Transmitral Pressure-Flow Velocity Relation

Importance of Regional Pressure Gradients in the Left Ventricle During Diastole

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Effects of regional diastolic pressure differences within the left ventricle on the measured transmitral pressure-flow relation were determined by simultaneous micromanometric left atrial (LAP) and left ventricular pressure (LVP) measurements, and Doppler echocardiograms in 11 anesthetized, closed-chest dogs. Intraventricular pressure recordings at sites that were 2, 4, and 6 cm from the apex were obtained. Profound differences between these sites were noted in the transmitral pressure relation during early (preatrial) diastolic filling. In measurements from apex to base, minimum LVP increased (1.6 ± 0.7 to 3.1 ± 0.8 mm Hg, mean ± SD); the time interval between the first crossover of transmitral pressures and minimum LVP increased (31 ± 3 to 50 ± 17 msec); the slope of the rapid-filling LVP wave decreased (74 ± 13 to 26 ± 5 mm Hg/sec); the maximum forward (i.e., LAP>LVP) transmitral pressure gradient decreased (3.6 ± 1.3 to 2.1 ± 0.7 mm Hg); the time interval between the first and second points of transmitral pressure crossover increased (71 ± 9 to 96 ± 13 msec); and the area of reversed (i.e., LVP>LAP) gradient between the second and third points of transmitral pressure crossover decreased (101 ± 41 to 40 ± 33 mm Hg · msec). During atrial contraction, significant regional ventricular apex-to-base gradients were also noted. The slope of the LV A wave decreased (26 ± 10 to 16 ± 4 mm Hg/sec); LV end-diastolic pressure decreased (8.1 ± 2.0 to 7.4 ± 2.0 mm Hg), and the upstroke of the LV A wave near the base was recorded earlier than near the apex. All differences were significant at the 0.05 level. Simultaneous transmitral Doppler velocity profiles and transmitral pressures were measured at the 4-cm intraventricular site. The average interval between the first and second points of pressure crossover and between the onset of early rapid filling and maximum E-wave velocity were statistically similar (81 ± 13 vs. 85 ± 12 msec; NS); and the average area of the forward transmitral pressure gradient associated with acceleration of early flow was significantly greater than the area of reversed gradient associated with deceleration of early flow (133 ± 36 vs. 80 ± 46 msec · mm Hg; p<0.025). Finally, the average forward transmitral pressure gradient before minimum LVP was greater than the average forward gradient present after minimum LVP (2.3 ± 0.4 vs. 1.4 ± 0.3 mm Hg; p<0.001), with significant differences in E-wave acceleration noted before and after minimum LVP (887 ± 230 vs. 455 ± 116 mm Hg/sec; p<0.001). Thus, the present study 1) confirms the existence of physiological, reversed pressure gradients during diastole, 2) shows that the magnitude and timing of the forward and reversed pressure gradients are a function of the site of intraventricular pressure measurement, 3) shows that the regional variations in pressure due to the atrial contribution to filling are opposite to that of early diastolic filling, 4) indicates that temporal features of the Doppler E-wave are related in a specific manner to temporal features of transmitral pressure. These findings are consistent with the view that during early diastole, filling is augmented by the mechanical suction of blood into the ventricular cavity, whereas during atrial contraction, the ventricle is filled passively. (Circulation 1988;78:661–671)
To describe left ventricular (LV) diastolic function comprehensively, it is crucial that the transmirtal pressure-flow relation be precisely characterized. In a preliminary report from this laboratory, significant regional differences in measured pressures in the LV during both the early and late phases of diastolic filling were described. Accordingly, the present study was designed to fully characterize the influence of the pressure sampling site within the LV upon the recorded transmitral pressure gradients during diastole and to characterize the relation between these gradients and the simultaneously recorded transmitral Doppler velocity profile.

Materials and Methods

Mongrel dogs of either gender weighing 27–41 kg (mean, 32 ± 4 kg) were sedated with morphine (1 mg/kg s.c.) 30 minutes before induction of general anesthesia with sodium pentothal (12.5 mg/kg i.v.), and α-chloralose (70 mg/kg i.v.). Each dog was intubated and ventilated with room air by a Harvard respirator (South Natick, Massachusetts). The right jugular vein, left common carotid artery, and right femoral artery and vein were isolated, and a valved sheath (Hemaquet 8F, U.S. Catheter and Instruments [USCI], Billerica, Massachusetts) was placed in each. A Swan-Ganz thermodilution catheter (model 93A-131-7F, American Edwards Laboratory, Santa Ana, California) was directed fluoroscopically from the jugular vein to the superior vena cava, and a fluid-filled pigtail catheter (7F, Cordis Laboratories, Miami, Florida) was directed from the femoral artery to the aortic arch.

