Pericardial Influences on Right and Left Ventricular Filling Dynamics

Brian D. Hoit, Nancy Dalton, Valmik Bhargava, and Ralph Shabetai

The influence of the pericardium on right and left ventricular filling was studied using two-dimensional and Doppler echocardiography in 14 open-chest dogs. Doppler echo parameters of filling included early (E) and late (A) velocities and their ratio (E/A) for the mitral and tricuspid valves. Right and left ventricular volumes were calculated from orthogonal two-dimensional echocardiographic images. Data were compared at three levels of left ventricular end-diastolic pressure (6±2, 13±3, and 21±4 mm Hg) at matched heart rates before and after pericardiectomy. The instantaneous diastolic pressure gradient was measured in 12 of the dogs. Pericardiectomy resulted in an increase in early mitral velocity, peak early diastolic pressure gradient, and E/A but not early mitral velocity normalized for end-diastolic volume. In contrast, for the tricuspid valve flow, pericardiectomy did not change E but caused a marked increase in A and a decrease in E/A. Right ventricular end-diastolic volumes at matched left ventricular end-diastolic volumes were similar before and after the pericardium was removed. However, removal of the pericardium caused a significant decrease of the slope for the right (86.0±27.0×10⁻⁴ versus 50.0±19.5×10⁻⁴ mm Hg/ml, p<0.01), but not left, ventricular in end-diastolic pressure–volume relation (21.2±9.2×10⁻⁵ versus 21.4±5.3×10⁻³ mm Hg/ml, p=NS), and a decrease of the pressure intercept for the left (3.0±2.0 versus 1.6±0.9 mm Hg, p<0.05), but not right, ventricular in end-diastolic pressure–volume relation (2.8±1.4 versus 1.4±0.8 mm Hg, p=NS). In conclusion, filling of the two ventricles is affected by the pericardium over a wide range of physiological ventricular volumes and pressures. At matched left ventricular end-diastolic volume, pericardiectomy causes a fundamental alteration in right, but not left, ventricular filling. (*Circulation Research* 1991;68:197–208)

Heart disease may cause abnormalities of both diastolic and systolic function.¹,² Assessment of diastolic function and identifying factors that influence diastolic pressure–volume relations therefore have significant clinical relevance. Pericardial restraint is one such factor³ and has been demonstrated by measurement of pericardial pressure in response to changes in cardiac filling pressure⁴–⁸ from shifts of the ventricular pressure–volume curve after pericardiectomy⁹–¹³ and by enhanced ventricular interaction in the presence of an intact pericardium.¹⁴–¹⁷ That the pericardium influences diastolic ventricular compliance is well established, but largely for methodological reasons, the magnitude and physiological significance of this pericardial effect is disputed.⁵,⁷–⁹,¹⁸ Compliance is derived from pressure and volume data either during diastasis or at end-diastole. However, ventricular filling occurs mostly during early diastole, and whether it is influenced by the pericardium is unknown. This gap in our knowledge is particularly relevant since peak filling rates and the pattern of ventricular filling are commonly used to assess diastolic function in pathological conditions such as hypertrophy and ischemia.¹⁹–²¹ With these conditions, a decreased early filling and low ratio of early to late filling is commonly interpreted as a manifestation of decreased left ventricular compliance, although this has recently been questioned.²² Based on these considerations and recent investigations,²³,²⁴ we reasoned that peak early left ventricular filling rate and its contribution to total left ventricular filling would be altered after pericardiectomy. A rightward shift of the left ventricular pressure–volume relation after pericardiectomy results in an increase in end-diastolic volume. Increased end-diastolic volume, in turn, increases peak early filling rate and the ratio of early to late filling.²³ Accordingly, we examined ventricular filling with Doppler echocardiography to test the hypothesis that peak early left ventricular filling rate and its total contribution to ventricular filling increases after pericardiectomy. In addition, although existing data suggest that the right ventricle is more

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Received November 1, 1988; accepted August 28, 1990.
vulnerable to the influence of the pericardium.9,11,13,17,25
studies addressing this question in a physiological pre-
paration with an intact pericardium have not been performed. Therefore, we also studied the influence of the pericardium on right ventricular filling by using Doppler echocardiography.

