwisting may contribute importantly to LV diastolic filling.

Pacing-induced HF dogs were used in this study. This model mimics the functional, structural, and neurohormonal properties of dilated cardiomyopathy.\textsuperscript{11} However, we cannot be certain that our findings apply to diastolic dysfunction produced by other conditions. Finally, our studies were performed in instrumented animals that required opening of the pericardium. Thus, our study may not fully reflect the influence of the pericardium after volume loading or HF.\textsuperscript{34}

**Conclusion**

The restrictive filling pattern is differentiated from overfilling of a normal ventricle by a decreased and delayed E' and a short E deceleration time, which reflect slow relaxation and increased operating stiffness.

**Acknowledgments**

We gratefully acknowledge the computer programming of Dr Ping Tan; the technical assistance of Michael Cross, Yi Zhao, and Chun Xian Zhang; and the administrative support of Amanda Burnette.

**Sources of Funding**

This study was supported in part by grants from the National Institutes of Health (AA12335, and HL074318) and the American Heart Association (0530079N).

**Disclosures**

None.

**References**

Diastolic function has been evaluated noninvasively from the dynamics of left ventricular filling, reflected in the pattern of mitral valve flow velocity measured by Doppler echocardiography and by tissue Doppler assessment of mitral annular velocity. A restrictive filling pattern with a high peak early diastolic peak filling velocity (E), short E deceleration time, and reduced and delayed peak early diastolic mitral annular velocity (E') has been thought to indicate severe diastolic dysfunction. However, because the restrictive filling pattern occurs in patients with elevated left atrial pressure, it may be merely a manifestation of an overfilled ventricle, not diastolic dysfunction. We tested this hypothesis by evaluating left ventricular filling in chronically instrumented animals in 2 situations with similar elevations of left atrial pressure: normal animals after acute volume loading and animals with severe heart failure with restrictive filling. We found that the restrictive filling pattern is differentiated from overfilling of a normal ventricle by a decreased and delayed E' reflecting slow relaxation and a short E deceleration time resulting from increased left ventricular operating stiffness. Thus, restrictive filling indicates the presence of diastolic dysfunction and is not due to elevated left atrial pressure alone.
Restrictive Left Ventricular Filling Pattern Does Not Result From Increased Left Atrial Pressure Alone

Satoshi Masutani, William C. Little, Hiroshi Hasegawa, Heng-Jie Cheng and Che-Ping Cheng

_Circulation_. 2008;117:1550-1554; originally published online March 10, 2008; doi: 10.1161/CIRCULATIONAHA.107.730564

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/117/12/1550

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/