Combined Influence of Ventricular Loading and Relaxation on the Transmirtal Flow Velocity Profile in Dogs Measured by Doppler Echocardiography

Christopher Y. Choong, MBChB, PhD, Vivian M. Abascal, MD, James D. Thomas, MD, J. Luis Guerrero, BS, Shawn McGlew, BS, and Arthur E. Weyman, MD

The relation of the Doppler transmirtal flow velocity profile to left ventricular loading conditions and diastolic properties remains poorly described. We studied seven adult mongrel dogs with an open-chest right heart bypass model in which left atrial pressure, representing preload, was varied by controlling blood flow into the pulmonary artery and left ventricular systolic pressure, representing afterload, was controlled independently by pumping blood into or from the femoral arteries. Heart rate was kept constant by crushing the sinus node and pacing the right atrium. Mitral inflow velocity profiles were measured by pulsed-wave Doppler echocardiography at multiple left atrial and left ventricular systolic pressures. In individual dogs, the peak E-wave velocity increased linearly with increasing left atrial V-wave pressure at constant left ventricular systolic pressure and decreased with increasing left ventricular systolic pressure at constant left atrial pressure. Stepwise multiple linear regression analysis of data pooled from all experimental stages in all dogs identified left atrial V-wave pressure, the time constant of relaxation (T1), and left ventricular systolic pressure, in order of decreasing significance, as predictors of the peak E-wave velocity (n = 82, multiple r = 0.87, p < 0.0001). Multivariate analysis with the same three factors in individual dogs yielded higher r values (mean r = 0.89; range, 0.85-0.97), suggesting the presence of important interdog differences that were not accounted for by these three factors alone. When the values of codeterminant hemodynamic factors were kept within narrower limits, correlations between peak E-wave velocity and left atrial V-wave pressure (n = 35, multiple r = 0.83, p < 0.0001), T1 (n = 76, multiple r = -0.54, p < 0.0001) and left ventricular systolic pressure (n = 20, multiple r = -0.59, p < 0.005) improved substantially. In the pooled data, the relation of the peak E-wave velocity to left atrial V-wave pressure was shifted downward by an increase in T1 (reduced relaxation rate), and the relation of the peak E-wave velocity to T1 was shifted upward by an increase in left atrial V-wave pressure. Multivariate analysis also selected left atrial V-wave pressure and T1 as the two most significant correlates of the velocity-time integral and deceleration rate of the E wave. Those Doppler parameters that represented proportions rather than absolute values (the peak E-wave velocity: peak A-wave velocity ratio, the A-wave velocity-time integral: total velocity-time integral ratio, and the first third velocity-time integral: total velocity-time integral ratio) correlated with T1 but were relatively independent of left atrial V-wave pressure. Thus, the mitral inflow velocity profile is determined in a complex manner by multiple factors, which include left atrial pressure, relaxation rate, and left ventricular systolic pressure. Simultaneous variations in each of these factors often obscure simple relations between individual Doppler parameters of interest and a single hemodynamic factor. These results suggest that Doppler filling parameters must be interpreted cautiously when used as indexes of diastolic function. (Circulation 1988;78:672–683)

The clinical importance of left ventricular function during diastole has been emphasized by increasing evidence that diastolic dysfunction contributes significantly to the pathophysiology and symptomology of a large number of cardiovascular disorders in humans.1–3 Unfortunately, the lack of an easily measured yet reliable index of diastolic function has hindered our un-
standing of the complex physiological mechanisms that operate in this area.

For many years, the pattern of filling of the left ventricle, measured by various techniques including contrast cine-ventriculography, radionuclide ventriculography, and M-mode echocardiography, has been used to reflect the diastolic function of the ventricle. Doppler echocardiography is a relatively new investigative tool that allows measurements of the velocity of blood flow across the mitral valve and, thus, the pattern of ventricular filling to be made with relative ease. The many advantages of this technique, such as its noninvasive nature, lack of radiation, absence of hemodynamic effects, high temporal resolution and beat-to-beat capability, make it a potentially valuable tool for the evaluation of ventricular diastolic function.