Transseptal catheterization of the left atrium (LA) was performed with a Mullins transseptal catheter introducer set (8F, USCI) and a Brockenbrough needle (18 gauge, USCI). The animal was placed in the supine position, and the transseptal catheter and needle were directed fluoroscopically through the right femoral vein into the right atrium. The entire assembly was then pressed against the interatrial septum and advanced through it into the LA. Successful puncture was confirmed by fluoroscopic visualization of contrast in the LA and LV. The sheath was then advanced into the LA, the dilator and needle removed, and a bolus injection of sodium heparin (4,000 USP units) was administered. Micromanometer-angiographic catheters (Model 484A-8F, Millar Instruments, Houston, Texas) were directed into the LA through the transseptal sheath and into the LV retrogradely across the aortic valve through the left common carotid artery. To minimize "drift," the micromanometers were immersed in saline for at least 12 hours before use. Immediately before introduction into the animal, the micromanometers were calibrated relative to atmospheric pressure. Before each recording, the LA catheter micromanometer was balanced by its fluid-filled lumen against a transducer aligned at the mitrotronic level. The period of late diastasis associated with slow heart rates (<90 beats/min) was then used to align the micromanometric LV pressure (LVP) signal with the micromanometric LA pressure (LAP) signal (Figure 1). The validity of this alignment was always verified by long compensatory pauses after premature ventricular contractions during which time the diastatic signals were superimposable. In the case of rapid heart rates, compensatory pauses associated with premature ventricular contractions were used exclusively for the alignment.

Low-gain LVP and aortic pressure signals (100 mm Hg = 12.5 cm), and a high-gain LAP signal (20 mm Hg = 10 cm) were transmitted to a photographic recorder (Model 1508B, Honeywell, Denver, Colorado). A high-gain signal from the LV micromanometer was fed to both the photographic recorder and to a heat sensitive recorder (Model 77500B, Hewlett-Packard, Palo Alto, California) attached to an ultrasound imaging system (Model 77020A, Hewlett-Packard). The signal was calibrated precisely to the same sensitivity on both recorders (20 mm Hg = 10 cm), and chart speed of both recorders was adjusted to exactly 100 mm/sec. At the commencement of each experimental recording, a square wave was fed to both recorders through the LV transducer control unit (Model TCB 100, Millar Instruments). This allowed for precise alignment of the high-gain transmitral pressures with the corresponding Doppler velocity profiles.

The position of the micromanometer within the LV cavity was estimated by advancing fluoroscopically the pigtail catheter to the cardiac apex (Figure 2). Once contact with the ventricular apex was made, the catheter was pulled back 0.5 cm. Because the known distance of the micromanometer from the leading edge of the pigtail was 1.5 cm, this maneuver positioned the transducer 2 cm from the LV apex. After measurements at this position, the catheter was withdrawn an additional 2 cm, positioning the micromanometer 4 cm from the apex. After recordings were made at this site, the catheter was again withdrawn 2 cm, and measurements were repeated. After each alteration of catheter position, the LVP signal was corrected for changes in hydrostatic pressure by the previously mentioned procedure.

To be relevant to transmitral flow, it is important that the micromanometer be located in, or in direct line with, the inflow tract of the LV. Through radiography, we are reasonably certain that the 2- and 4-cm positions are located in the direct line of the inflow stream. We are less certain of the 6-cm position, though, because the anteroposterior transducer position was not specifically assessed radiographically. However, the consistent presence of pressure artifact, most probably due to high-velocity flow impacting the transducer, in all 6-cm recordings would indicate that the transducer was near or in the direct line of transmitral flow. The highest amplitude artifact in the signal always occurred nearly simultaneously with the occurrence of peak transmitral flow. In
addition, our 6-cm position probably corresponds closely to the catheter position used in a similar study by Van de Werf et al., which was located 2 cm below the mitral valve and was clearly in the mitral inflow tract. The marked similarity between the conformation of their LVP signal and ours at the most basal position provides strong evidence that our measurements were made in or near the functional path of the inflow tract.