Materials and Methods

Fourteen mongrel dogs of either sex weighing 17–41 kg (mean, 25.4±6.1 kg) were anesthetized with either morphine (3 mg/kg) and α-chloralose anesthesia (100 mg/kg, n=8) or sodium pentobarbital (30 mg/kg, n=6), intubated, and ventilated with a respirator (Harvard Apparatus, South Natick, Mass.). Additional doses of anesthetic were administered as necessary, but no measurements were made until the animals had returned to a stable hemodynamic state. In the dogs anesthetized with pentobarbital, propanolol (1 mg/kg) was administered to slow the heart rate. After the first four experiments, morphine and chloralose anesthesia were used because heart rates slow enough to permit clear distinction of early and late filling velocities were difficult to obtain using pentobarbital anesthesia. The heart rate in the pentobarbital-anesthetized animals was 105±9 beats/min before, and 110±7 beats/min after, pericardectomy and was 77±17 beats/min before, and 80±18 beats/min after, pericardectomy in the animals given morphine and chloralose. Despite these heart rate differences and the different reflex effects of the anesthetic agents, changes in Doppler velocities were similar in both groups of animals; therefore, the data were combined. The chest was opened with a midline sternotomy and bilateral fifth interspace thoracot- omy. Inflatable occlusion cuffs were positioned around the inferior and superior venae cavae, and a large-bore cannula was placed in a femoral vein for administration of fluids. In all animals, a 7F micro-
manometer (Millar Instruments, Houston) or 5F high-fidelity fiber-optic catheter (Camino Labora-
tory, San Diego, Calif.) was placed in the left ventri-
icle through a carotid artery. A 7F fluid-filled pigtail catheter was advanced into the left ventricle via a femoral artery. The left ventricular pressure wave-
form from the micromanometer and fiber-optic cath-
er was matched to that of the fluid-filled catheter. Fluid-filled catheters were zeroed to the level of the mid-right atrium. A limb lead electrocardiogram was recorded throughout.

Once this basic instrumentation had been accom-
plished in all animals, two different preparations were used. In the left heart preparation, a 7F Millar or 5F Camino micromanometer was advanced into the left ventricle via a pulmonary vein; its waveform was matched with the waveform of the left ventricu-
lar micromanometer placed previously, and then withdrawn into the left atrium. A short (15–20-cm) piece of polyethylene tubing was advanced into the left atrium via another pulmonary vein to calibrate the high-fidelity left atrial pressure and to check for drift. In the right heart preparation, fluid-filled and micromanometer right ventricular and right atrial catheters were placed via the jugular veins. In the eight dogs studied with the left heart preparation and in four of the six dogs studied with the right heart preparation, the atrioventricular pressure gradient was electronically derived using an analog computer (Coulborn Instruments Inc., Lehigh Valley, Pa.) and was recorded on-line. In the two remaining dogs instrumented with the right heart model, technical difficulties precluded measurement of the diastolic pressure gradient. Micromanometers were calibrated electronically and mechanically (full scale, 0–40 mm Hg over ±2 V, measured with a digital voltmeter), such that the atrial and ventricular catheters were equisensitive. The gradient was mechanically cali-
bred with full scale (±2 V) either 0–10 or 0–20 mm Hg. During the experiment, baseline drift was cor-
rected by adjustments on the Millar or Camino box that did not affect the gain of the transducer. Long postextrasystolic diastoles were used to identify zero gradient.

The electrocardiogram, left and right ventricular pressures, left and right atrial pressures, and the electronically derived diastolic atrioventricular pressure gradients were recorded on an eight-channel forced-ink polygraph (model 2000, Gould Brush, Cleve-
lund, Ohio) at a paper speed of 100 mm/sec. Fluid-filled catheters were attached to Statham P23 DB transducers (Gould) with zero established at the level of the right atrium. Respiration was suspended at end-expiration during all measurements.

Two-dimensional and Doppler echocardiographic studies were performed using a commercially avail-
able ultrasonograph (model 7750C, Hewlett-Packard Co., Palo Alto, Calif.) with a 5.0 MHz short focus imaging and 2.0 MHz Doppler phased array trans-
ducer. This system has pulsed Doppler and color flow Doppler capability. Imaging was performed with the transducer gently placed on the heart to obtain four-chamber long axis and short axis views. Pressures were monitored with and without the trans-
ducer placed on the heart to ensure that imaging did not influence the measurements under study.

Flow across the mitral and tricuspid valves was sampled from the apical four-chamber view and short axis, respectively. A 5-mm sample volume was placed between the open tips of the mitral and tricuspid valve leaflets during diastole, and small angulations of the transducer were made to optimize the audio and graphic quality of the Doppler signal. In certain instances, color flow imaging was used to identify the direction of atrioventricular flow and ensure sample volume placement with a minimum angle of occlusion. Doppler velocity was recorded with the simultaneous high-fidelity pressures and the electrocardio-
graphic lead and was recorded on 0.5-in. VHS videotape and strip-chart paper at 100 mm/sec.

Experimental Protocol

Once instrumentation was complete, the caval occlusion cuffs were inflated as necessary to lower the
left ventricular end-diastolic pressure to approximately 5–7 mm Hg. The cuffs were then deflated, and 6% dextran was infused to raise left ventricular diastolic pressure to 20–25 mm Hg. Ultrasound studies and hemodynamic measurements were performed at several stable hemodynamic states at 3–5 mm Hg increments of end-diastolic pressure. The pericardium was then opened wide, and the heart was supported in the pericardial cradle. The sinus node was crushed, and right atrial pacing was instituted so that data were obtained at prepericardectomy heart rates. By inflating the vena caval cuffs and or phlebotomy, runs were repeated at stable hemodynamic states matched for prepericardectomy left ventricular end-diastolic pressure.