Abnormal characteristics of the Doppler mitral velocity profile have been reported in a variety of diseases associated with abnormal left ventricular diastolic function. Although these Doppler abnormalities are usually attributed to diastolic dysfunction, disappointingly poor correlations have been found whenever Doppler parameters of ventricular filling have been compared to invasive measurements of diastolic function, such as active relaxation and passive compliance.

While theoretical principles dictate that ventricular diastolic properties should influence the pressure gradient between the left atrium and left ventricle, and, therefore, the velocity of blood flow across the mitral valve, loading conditions of the ventricle also play an important role. We previously demonstrated in patients that a reduction in left ventricular filling pressure by nitroglycerin altered the transmitral Doppler velocity profile in a manner that mimicked a worsening of diastolic function, even though relaxation rate actually increased. Similar results have also been found when other interventions were used to alter left atrial pressure in patients. These observations corroborate previous reports in dogs in which peak volumetric filling rates were measured by electromagnetic flow probes.

Studies in isolated muscle and intact hearts indicate that active relaxation is afterload-dependent. Left ventricular systolic pressure, therefore, may influence the pattern of ventricular filling through the alteration of relaxation quite independently of any chronic effects on ventricular hypertrophy and passive chamber stiffness. Ishida et al found that an acute increase in aortic pressure by angiotensin II slowed relaxation rate and reduced the peak rate of left ventricular filling measured by electromagnetic flow probes, even though left atrial pressure increased. The acute effects of left ventricular afterload on the transmitral Doppler velocity profile have not been described.

Before Doppler parameters of ventricular filling can be used as meaningful and reliable descriptors of ventricular diastolic function, the relation of transmural blood flow velocities to ventricular diastolic properties (i.e., relaxation rate and passive compliance) as well as factors that may alter flow velocity independently of ventricular diastolic function (such as filling pressure) must be clearly understood. The purpose of this study was to assess in a controlled manner the effects of ventricular preload, afterload, and relaxation on the Doppler mitral velocity profile. Because of the obvious difficulties with simultaneously controlling multiple hemodynamic factors in humans, we chose instead to use a canine right heart bypass model, in which we were able to adjust heart rate, left ventricular filling pressure, and afterload separately.

Materials and Methods

Experimental Model

The study conforms to the guiding principles of the American Physiological Society. Seven adult mongrel dogs, weighing 16.6 ± 1.2 (SEM) kg were anesthetized with 30 mg/kg i.v. sodium pentobarbital, intubated, and placed on a Harvard respirator. The concentration of inspired oxygen and ventilation rate were adjusted to keep blood gases within physiological ranges.

A central thoracotomy was performed with the animals supine. The pericardium was opened, and pressure catheters were inserted in the following manner. A micromanometer-tip catheter (Millar Mikro-tip, Millar Instruments, Houston, Texas) and a short, narrow-bore fluid-filled catheter connected to a pressure transducer (Statham P23DB, Statham Instruments, Oxnard, California) were inserted at the left ventricular apex to record ventricular pressure. A similar pair of micromanometer-tip and fluid-filled catheters were inserted from a pulmonary vein into the left atrium to record left atrial pressure. Finally, a third micromanometer-tip catheter was inserted from the internal mammary artery into the aortic root to record aortic pressure.

Great care was taken to ensure the accuracy of the pressure measurements, particularly those obtained during diastole. Fluid-filled transducers were balanced at atmospheric pressure and calibrated against a mercury column. Micromanometer-tip catheters were calibrated against the zero and mean pressures recorded by the fluid-filled transducers. Checks were made to ensure that left ventricular and left atrial diastolic pressures were identical at the end of long periods of diastasis. At the end of the experiments, the three micromanometer-tip catheters were placed in blood kept at body temperature and exposed to air to confirm the accurate registration of zero pressures.