At the heart rates obtained and at the respiratory rates used (15–18 breaths/min) in this study, end expiration consistently provided a period during which the LAP signal remained stable during a 2–3-minute period, which allowed us to assess confidently the intraventricular gradients. Pressures during the inspiratory and early expiratory phases are extremely variable, so comparisons could not be made confidently during these periods. In addition, recent reports indicate that during the inspiratory and early expiratory phases of positive pressure ventilation the heart is subjected to variations in pulmonary blood return and to physical compression by the lungs, both of which may alter diastolic function. Because regional ventricular pressure was measured sequentially, it was crucial that we iden-

Figure 1. Records of measurements (obtained by micromanometric pressure sensors) designed to characterize the transmitral pressure relation. Measurements include minimum left ventricular pressure (LVP), the first crossover point of transmitral pressures (X1), the maximum early forward pressure gradient where left atrial pressure (LAP) exceeds LVP, the slope of the rapid-filling pressure wave (dashed line on left), the time between the first (X1) and the second (X2) points of LAP and LVP crossover, the area of the reversed gradient between the second (X2) and third (X3) points of atrial and ventricular pressure crossover where LVP exceeds LAP, the upslope of the LVP A wave (dashed line on right), and end-diastolic LVP, ECG, electrocardiogram.

tify three beats during which the LAP tracings were identical to each other and during which accurately aligned LVP traces from each of the three levels could be obtained. This level of accuracy was generally found only once for each dog. Thus, summary data presented in this study represent one data point for each dog. After the assessment of intraventricular pressures at the three LV levels, the micromanometer was positioned at the 4-cm level, and simultaneously recorded Doppler flow velocity and transmitral pressure were obtained.

All hemodynamic and echocardiographic measurements were made with the animal in the left decubitus position. Transmitral flow-velocity Doppler profiles were recorded with a 5-MHz transducer by the four-chamber apical view with the sample volume located at the level of the mitral anulus. The electrocardiogram was monitored by a precordial (V4) electrode. Because diastolic LV function has been shown to be highly sensitive to hypothermia, core temperature was maintained constant with use of a circulating water (38°C) heating pad and was monitored continuously by the Swan-Ganz catheter thermistor. The temperature never dropped below 36.5°C. Blood gases were measured at repeated intervals, and ventilator respiratory rate and volume were adjusted accordingly.

Analysis of Data

The following three pressure-time intervals were recorded (Figure 1): 1) the time between the first crossover of LAP and LVP (X1) and minimum LVP, 2) the time between X1 and the second crossover of LAP and LVP (X3), and 3) the time between X1 and the third crossover of LAP and LVP (X3). Velocity–time interval measurements included the time between initial increase of the early Doppler velocity profile and peak transmitral flow velocity; and the time between initial increase of the early diastolic Doppler time-velocity signal and its return to zero.

Mean pressure gradients were calculated for the following two time intervals: average pressure gradient for the time interval between X1 and minimum

Figure 2. Schematic representation of sequential placement of micromanometric catheter within the left ventricular cavity. Note that the micromanometer is located 1.5 cm proximal to the leading edge of the pigtail.
LVP; and average pressure gradient for the time interval between minimum LVP and X₂.

Transmitral pressure-time integrals were measured as the area circumscribed by the LAP and LVP signals during the interval from X₁ to X₂, and from X₂ to X₃. To facilitate precise measurement of these areas and timing intervals, the pressure recordings were enlarged with a high-quality photographic copier. Areas were measured three times by manual planimetry, corrected for magnification, and averaged. Timing of maximum pressure gradients was also identified on magnified copies.