The experimental protocol was approved by the Committee on Investigations Involving Animal Subjects at the University of California, San Diego.

Data Analysis

The mitral and tricuspid Doppler diastolic waveforms were analyzed for the maximal early (E) and late (A) diastolic filling velocities (Figure 1) and the area under the velocity curve (flow velocity integral). Derived values for each Doppler waveform analyzed included the ratio of the peak E and A velocities and the peak early transmitral velocity normalized for end-diastolic volume. All echocardiographic measurements were made from the original tracings with the average data from three cardiac cycles with well-defined spectral envelopes.

Left ventricular volume was computed as the product of the short axis at the level of the papillary muscles and the long axis area from the four-chamber view divided by the short axis diameter.30 Thus, relative left ventricular volumes were calculated since a regression to calibrate the resulting computed volume is not used for this simplified ellipsoid-biplane method. An index of right ventricular volume was computed as the product of the short axis area containing the right ventricular inflow and outflow tracts and the four-chamber long axis area. To check the validity of this method, the right ventricular volume (area squared) derived in this manner was raised to the \( \frac{3}{2} \) power to obtain units of volume (milliliters) in six of the dogs and compared with right ventricular volume obtained using a cast-validated formula:27

\[ \text{right ventricular volume} = \frac{A_1 \times L_2}{A} \]

where \( A_1 \) is the cross-sectional area of the right ventricle and \( L_2 \) is the long axis of the right ventricle in the orthogonal view. The correlation between right ventricular volumes obtained in this manner was excellent (\( r=0.94, \text{SEE}=6 \text{ ml}, 68 \text{ observations} \)).

Right and left ventricular end-diastolic volumes were measured from the video frame containing the largest right and left ventricular area, respectively. The diameter of the mitral and tricuspid annulus (D) was measured from the four-chamber view and short axis, respectively, at end-diastole. The cross-sectional area of the annulus was derived assuming circular geometry, such that the area equals \( \pi D^2/2 \). The left ventricular filling volume was calculated as the product of the transmitral FVI and the mitral annulus area. All two-dimensional and Doppler echocardiographic measurements were made on the echocardiograph system with the analysis package supplied by the manufacturer (Hewlett-Packard).

End-diastolic pressure was taken from high-gain ventricular pressure tracings as the pressure trough after atrial systole. When a trough was not readily apparent, the peak of the R wave on the electrocardiogram was used.

For purposes of comparing the effect of pericardiectomy at varying ventricular volumes, beats that were as close as possible to a left ventricular end-diastolic pressure (LVEDP) of 6, 12, and 20 mm Hg were selected from each study. Hemodynamic data were averaged over three to five consecutive cardiac cycles.

The absolute and percent changes in right and left ventricular volume after pericardiectomy were calculated at each level of LVEDP. In addition, the change in ventricular volume after pericardiectomy was assessed without reference to ventricular pressure as follows. Matched left ventricular end-diastolic volumes were selected before and after pericardiectomy at three different levels of left ventricular end-diastolic volume, and the corresponding right ventricular end-diastolic volumes were compared.
To evaluate pericardial effects on ventricular compliance, end-diastolic pressure-volume data derived from steady-state volume infusions were fitted to the exponential equation \[ P = A e^{KV} \] in a subset of six dogs, and the slopes and intercepts of the ln pressure-volume curves for the right and left ventricles were compared before and after pericardiectomy.

To determine how the pericardium influences the components of the left early diastolic pressure gradient, changes in the left atrial \( v \) wave and left ventricular minimum pressure after pericardiectomy were computed at matched left ventricular end-diastolic pressure.

**Interobserver Differences**

Twenty-one beats were randomly selected and analyzed for peak transmitral velocity and flow velocity integral by two independent observers. Interobserver differences were calculated as the difference between two observations divided by the mean of the two observations.

**Statistical Analysis**

Hemodynamic, two-dimensional and Doppler echocardiographic measurements at each stable hemodynamic state, before and after pericardiectomy, were compared by a two-way repeated measures analysis of variance.\(^{28}\) When an interaction between the effect of pericardiectomy and level of LVEDP was present, Tukey's test was used to find out where the differences were. Student's \( t \) test was used to compare heart rates and the slopes and intercepts of the ln pressure-volume curves before and after pericardiectomy. A one-sample \( t \) test was used to determine whether the difference between prepericardiectomy and postpericardiectomy values for left atrial and ventricular pressures were significantly different from zero. In all cases, a value of \( p<0.05 \) was considered to indicate statistical significance. Data are expressed as mean±SD.

**Results**

**Hemodynamic Measurements**

The heart rate was 87.5±19.6 beats/min before pericardiectomy and 90.0±20.8 beats/min after pericardiectomy. The left ventricular end-diastolic pressure for the three steady states was 6.4±2.2, 12.7±3.2, and 20.9±4.5 mm Hg before, and 6.6±1.8, 13.0±3.3, and 21.4±4.9 mm Hg after, pericardiectomy (\( p=NS \) at each level of LVEDP before and after pericardiectomy).