All pressure measurements and a single electrocardiographic lead were continuously recorded on an eight-channel strip chart recorder (Hewlett-Packard Model 7700, Hewlett-Packard, Waltham, Massachusetts). To increase the resolution of the recordings, ventricular diastolic and left atrial pressures were recorded on × 40 scale, while aortic and
ventricular systolic and mean pressures were recorded on \( \times 100 \) or \( \times 200 \) scales. Paper speed was increased to 100 mm/sec when data for each experimental stage were formally recorded.

The sinus node was crushed and the right atrium was artificially paced to keep the heart rate constant throughout all experimental stages in each dog. The lowest possible heart rate was sought at the beginning of the experiment. However, the development of escape rhythms and multiple premature beats at lower heart rates precluded the attainment of stable rates of less than 113 beats/min. Heart rates were similar between dogs and ranged from 113 to 120 beats/min. In all instances, the early filling (E) and atrial contraction (A) waves of the Doppler mitral velocity profile remained clearly separate.

The animals were placed on right heart bypass, as depicted diagrammatically in Figure 1. All venous return was drained from the superior and inferior vena cavae and coronary sinus. The venous blood was filtered, warmed and oxygenated, and then pumped by calibrated roller pump back into the dog through a wide-bore cannula inserted into the pulmonary artery. In this way, left atrial pressure could be controlled by altering the rate of roller-pump flow into the pulmonary artery.

With a second calibrated roller pump, blood could also be pumped into or sucked from the systemic arterial circuit through cannulae inserted into the femoral arteries. This maneuver allowed left ventricular systolic pressure, used as an index of ventricular afterload, to be controlled relatively independently of left atrial pressure.

**Echocardiographic Examination**

For echocardiographic examination, the heart was stabilized on a pericardial cradle and a shallow water bath was constructed to allow transducer standoff. Two-dimensional and pulsed-wave Doppler data were acquired with an Advanced Technology Laboratories Mk 600 ultrasound imager equipped with a 5.0-MHz mechanical transducer. An apical four-chamber view was used for the recording of transmital flow velocities. The Doppler ultrasound beam was aligned as close to perpendicular as possible to the mitral annular plane, and the sample volume (4-mm axial length) was positioned just within the left ventricle, midway between the annular margins. Transducer orientation was then finely adjusted to obtain the highest velocities of the E wave. The position of the sample volume was altered with changes in ventricular size to keep its spatial relation to the mitral annular plane constant. All two-dimensional images and Doppler spectral velocity profiles were recorded on \( \frac{1}{2} \)-in. videotape. Doppler tracings were also recorded on paper at a speed of 100 mm/sec for further analysis.

**Experimental Protocol**

In the first phase of the experiment, left atrial V-wave pressure, representing the pressure at mitral valve opening (crossover pressure), was altered in a
stepwise fashion by manipulating roller pump flow into the pulmonary artery. Ranges of left atrial V-wave pressure from approximately 4 to 18 mm Hg were sought in each dog. At each experimental stage, left ventricular systolic pressure was kept constant (approximately 100 mm Hg) by adjusting the rate of blood pumped into or from the femoral arteries. Because alterations to left systolic ventricular pressure also affected left atrial pressure, and vice versa, the desired hemodynamic endpoints were usually achieved by the careful final adjustment of flow rates in both roller pumps. Between seven and nine experimental stages were obtained in each of six dogs. In one dog, data could be obtained from only four stages. Left atrial pressures were selected in randomly ascending or descending order.

At each experimental stage, respiration was suspended, and electrocardiographic, hemodynamic, and echocardiographic measurements were simultaneously recorded after pressure tracings had stabilized.

In the second phase of the experiment, left ventricular systolic pressure was altered in a stepwise manner by adjusting roller pump flow into or out of the femoral arteries, while left atrial V-wave pressure was kept constant (approximately 10 mm Hg) by adjusting flow rate into the pulmonary artery. Ranges of left ventricular systolic pressure from approximately 75 to 170 mm Hg were sought in each dog. Between four and six experimental stages were obtained. At each experimental stage, electrocardiographic, hemodynamic, and echocardiographic measurements were recorded simultaneously, as previously described.