Group data were analyzed with a one-way ANOVA. Differences between individual groups were detected with Fisher’s least-significant difference test.⁸

Results

Effect of Left Ventricular Pressure

Sampling Site on the Measured Transmitral Pressure Relation

Figures 3A–3C, recorded from a representative animal during a 2-minute period, illustrate the characteristic changes in transmitral pressure relations that occurred when the micromanometer was moved sequentially from the cardiac apex toward base. The mean values for the measured variables during the rapid-filling phase for the 11 animals are listed in Table 1. Significant differences were observed for all measured variables except for the pressure at the time of the first crossover of LAP and LVP (X₁), the time interval between X₁ and the third crossover of LAP and LVP (X₁-X₃), heart rate, and mean aortic pressure. In addition, Figures 4A–4C demonstrate that regional pressure differences existed in the LV not only during the early rapid-filling phase but also during the late filling phase associated with atrial contraction. Two centimeters from the apex (Figure 4A), the LV A wave began to rise well after the initial upstroke of the LA A wave, and it assumed a nearly linear configuration until the steep rise in pressure occurred that marked the commencement of isovolumic contraction. Four centimeters from the apex (Figure 4B), the rise of the LV A wave began closer to the initial rise of the LA A wave, and it assumed a more pronounced curvilinear configuration before isovolumic contraction. Six centimeters from the apex (Figure 4C), the rise of the LA and LV A waves occurred nearly simultaneously, and the LV A wave was characterized by a slight pressure decay (downward notch) before isovolumic contraction. Significant differences were noted in the upslope of the LV A wave and end-diastolic LVP (Table 1).

Relation Between Transmitral Pressure and the Transmitral Doppler Flow-Velocity Profile

Figures 5A–5C recorded with the micromanometer in the midventricular position (4 cm from the apex), demonstrate that the same basic relation is observed throughout a wide range of heart rates.

At slow heart rates (Figure 5A), after the decline of LVP to that of LAP (X₁), early transmitral flow (E) accelerated rapidly, reached its peak at or near the second crossover of LAP and LVP (X₂), then decelerated rapidly to zero at or near the third crossover of LAP and LVP (X₃). A period of diastasis then followed during which LAP and LVP remained essentially equal until a forward (LAP>LVP) pressure gradient associated with atrial contraction produced flow across the mitral valve as evidenced by the A wave in the Doppler flow-velocity profile.
TABLE 1. Transmitial Pressure Variables Measured at 2, 4, and 6 cm From the Ventricular Apex

<table>
<thead>
<tr>
<th>Variable</th>
<th>2 cm</th>
<th>4 cm</th>
<th>6 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>X₁ (mm Hg)</td>
<td>6.7±1.4</td>
<td>6.7±1.4</td>
<td>6.7±1.5</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>88±23</td>
<td>89±23</td>
<td>87±22</td>
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<tr>
<td>AoM (mm Hg)</td>
<td>96±13</td>
<td>97±13</td>
<td>96±13</td>
</tr>
<tr>
<td>LVP&lt;sub&gt;min&lt;/sub&gt; (mm Hg)</td>
<td>1.6±0.7</td>
<td>2.3±0.6</td>
<td>3.1±0.8†</td>
</tr>
<tr>
<td>RFW&lt;sub&gt;slope&lt;/sub&gt; (mm Hg/sec)</td>
<td>74±13</td>
<td>37±13†</td>
<td>26±5†</td>
</tr>
<tr>
<td>ETP&lt;sub&gt;max&lt;/sub&gt; (mm Hg)</td>
<td>3.6±1.3</td>
<td>3.0±1.1</td>
<td>2.1±0.7†</td>
</tr>
<tr>
<td>LVP&lt;sub&gt;ave&lt;/sub&gt;F (mm Hg)</td>
<td>3.8±0.7</td>
<td>2.7±0.7</td>
<td>1.9±0.4†</td>
</tr>
<tr>
<td>X₁-X₂ interval (msec)</td>
<td>71±9</td>
<td>82±10†</td>
<td>96±13†</td>
</tr>
<tr>
<td>X₁-X₂ &lt;sub&gt;interval&lt;/sub&gt;</td>
<td>175±17</td>
<td>175±20</td>
<td>179±15†</td>
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<tr>
<td>ARP (mm Hg · msec)</td>
<td>101±41</td>
<td>68±37†</td>
<td>40±33†</td>
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<td>A wave&lt;sub&gt;slope&lt;/sub&gt; (mm Hg/sec)</td>
<td>26±10</td>
<td>19±7†</td>
<td>16±4†</td>
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<td>A wave&lt;sub&gt;peak&lt;/sub&gt; (mm Hg)</td>
<td>8.2±2.0</td>
<td>7.8±2.3</td>
<td>7.6±2.0†</td>
</tr>
<tr>
<td>t-LVP&lt;sub&gt;min&lt;/sub&gt; (msec)</td>
<td>31±3</td>
<td>32±3</td>
<td>50±17†</td>
</tr>
<tr>
<td>LVED (mm Hg)</td>
<td>8.1±2.0</td>
<td>7.6±2.2</td>
<td>7.4±2.0†</td>
</tr>
</tbody>
</table>

Data are mean±SD; n=11 dogs.