**Transmitral Flow and Left Ventricular Filling Volume**

An example of the Doppler transmitral velocity and the instantaneous left atrioventricular diastolic pressure gradient is shown in Figure 1, and an original recording from a representative experiment is shown in Figure 2. The diastolic pressure gradient closely resembled the Doppler transmitral waveform in contour and relative magnitude. There was good correlation between peak early velocity and peak early diastolic pressure gradient (\( r=0.82, n=38 \)). The influence of the pericardium on peak early filling velocity at the three levels of LVEDP is shown in Table 1. Early filling velocity increased significantly as LVEDP increased and also independently after pericardiectomy at each level of LVEDP. Similar
TABLE 1. Mitral Valve Flow Velocities

<table>
<thead>
<tr>
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<th>Low LVEDP</th>
<th>Mid LVEDP</th>
<th>High LVEDP</th>
</tr>
</thead>
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<tr>
<td></td>
<td>+Pericardium</td>
<td>-Pericardium</td>
<td>+Pericardium</td>
</tr>
<tr>
<td>MVE COR</td>
<td>1.8±1.1</td>
<td>1.4±0.6*</td>
<td>1.4±0.5</td>
</tr>
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<td>MVE/MVA</td>
<td>1.4±0.4</td>
<td>1.9±0.5*</td>
<td>2.0±0.7</td>
</tr>
<tr>
<td>MVE</td>
<td>42.5±5.8</td>
<td>60.9±9.7*</td>
<td>63.1±10.5†</td>
</tr>
<tr>
<td>MVA</td>
<td>30.4±9.3</td>
<td>33.8±10.1</td>
<td>31.8±9.4</td>
</tr>
<tr>
<td>MVE/MVA</td>
<td>1.4±0.4</td>
<td>1.9±0.5*</td>
<td>2.0±0.7</td>
</tr>
</tbody>
</table>

Values are mean±SD. LVEDP, left ventricular end-diastolic pressure; +Pericardium, pericardium on; −Pericardium, pericardium off; MVE, early transmitral flow velocity in centimeters per second; MVA, late transmitral flow velocity in centimeters per second; MVE COR, early transmitral flow velocity normalized by left ventricular end-diastolic volume in centimeters per milliliter.

*p<0.05, pericardium on vs. pericardium off. †p<0.05 compared with low LVEDP.

Results were obtained for the early diastolic pressure gradient (2.0±1.1, 3.6±1.5, and 4.7±1.2 mm Hg before, and 3.6±1.0, 5.3±1.5, and 6.9±1.5 mm Hg after, pericardiectomy at low, mid, and high levels of LVEDP, respectively; p<0.001 after pericardiectomy and volume infusion). The change in the peak early diastolic pressure gradient after pericardiectomy was due to a 1.5±3.0 mm Hg increase in the left atrial v wave (p<0.05) and a 1.3±1.5 mm Hg decrease in the minimum left ventricular pressure (p<0.01).

In eight of the dogs, heart rates were slow enough to permit a clear distinction between early and late transmitral velocities and calculation of the E/A ratio. The E/A ratio did not significantly change with volume infusion, but increased significantly with pericardiectomy (Table 1).

When normalized for end-diastolic volume, early diastolic velocity no longer increased with either volume infusion or pericardiectomy. Rather, there was a small, but significant, decrease in early velocity with increasing LVEDP and after pericardiectomy at the low level of LVEDP (Table 1).

The effect of pericardiectomy on stroke filling volume is shown in Figure 3. At each LVEDP, pericardiectomy resulted in an increase in absolute stroke filling volume (Figure 3, left panel), but pericardiectomy had no effect (right panel) when the change in stroke filling volume was plotted versus end-diastolic volume.

Transticuspid Flow

A typical example of the Doppler transticuspid velocity with the instantaneous right atrioventricular diastolic pressure gradient is shown in Figure 4. The diastolic pressure gradient closely mirrored the contour and relative magnitude of the Doppler filling waveform, and there was good correlation between the peak transticuspid velocity and right atrioventricular pressure gradient (r=0.78, n=30).

An example of the effect of pericardiectomy on the Doppler waveform and diastolic pressure gradient is shown in Figure 5, and group data concerning early and late filling velocities and their ratio are summarized in Table 2. Increasing LVEDP resulted in a small, but significant, increase in early transticuspid velocity. However, in contrast to its effect on transmitral velocities, early filling velocity did not increase after pericardiectomy. Late filling velocity increased.

**Figure 3.** Effect of pericardiectomy on left ventricular (LV) stroke (filling) volume. Stroke volume was computed as the product of the diastolic mitral flow velocity integral and the mitral annulus. Stroke volume is plotted against LV end-diastolic pressure (left panel) and LV end-diastolic volume (right panel) with pericardium on (PERI ON) and off (PERI OFF). Data are displayed as the mean, with error bars denoting the SEM for the variables on each axis. At each level of LV end-diastolic pressure, stroke volume increased after removal of the pericardium. When referenced to LV end-diastolic volume, pericardiectomy had no effect on stroke volume. See text for details.
with volume infusion and, at each level of LVEDP, increased dramatically after pericardiectomy. The result was no change in the early to late transtricuspid velocity ratio after volume infusion, but a significant reduction after pericardiectomy.