Data Analysis

Hemodynamics. All hemodynamic and Doppler measurements were analyzed blindly without knowledge of one another. At each experimental stage, left ventricular, left atrial, and aortic micromanometer pressure tracings obtained from three consecutive beats were analyzed and averaged. Left ventricular systolic, minimal and end-diastolic pressures, left atrial peak V-wave pressures, and aortic systolic, diastolic, and mean pressures were measured.

The logarithmic time constant of isovolumic relaxation (T1) was obtained in the standard manner by digitizing left ventricular pressure from the time of peak negative dP/dt to a point on its downslope that was 5 mm Hg above the end-diastolic pressure.23 A natural logarithmic function was fitted to the curve P = e\(^{At+B}\) (P is isovolumic left ventricular pressure at time t, A is the slope of log P vs. t, and B is the natural logarithm of the highest pressure on the digitized curve). The time constant T1 was calculated as the negative reciprocal of A. The same three beats used for the measurement of left ventricular diastolic pressures were used for calculating T1, and the three values were then averaged.

Doppler mitral velocity profile. At each experimental stage, the peak velocities of the E and A waves were measured. The mitral velocity profiles were digitized along the darkest lines of the velocity spectra with a commercially available computer analysis package (Freeland Medical Systems, Indianapolis, Indiana), and the velocity-time integrals of the E and A waves, the deceleration rate of the E wave, the total velocity-time integral, the ratio of the A-wave velocity-time integral to the total velocity-time integral (relative contribution of atrial contraction to total filling), and the first third diastolic filling fraction (proportion of total velocity-time integral occurring in the first one third of the diastolic period) were calculated. Values from three consecutive beats were averaged.

Statistical Analysis

Univariate correlations between Doppler and hemodynamic measurements were performed with simple least-squares linear regression analysis. Multiple stepwise linear regression analysis was used to identify simultaneously the hemodynamic factors that correlated best with individual Doppler parameters of interest. In data pooled from all dogs, six dog-specific variables (number of dogs minus one) were introduced into the statistical model to account for variance arising from differences among dogs.

In addition, because of the multifactorial nature of these relations, univariate regression analyses of the pooled data were performed on only those experimental stages where the values of other codeterminant factors fell within relatively narrow ranges. By arbitrarily limiting the ranges of the codeterminant factors in this way, we hoped to minimize their confounding influence on the specific relations being studied.

Linear regression analysis was used to examine the effect of left atrial V-wave pressure on the peak E-wave velocity across different ranges of T1 and, similarly, the effect of T1 on the peak E-wave velocity across different ranges of left atrial V-wave pressure.

Results

Peak E-Wave Velocity

In the first phase of the experiment, peak E-wave velocity in individual dogs increased with increasing left atrial V-wave pressure while left ventricular systolic pressure was held relatively constant. Excellent correlations between the peak E-wave velocity and left atrial V-wave pressure were found in all dogs (mean r = 0.90; range, 0.77–0.99). This relation appeared to be linear in the physiological ranges studied. An example of this relation from one of the dogs is shown in Figure 2.

In the second phase of the experiment, the peak E-wave velocity in individual dogs tended to decrease with increasing left ventricular systolic pressure while left atrial pressure was kept relatively constant (less than 2-mm Hg range in each dog). The mean correlation coefficient for all dogs was −0.79, with a range of −0.61 to −0.98. An
example of this relation from one of the dogs is shown in Figure 3.