X₁, first crossover point of transmitial pressures; HR, heart rate; AoM, mean aortic pressure; LVP<sub>min</sub>, minimum left ventricular pressure; RFW<sub>slope</sub>, slope of left ventricular rapid-filling pressure wave; ETP<sub>max</sub>, maximum early transmitial pressure gradient; LVP<sub>ave</sub>F, height of the rapid-filling pressure wave from minimum left ventricular pressure to the peak of the F wave; X₁-X₂, time interval between the first and second crossovers of transmitial pressures; X₁-X₂ <sub>interval</sub>, time interval between first and third crossovers of transmitial pressures; ARP, area of reversed pressure gradient where left ventricular pressure exceeds left atrial pressure; A wave<sub>peak</sub>, peak pressure of the left ventricular A wave; A wave<sub>slope</sub>, upslope of left ventricular A wave; t-LVP<sub>min</sub>, time interval between first crossover of transmitial pressures and minimum left ventricular pressure.

*<i>p</i>&lt;0.05 vs. 4 cm group; †<i>p</i>&lt;0.05 vs. 2-cm group.

Values at this position do not include data points from two animals in which no detectable reversal of gradient was observed.

At moderate heart rates (Figure 5B), the pressure-flow relation was similar. In addition, in eight of the 11 animals in which slow-to-moderate heart rates were observed (49–91 beats/min), a distinct mid-diastolic deflection in the Doppler signal (L) was recorded and was accompanied by a forward transmitial pressure gradient (arrow) as has been previously described. A small, reversed gradient temporally associated with the decelerative portion of the L wave was also a routine observation.

At rapid heart rates (Figure 5C), diastole was shortened; hence, atrial flow (A wave in Doppler profile) occurred earlier. This resulted in incomplete separation of the E and A waves.

Figure 6 illustrates timing of pressure and Doppler-derived events during the early diastolic filling phase recorded with the LV micromanometer positioned 4 cm from the apex in the eight dogs in which clear separation of the A and E waves was observed. For recordings at this position in the LV, the average intervals between crossover points X₁ and X₂, and between the onset of early-rapid-filling and maximum E-wave velocity were statistically similar (81±13 vs. 85±12 msec, NS), and the average forward (LAP>LVP) pressure-time integral associated with acceleration of early flow was significantly greater than the reversed (LVP>LAP) pressure-time integral associated with deceleration of early flow (133±36 vs. 80±46 msec · mm Hg; <i>p</i>&lt;0.025, paired <i>t</i> test).

Temporal Occurrence of the Maximum Transmitial Pressure Gradient

As shown in Figure 7, the maximum transmitial pressure gradient occurred approximately 5–10 msec before the occurrence of minimum LVP. The transmitial gradient was consistently less at the time of minimum LVP compared with the gradient recorded 5 msec earlier (2.6±0.3 mm Hg). Fifteen milliseconds before the occurrence of minimum LVP, the gradient was still increasing relative to the gradient that was recorded 5 msec later (2.4±0.2 vs. 2.6±0.3 mm Hg).

Finally, the average transmitial pressure gradient before the occurrence of minimum LVP was calculated to be 64% greater than the average gradient after minimum LVP (2.3±0.4 vs. 1.4±0.3 mm Hg, <i>p</i>&lt;0.001) (Figure 8). This difference in the pressure gradient was reflected in an inflection point noted in the Doppler velocity profile corresponding closely in time with minimum LVP. If approximated by straight lines with the use of a straightedge (a technique accurate to at least two significant figures), significant differences in E-wave acceleration were noted before and after this inflection point (887±230 vs. 455±116 cm/sec², <i>p</i>&lt;0.001).