**Measurements of Mitral and Tricuspid Annuli**

Both tricuspid and mitral end-diastolic annular sizes increased significantly with volume loading and after pericardiectomy. The tricuspid annulus measured 3.2±0.9, 4.2±0.9, and 5.0±1.3 cm² at low, mid, and high LVEDP before, and 4.1±1.8, 5.2±1.4, and 6.4±1.7 cm² after, pericardiectomy (p<0.014 before versus after pericardiectomy; p<0.01 with volume loading). The mitral annulus was 3.7±1.2, 4.6±1.2, and 5.7±1.3 cm² at low, mid, and high LVEDP before, and 4.7±1.4, 5.9±1.1, and 6.7±1.4 cm² after, pericardiectomy (p<0.001 before versus after pericardiectomy; p<0.01 with volume loading). The change in tricuspid and mitral annulus dimension after pericardiectomy was similar.

**Effect on Ventricular Volumes**

Pericardiectomy caused a significant increase in right and left ventricular volumes at each level of LVEDP, as shown in Table 3. There were no significant differences in the percent increase in left versus right ventricular volume after pericardiectomy at each level of left ventricular end-diastolic pressure (74.9±39.7% versus 56.7±41.2% at low, 45±26.1% versus 64.2±54.8% at mid, and 23.5±13.4% versus 34±26.4% at high LVEDP). Furthermore, at matched left ventricular end-diastolic volumes, right ventricular end-diastolic volumes before and after pericardiectomy were similar (Figure 6). Thus, removal of the pericardium increased both ventricular volumes equally, whether referenced to left ventricular end-diastolic pressure or volume.

Slopes and intercepts of the ln pressure–volume relations are shown in Table 4, and an example of pressure–volume data from a representative animal is shown in Figure 7. Pericardiectomy caused a significant decrease of the pressure intercept without a change in slope (parallel rightward shift) for the left

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**Figure 4.** Transtricuspid Doppler waveform with the simultaneous right atrioventricular diastolic pressure gradient superimposed. Like transmitral flow, there is beat to beat similarity of the pressure and velocity tracings. E, maximal early diastolic filling velocity; A, maximal late diastolic velocity.

**Figure 5.** Original tracings demonstrating the effect of pericardiectomy on transtricuspid flow velocity and the right atrioventricular (RA-RV) diastolic pressure gradient. Beats were matched at a middle level of left ventricular end-diastolic pressure (LVEDP). Note the increase in late diastolic velocity and the reversal of the ratio of maximal early diastolic filling velocity to maximal late diastolic velocity (Doppler and gradient) after pericardiectomy. See text for details. RA, mean right atrial pressure.
TABLE 2. Tricuspid Valve Flow Velocities

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<th>Low LVEDP</th>
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<tbody>
<tr>
<td></td>
<td>+Pericardium</td>
<td>−Pericardium</td>
<td>+Pericardium</td>
<td>−Pericardium</td>
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<tr>
<td>TVE</td>
<td>26.8±7.6</td>
<td>27.3±12.4</td>
<td>28.5±7.8</td>
<td>30.8±6.8</td>
<td>39.4±6.0†</td>
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<tr>
<td>TVA</td>
<td>23.8±7.8</td>
<td>39.7±10.4‡</td>
<td>28.9±12.8</td>
<td>43.3±10.8‡</td>
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<td>TVE/TVA</td>
<td>1.2±0.4</td>
<td>0.8±0.3‡</td>
<td>1.3±0.9</td>
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<td>1.5±0.6</td>
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Values are mean±SD. LVEDP, left ventricular end-diastolic pressure; +Pericardium, pericardium on; −Pericardium, pericardium off; TVE, early transtricuspid flow velocity in centimeters per second; TVA, late transtricuspid flow velocity in centimeters per second.

*p<0.05 compared with low LVEDP.
†p<0.05 compared with mid LVEDP.
‡p<0.05, pericardium on vs. pericardium off.

TABLE 3. Right and Left Ventricular Volumes

<table>
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<td>+Pericardium</td>
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<td>LVV</td>
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<td>50.9±17.6†</td>
<td>71.5±21.7*</td>
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<td>15.2±4.4</td>
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<td>31.7±10.5*</td>
<td>35.1±10.6‡</td>
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Values are mean±SD. LVEDP, left ventricular end-diastolic pressure; +Pericardium, pericardium on; −Pericardium, pericardium off; LVV, left ventricular end-diastolic volume in milliliters; RVV, right ventricular volume index (cm²×cm²); RVVc, RVV taken to the 0.75 power in milliliters.

*p<0.05, pericardium on vs. pericardium off.
†p<0.05 compared with low LVEDP.
‡p<0.05 compared with mid LVEDP.

ventricle. In contrast, there was a significant decrease in slope without a change in intercept for the right ventricle (nonparallel rightward shift). Thus, the pericardium has qualitatively different effects on left and right ventricular chamber compliance.