Discussion

Our findings confirm and substantially extend the observations of Ling et al, who reported signifi-
ciant LVP gradients during early diastolic filling. In the present study, as the site of pressure measurement was moved from the apex toward the base, important regional pressure differences were recorded during the early phase of diastolic filling: minimum diastolic pressure and the time to achieve it increased; the maximum forward (LAP>LVP) transmitral pressure gradient decreased; the slope and height of the LV rapid-filling pressure wave decreased; the timing of the second crossover of LAP and LVP occurred later; and the magnitude of the reversed (LVP>LAP) gradient decreased. In addition, systematic regional pressure gradients were also recorded during the late phase of diastolic filling associated with atrial contraction. To our knowledge, regional pressure gradients during both the early (preatrial) and late (atrial) phases of diastole have not been previously reported.

Regional Pressure Gradients as Evidence For Ventricular Suction

As early as 1930, Katz\textsuperscript{12} observed that ventricular pressure continued to decline during early diastole despite rapid filling. Based on this observation, he deduced that “the relaxing ventricle, therefore, not only can but does exert a sucking action to draw blood into its chamber.” From this reasoning, it follows that the time during early diastolic filling at which the ventricular pressure begins to increase after minimum LVP would mark the completion of the generation of ventricular suction. Because such an increase in pressure occurs earlier near the apex of the heart than near the base (Figure 9), it can be inferred that suction is completed earlier near the apex than near the base.

In addition, because pressure begins to increase after minimum LVP first near the apex and last near the base, this implies that blood is being decelerated by the ventricular wall\textsuperscript{3,13} first near the apex and last near the base; hence, blood accumulates first near the apex and last near the base. Closely related to this point, recent simultaneous intraventricular pressures recorded in our laboratory with a dual micromanometer catheter (Model PC 771-7F, Millar Instruments) with 3-cm spacing between the sensors strongly support this conclusion. These recordings reveal a consistent intraventricular pressure pattern that can easily be missed with the sequential positioning technique. As surmised from the pressure tracings (Figure 10), filling is not only completed first in the apex, which is indicated by the timing of the peak of the F wave, but pressure in this region actually begins to oscillate\textsuperscript{14} which indicates that the apex itself may be oscillating. These two phenomena take place while filling near the base is still occurring, which is indicated by the continuing increase in pressure at that level. This same pattern has been observed in the nine animals in our laboratory in which dual sensor catheter measurements have been made. In addition, with careful comparison of the sequential recordings already described

**FIGURE 4.** Records of transmitral pressures recorded (by micromanometric pressure sensors) during atrial contraction with the left ventricular micromanometer positioned 2, 4, and 6 cm from the apex. Panel A: Micromanometer positioned at 2 cm. Left ventricular A wave begins its rise well after the initial rise of left atrial A wave and appears nearly linear in shape until the steep rise of isovolumic contraction. Panel B: Micromanometer positioned at 4 cm. Rise of the left ventricular A wave begins closer to the initial rise of the left atrial A wave than at 2 cm from the apex, and it demonstrates more pronounced curvature before isovolumic contraction. Panel C: Micromanometer positioned at 6 cm. Left ventricular A wave begins its rise nearly simultaneously with the left atrial A wave and demonstrates a downward component before isovolumic contraction. LAP, left atrial pressure; LVP, left ventricular pressure.
in the present study, this pattern can also be observed in all 11 animals. This pattern is also seen clearly in the intraventricular pressure recording presented by Ling et al11 (Figure 3 of their study). The observation that the apical region fills first, as surmised from the pressure tracings, and begins to oscillate while filling is still occurring in the basal region is also consistent with a model of diastolic function that treats the apex as recoiling during early diastole and contributing to filling by actively drawing blood into the ventricular chamber.15

In addition to the regional intraventricular pressure gradients observed during the early rapid-filling phase, regional differences were also noted during atrial contraction, during which the initial upstroke of the LV A wave was recorded first near the base of the heart and last near the apex. This pattern is consistent with a model of passive ventricular filling during atrial contraction. Thus, sensing the pressure of the blood as it enters the ventricle first near the base of the heart and last near the apex is predictable because a finite time would be required for the pressure wave to travel from base to apex. Because velocity equals distance divided by time, we estimate from our data that this pressure wave advances approximately 2 m/sec because the delay in the upward deflection of the LV A wave was consistently about 20 msec throughout a distance of 4 cm. In addition, it is noteworthy that the regional pressure-wave pattern recorded during atrial contraction is exactly opposite to the pattern recorded during the rapid-filling phase during which the upstroke of the LV rapid-filling pressure wave occurs first near the apex and last near the base of the heart, again suggesting that some mechanism other than passive filling exists during the rapid-filling phase.

Reversed Transmitral Pressure Gradient

Our observations, consistent with those of Van de Werf et al,3 indicate that a reversed gradient between the atrium and ventricle during early diastolic filling is a normal physiological event. Ling et al11 also reported a reversed pressure gradient between the midventricular and apical regions to be a normal occurrence. However, other investigators have not consistently confirmed the existence of reversed transmitral pressure gradients. For example, Keren et al9 postulated that the presence of an electromagnetic flow probe in their experimental preparation created a "mild mitral stenosis" that prevented early diastolic transmitral pressure gradient reversal. On the basis of our observations, it may be inferred that the position of the recording catheter may also have contributed to this discrepancy. These investigators placed their catheters in the LV by means of apical puncture, which may move the transducer away from the apex, near the mitral valve where in two of the 11 animals we did not detect a reversed gradient at the 6-cm level.

Van de Werf et al3 consistently observed reversed gradients while using a catheter to which an electromagnetic flow transducer was affixed 2 cm proximal to a pressure transducer at the distal tip. The
catheter was positioned through a pulmonary vein such that the flow transducer was at the level of the mitral anulus. These authors have previously related the reversal of pressure gradients during early diastole to deceleration of flow and to the genesis of the third heart sound.\textsuperscript{3,13} They inferred that the LV wall was the major cardiac structure set into vibration, producing the third heart sound during deceleration of flow. Because higher reversed gradients are observed near the apex, the present investigation suggests that the apical wall may be the specific locus of the third heart sound. This may also be true for the fourth heart sound because the steepest A wave and pressure overshoot in the form of a reversed gradient are also found near the apex during this phase of diastole. This is consistent with the clinical auscultatory observation that the third and fourth heart sounds are heard best over “the apex” of the heart.

The similarity of the measurements and calculations in the Van de Werf et al\textsuperscript{3} study to those of the present study invites a comparison. Assuming that their micromanometer position corresponds most closely to our 6-cm position, a number of direct comparisons can be made. Time to minimum LVP is somewhat longer in their study (66 ± 3 msec) than in ours (50 ± 17), whereas the X\textsubscript{1}-X\textsubscript{2} interval for the two studies is remarkably similar (101 ± 4 vs. 96 ± 13 msec). The mean X\textsubscript{1}-X\textsubscript{3} interval estimated from their X\textsubscript{1}-X\textsubscript{2} and X\textsubscript{2}-X\textsubscript{3} data to be approximately 220 msec is also somewhat longer than the mean interval of the present study (179 msec), whereas a large difference is found between their reported mean area of reversed gradient (85 ± 9 mm Hg · msec) and ours (40 ± 33 mm Hg · msec). These differences can most probably be attributed to variations in animal size and preparation and to differences in LV and LA intracavitary pressure measurement site used in the two studies. In addition, very large differences exist between the variables of rapid filling (acceleration, deceleration, and peak transmitral velocity) reported in their study (132 ± 9 cm/sec\textsuperscript{2}, −101 ± 7 cm/sec\textsuperscript{2}, and 12 ± 0.7 cm/sec, respectively) and in ours (887 ± 230 cm/sec\textsuperscript{2}, −492 ± 158 cm/sec\textsuperscript{2}, and 54 ± 11 cm/sec, respectively). The reason for such low values of mitral inflow variables in the Van de Werf et al\textsuperscript{3} study

**FIGURE 6.** Records of timing measurements (by micromanometric pressure sensors) for the early transmitral Doppler time-velocity filling wave for eight dogs in which clear separation of the E and A waves was observed, aligned with simultaneous transmitral pressures measured at the midatrial and midventricular levels. No significant difference was found between the average X\textsubscript{1}-X\textsubscript{3} time interval and the time interval between E wave onset and maximum E velocity, or between X\textsubscript{1} and X\textsubscript{2} and E-wave onset and its decline to zero. Average forward gradient associated with acceleration is significantly greater than the reversed gradient associated with deceleration. For these eight animals, peak velocity of the Doppler E wave=54 ± 11 cm/sec. LVP, left ventricular pressure; LAP, left atrial pressure.