Interobserver Differences

The percent interobserver error for measurements of peak early velocity and flow velocity integral was 2.8±2.4% and 3.8±3.0%, respectively.

Discussion

Although the pattern of left ventricular filling has attracted considerable attention from clinicians and investigators, the potential for modulation of filling patterns of the ventricle by the pericardium has not been explored. Previous studies have assessed pericardial effects on ventricular filling by measurement of pericardial pressure and left ventricular diastolic pressure and dimensions.5–13 However, ventricular filling is predominantly in early diastole, and no experimental data have been reported on how the pericardium may influence early rapid filling. The present study provides analysis of pericardial influences on dynamic inflow into the left and right ventricles.

There are several advantages of the Doppler and two-dimensional echocardiographic technique used in the present study to evaluate how the pericardium may alter the manner in which the ventricles fill. Of critical importance, our method does not exaggerate pericardial effects. Although application of the trans-
Table 4. Slopes and Intercepts of the Right and Left Ventricular In Pressure–Volume Curve P=Ae³

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Pericardium on</th>
<th>Pericardium off</th>
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<tbody>
<tr>
<td></td>
<td>Slope (K) (mm Hg/ml)</td>
<td>Pressure intercept (mm Hg)</td>
</tr>
<tr>
<td>Left ventricle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>20.0 x 10⁻³</td>
<td>4.1</td>
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<tr>
<td>2</td>
<td>27.5 x 10⁻³</td>
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<tr>
<td>3</td>
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<td>4</td>
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<td>4.5</td>
</tr>
<tr>
<td>5</td>
<td>36.7 x 10⁻³</td>
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</tr>
<tr>
<td>6</td>
<td>16.0 x 10⁻³</td>
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</tr>
<tr>
<td>Mean</td>
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</tr>
<tr>
<td>±SD</td>
<td>±9.2 x 10⁻³</td>
<td>±2.0</td>
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<td>Right ventricle</td>
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<td>1</td>
<td>99.0 x 10⁻⁴</td>
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<tr>
<td>2</td>
<td>88.8 x 10⁻⁴</td>
<td>2.9</td>
</tr>
<tr>
<td>3</td>
<td>105.2 x 10⁻⁴</td>
<td>3.4</td>
</tr>
<tr>
<td>4</td>
<td>35.3 x 10⁻⁴</td>
<td>5.0</td>
</tr>
<tr>
<td>5</td>
<td>110.0 x 10⁻⁴</td>
<td>1.1</td>
</tr>
<tr>
<td>6</td>
<td>80.5 x 10⁻⁴</td>
<td>1.5</td>
</tr>
<tr>
<td>Mean</td>
<td>86.0 x 10⁻⁴</td>
<td>2.8</td>
</tr>
<tr>
<td>±SD</td>
<td>±27.0 x 10⁻⁴</td>
<td>±1.4</td>
</tr>
</tbody>
</table>

*p<0.05, pericardium on vs. pericardium off.
*p<0.01, pericardium on vs. pericardium off.

ducer has the potential for pericardial influences to be exaggerated, pressures recorded with and without placement of the transducer were unchanged. Our echo-Doppler studies compare favorably in this regard with other studies in which the pericardium was opened and sutured.7–9,12 Another important advantage is that measurement of pericardial pressure was not used. We thus avoided the unsolved dilemma of how pericardial pressure should be measured. Substantially different estimates of pericardial restraint are obtained with flat balloons7,8,29 compared with fluid-filled catheters or micromanometers.5–7

We assessed biplane ventricular volume changes in response to pericardiectomy, rather than relying on changes in representative segment length, and we did not violate the integrity of the pericardium. The former is particularly important for estimates of right ventricular volume, since considerably different results are obtained from segment length gauges implanted in the inflow or outflow tract.13 Finally, analysis of Doppler waveforms, unlike volume analysis of ventricular filling, do not require assumptions regarding the geometry of the ventricles, and Doppler velocimetry allows assessment of peak filling rate and other dynamic aspects of ventricular filling for individual beats.

The large increases in ventricular end-diastolic volume after pericardiectomy are surprising in view of the findings of Walley et al.30 Using implanted tantalum screws in the left ventricular endocardium, these
investigators found an insignificant increase in left ventricular eigenvolume after pericardiectomy. In their study, however, neither LVEDP nor heart rates were matched before and after pericardiectomy. In contrast, investigators using ultrasonic segment length gauges report significant increases of variable magnitude in left and right ventricular dimension after pericardiectomy.9,13 Using methods similar to ours, Crawford et al18 found a 60% increase in left ventricular volume after pericardiectomy at a relatively low LVEDP and a 14% increase at high LVEDP. Two-dimensional echo may show a less than maximal contour of the left ventricle, particularly at low LVEDP when trabeculae and papillary muscles constitute a large percentage of cardiac volume.31 Thus, two-dimensional echo is likely to underestimate low volumes and may be responsible in part for the large increases after pericardiectomy at low LVEDP.

Transmitral Flow

Pericardiectomy increased peak transmitral filling velocity and the peak instantaneous diastolic pressure gradient at all levels of LVEDP. The high correlation between the Doppler velocity and gradient confirm the mathematical predictions of Yellin et al32 but do not explain the different effects of volume loading and pericardiectomy on the right and left heart. The increase in early transmitral velocity and gradient may have been due to increased left ventricular end-diastolic volume, since there was a concordant response of the Doppler waveform and gradient to volume infusion and pericardiectomy. Furthermore, effects of pericardiectomy on Doppler transmitral velocities and the diastolic pressure gradient were not observed after normalization of the early transmitral velocity to end-diastolic volume. Thus, it seemed likely that the changes in left ventricular filling after pericardiectomy were due to the resultant increase in left ventricular volume. However, studies suggest that stroke volume, which in the absence of atrioventricular valve regurgitation is the same as ventricular filling volume, is a more important determinant of peak filling rate than end-diastolic volume is33,34: stroke volume and peak filling rates increase when left ventricular end-diastolic volume is increased by volume infusion but decrease when an afterload stress causes the left ventricle to dilate. It is therefore important that the relation between filling volume and end-diastolic pressure but not end-diastolic volume was altered after pericardiectomy (Figure 3). The left ventricular end-diastolic volume increased at each level of LVEDP after pericardiectomy (Table 3); this increase in preload resulted in an increase in stroke volume (and hence filling volume) by the Frank-Starling mechanism. Thus, our data suggest that the increase in the early transmitral velocity and gradient after pericardiectomy is not a direct effect of the pericardium on early left ventricular filling, but rather occurs indirectly through an increase in stroke volume. The linear relation between flow and pressure gradient across unrestricted orifices35 is consistent with this hypothesis. Furthermore, our data suggest that the increased pressure gradient is mediated by nearly equal, but opposite, changes in the left atrial V wave and the minimum left ventricular pressure. The mechanisms for these changes are unclear. The influence of the pericardium on left atrial compliance and left ventricular distensibility during early diastole may play a role, but this remains to be determined.

Transtricuspid Flow

Pericardial influences on transtricuspid flow are more complex. Like transmitral flow, early transtricuspid velocity was increased by volume infusion. However, after pericardiectomy, early peak velocity did not change, but velocity caused by atrial systole increased, and the ratio of early to late filling velocity fell. Thus, the change brought about by pericardiectomy in right versus left ventricular inflow differed, suggesting a fundamental difference in pericardial modulation of filling of the two ventricles. The concordant changes in transtricuspid velocity and right atrioventricular pressure gradient suggest that pericardiectomy alters right ventricular filling by influencing the determinants of the atrioventricular pressure gradient.

Several possible mechanisms may explain the different effects of pericardiectomy on left versus right ventricular filling. Differences between right and left atrial compliance may be responsible. A more compliant right atrium would limit the increase in peak velocity expected from an increase in its volume because of a smaller change in the right atrial pressure and transtricuspid diastolic pressure gradient. The increased volume should nevertheless increase the force of atrial systole by the Frank-Starling mechanism. The left atrium is less compliant, and therefore the additional left atrial volume after pericardiectomy would result in a higher left atrial pressure and early transmitral diastolic pressure gradient. This should increase ventricular filling and peak velocity during early diastole. The close relation we observed between velocity and pressure gradient is consistent with this mechanism. However, the relation between atrial volume and peak filling rate is complex, since peak filling rates are also directly related to atrial compliance.36

It is unlikely that alterations in passive diastolic properties can account for the differences in the right and left ventricular filling patterns after pericardiectomy because passive diastolic behavior of the left ventricle calculated during diastasis or at end-diastole cannot be applied to early filling, when viscous elements continuously reduce ventricular compliance.37

The different effects of pericardiectomy on right compared with left ventricular filling patterns may have been the result of unequal increases in right and left ventricular volumes caused by removal of the pericardium. However, we showed that for any left ventricular end-diastolic pressure, pericardiectomy restrained right and left ventricular volumes equally.
This equal volume restraint on the two ventricles was confirmed by analysis of volumes independent of the changes in diastolic pressures after pericardiectomy (Figure 6). When the left ventricular end-diastolic volume after pericardiectomy was matched to the prepericardiectomy left ventricular end-diastolic volume (left panel), the prepericardiectomy and post-pericardiectomy right ventricular volumes were similar (right panel). If volume restraint were greater for the right than the left ventricle, at matched left ventricular end-diastolic volume, the right ventricular end-diastolic volume would be larger than before pericardiectomy. Conversely, if volume restraint were greater for the left than right ventricle, at matched left ventricular end-diastolic volume, the right ventricular end-diastolic volume would be smaller after than before pericardiectomy. Equal volume restraint does not mean that the pericardium influences all aspects of ventricular diastolic function of the two sides in an equal or even comparable manner. Removal of the pericardium altered the slope of the right ventricular diastolic pressure-volume relation, but not the left. Thus, for similar increases in volume induced by pericardiectomy, right ventricular diastolic pressure decreased less than left. This observation is consistent with recent work from our laboratory, in which we showed regional differences in pericardial contact pressure.4 Thus, although pericardiectomy caused a similar increase in right and left ventricular volumes, pericardial influences on the pattern, rate, and mechanism of right and left ventricular filling were markedly different on the two sides.