![Graph](https://via.placeholder.com/150)
Between Atrial and Ventricular Relations

FIGURE 7. Records of simultaneous transmitral pressures (n=11) recorded (by micromanometric pressure sensors) at the midatrial and midventricular (4 cm from apex) levels. Maximum pressure gradient occurs 5–10 msec before minimum left ventricular pressure. LVP, left ventricular pressure; LAP, left atrial pressure.

compared with those reported in the present study is not clear. However, such a large disparity would certainly be another factor that may contribute to the differences between the two studies.

Relation Between Atrial and Ventricular Pressures and the Doppler Velocity Profile

Although our technique precluded systematic positioning of the catheter at various sites in the atrium, it is probable, because flow is directed from the pulmonary veins toward the mitral valve, that regional pressure differences also exist in the LA. Mitral pressure-flow relations are thus highly dependent on the site of pressure measurement. Any meaningful quantitative or qualitative descriptions must necessarily make some arbitrary decisions concerning pressure sampling position in both the LA and LV. As a first step toward systematically defining transmitral pressure-flow relations, we examined in detail the relation between the Doppler flow-velocity profile recorded at the anulus, LVP recorded 4 cm from the apex (approximately midventricular), and LAP recorded at approximately the midatrial level as viewed by two-dimensional echocardiography. Assessment of the transmitral pressure-flow velocity relation at these sites revealed that 1) during acceleration of early flow, a forward (LAP>LVP) pressure gradient is always present, 2) at or near peak flow velocity, the transmirtal pressure gradient is zero (transmirtal pressure cross-over point X2), 3) during deceleration of early flow, a reversed (LVP>LAP) gradient is always present, 4) the total area circumscribed by the forward pressure gradient exceeds that of the reversed gradient, and 5) the maximum forward transmitral pressure gradient occurs immediately before minimum LVP. The mean forward gradient before minimum LVP is, on average, greater than the mean gradient present after minimum LVP. Minimum LVP also appears to be associated with an inflection point in the early diastolic Doppler time-velocity signal where acceleration of flow is significantly greater before than after it.

Implications for Research in Diastolic Function

The results of the present study have important implications with regard to the characterization of LV diastolic function.
First, the patterns of early and late regional pressure gradients and the presence of regional pressure oscillations strongly suggest that ventricular suction plays a role in early filling in the normal heart. Thus, early diastole is not amenable to analysis with simple passive-filling models and any complete description of diastole must account for ventricular suction. However, a recent model has been developed that characterizes the entire diastolic period as passive filling.

Second, the presence of regional intraventricular pressure gradients indicates that studies with techniques for assessment of LV compliance by curve-fitting LV diastolic pressure-dimension data must use a standardized catheter position, particularly if serial measurements are involved. The most appropriate position at which to record intraventricular pressure remains unresolved, although it is clear that diastolic pressures and ventricular dimensions must be measured at the same level when assessing LV diastolic mechanics. Because different regions of the LV are subjected to differing pressures, and thus differing wall stresses, at different points in time, an ideal description of LV diastolic function must necessarily be regional in nature. However, the technical difficulties involved in multisite measurement of pressure within the ventricle, coupled with the recent observation that regional variations in pericardial constraint may also exist, make regional stress-strain measurements a challenge.

Third, the ascending limb of the early diastolic Doppler flow-velocity profile is curvilinear. If this curvilinear relation is approximated by straight lines, the point where the slope decreases corresponds temporally to a transmitral pressure transition point. This indicates that simple measures of acceleration of flow that assume the upslope of the Doppler flow-velocity profile is linear may be oversimplifications. Thus, commonly measured variables such as acceleration time, acceleration half-time, and acceleration rate may ignore important dynamic information that is present in the signal.

Finally, our data also indicate that a complete description of transmitral pressure-flow relations during early and late diastole must take into account...
regional variations in the size of forward and reversed transmural pressure gradients, the relation of the flow-velocity profile to the various points of transmural pressure crossover, the timing of the maximum transmural pressure gradient during rapid filling, and differences in the timing, rate of increase, height, and configuration of the LV A wave.

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