Finally, early filling of the right ventricle measured with Doppler may have only appeared unchanged after pericardiectomy because of a greater increase in the size of the tricuspid than mitral annulus; that is, although total early diastolic flow was increased, velocity remained unchanged because of a disproportionate increase in the cross-sectional area available for flow. Although the end-diastolic mitral and tricuspid annulus did enlarge significantly with volume infusion and pericardiectomy, we did not find a greater increase in the tricuspid than mitral valve annulus at end-diastole. Furthermore, the changes in annulus diameter alone cannot explain the differences in relative filling patterns (E/A ratios) seen after pericardiectomy. Thus, it is highly unlikely that the use of velocity alone rather than volume filling rates yielded an incorrect assessment of the effects of pericardiectomy on atrioventricular inflow.

Critique of the Methods

We calculated relative, not absolute, ventricular volumes, which we considered sufficient since each animal served as its own control. A related criticism is that geometric assumptions used for volume estimates with the intact pericardium are not necessarily the same after pericardiectomy. This concern is greatest for the more geometrically complex right ventricle. For this reason, the product of ventricular areas from two orthogonal views was used to minimize the effect of altered geometry resulting from volume infusion and pericardiectomy. Furthermore, in a subset of animals, we validated our method for calculating right ventricular volume with a method that had been previously checked against right ventricular casts.27 Right ventricular volumes computed from the product of two orthogonal right ventricular areas before and after pericardiectomy were highly correlated with volumes calculated using the cast method, suggesting that these concerns are of minor importance. The relatively large standard error of the estimate is comparable to other published reports.27 Furthermore, this error is small relative to the large changes in right ventricular volume we observed in most instances after volume loading and pericardiectomy.

Doppler measures velocity, not flow. Volumetric measurements of flow and peak filling rate require an estimate of the corresponding cross-sectional area. However, if the directional changes of the cross-sectional area of flow are concordant with the velocity changes, only absolute values are affected. Furthermore, peak Doppler velocity alone correlates with peak volumetric filling rates obtained by cineangiography or radionuclide ventriculography.38,39 Thus, although peak filling rates were not calculated, our conclusions are unlikely to be affected by the use of Doppler velocity alone.

Finally, our use of a simple exponential end-diastolic pressure–volume fit deserves comment. Complete characterization of ventricular chamber stiffness should incorporate terms for elastic and viscous forces and requires computation of several constants. Polynomial curve fitting may identify parallel shifts of the pressure–volume relation,40 but any fitting procedure is inherently limited and arbitrary. We used a simple exponential fit to compare pressure–volume data between the right and left ventricles, since we were not interested in rigorously modeling the elastic properties of the myocardium. This approach has been used by other investigators.13 Furthermore, linear regression analysis of the end-diastolic pressure–volume relation for both ventricles resulted in high correlation coefficients for each dog (Table 4), indicating that use of a simple exponential equation was adequate for the purposes of our study.

Implications for Physiology and Pathophysiology

The significance of pericardial influences on ventricular filling and compliance remains uncertain in spite of much investigation. We have clarified some aspects of this question by showing that filling of the right and left ventricles is restrained by the pericardium over a wide range of physiological ventricular volumes and pressures. Right and left ventricular volumes are equally restrained by the pericardium, but perhaps as a result of regional pericardial effects, cavitary pressures fall more in the right than left ventricle after pericardiectomy. Thus, pericardial effects on ventricular filling are complex and cannot be considered simply a result of volume restraint. Peri-
cardiac influences on left ventricular filling are mediated by changes in left ventricular end-diastolic and stroke volumes; the influences on right ventricular filling are more fundamental. Although volume loading alters the pattern of right and left ventricular filling in a similar fashion, ventricular inflow patterns are altered in a strikingly different way by pericardiectomy. Concordance of pressure gradient and flow through the atriocardi valves suggests that the differences in right and left ventricular filling caused by volume loading and pericardiectomy result from the influence of these interventions on the determinants of the atriocardi pressure gradient. The differences in right and left ventricular filling may relate to differences in atrial compliance and ventricular distensibility on the two sides. Perhaps the most important implication of our findings is that the effect of an intervention on peak filling rate and the pattern of left ventricular filling may well result from the effects of that intervention on the total cardiopericardi volume and cannot necessarily be interpreted as a change in diastolic properties of the left ventricular myocardium.

References


KEY WORDS • pericardium • ventricular filling • Doppler echocardiography • diastole
Pericardial influences on right and left ventricular filling dynamics.
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Circ Res. 1991;68:197-208
doi: 10.1161/01.RES.68.1.197

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