In pooled data taken from all 82 experimental stages in all dogs, the peak E-wave velocity correlated modestly but highly significantly with left atrial V wave pressure \((r = 0.58, p < 0.001)\), \(T_L\) \((r = -0.32, p < 0.001)\), and left ventricular end-diastolic pressure \((r = 0.50, p < 0.001)\) (Table 1). Multiple stepwise linear regression analysis was then used to examine simultaneously the relation between the peak E-wave velocity and the following hemodynamic parameters: left atrial V-wave pressure, left ventricular systolic pressure, left ventricular minimal pressure, left ventricular end-diastolic pressure, and \(T_L\). Left atrial V-wave pressure, \(T_L\), and left ventricular systolic pressure, were identified in order of decreasing significance, as predictors of the peak E-wave velocity. The multiple correlation coefficient improved to 0.87 \((p < 0.0001, \text{SD} = 9 \text{ cm/sec})\) compared with the univariate coefficients above (Table 2).

Multiple linear regression analysis of the same three factors (viz, left atrial V-wave pressure, \(T_L\), and left ventricular systolic pressure) in individual dogs yielded high correlations with the peak E-wave velocity. The mean multiple \(r\) value for all dogs was 0.89, with a range of 0.85 to 0.97. Illustrative examples of the effects of left atrial V-wave pressure at constant \(T_L\) and of the effects of \(T_L\) at constant left atrial V-wave pressure on the Doppler transmitral velocity profile are shown in Figures 4 and 5, respectively.

In data pooled from all experimental stages in all dogs, the univariate correlations of the peak E-wave velocity to each of the three hemodynamic factors were substantially improved by selecting for analysis only those stages in which the values of other codeterminant factors fell within relatively narrow ranges. For example, when only those stages with left ventricular systolic pressures of between 90 and 110 mm Hg and \(T_L\) of less than 45 msec were selected for analysis, thus avoiding markedly abnormal values of systolic pressure and \(T_L\), the univariate correlation of peak E-wave velocity to left atrial V-wave pressure improved \((r = 0.83, p < 0.0001, \text{SD} = 9 \text{ cm/sec}, n = 35)\) compared with the univariate correlation obtained with all 82 experimental stages (Figure 6).

Similarly, when only those stages with left atrial V-wave pressures of 14 mm Hg or less were selected for analysis, thus avoiding abnormally high values of left atrial pressure, the correlation coefficient of peak E-wave velocity to \(T_L\) improved to \(-0.54 (p < 0.0001, \text{SD} = 12 \text{ cm/sec}, n = 76)\) compared with the univariate correlation obtained with all experimental stages (Figure 7).

A simple univariate relation between peak E-wave velocity and left ventricular systolic pressure was more difficult to demonstrate. There was no correlation between these two measurements in the pooled data because marked overlap of data points occurred at left ventricular systolic pressures of or less than 100 mm Hg. Only after applying arbitrary thresholds to limit the range of values of other hemodynamic determinants could a significant correlation be found between peak E-wave velocity and left ventricular systolic pressure \((n = 20, r = -0.59, p < 0.007, \text{SD} = 15 \text{ cm/sec})\) for those data points with systolic pressure

\[ y = -0.24x + 88 \]
\[ r = -0.85 \]
\[ p < 0.02 \]
\[ \text{SD} = 4 \text{ cm/sec}, n = 7 \]
Table 1. Univariate Correlations Between Doppler Parameters of Transmural Flow and Hemodynamic Parameters in Data Pooled From All Dogs (n=82)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LV_{ep}_P</th>
<th>LV_{ed}_P</th>
<th>LV_{min}_P</th>
<th>LA_P</th>
<th>T_{L}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak E velocity</td>
<td>r 0.001</td>
<td>0.50</td>
<td>0.23</td>
<td>0.58</td>
<td>-0.32</td>
</tr>
<tr>
<td>p NS</td>
<td>&lt;0.0001</td>
<td>&lt;0.04</td>
<td>&lt;0.0001</td>
<td>&lt;0.004</td>
<td></td>
</tr>
<tr>
<td>E-wave VTI</td>
<td>r -0.13</td>
<td>0.38</td>
<td>0.13</td>
<td>0.46</td>
<td>-0.34</td>
</tr>
<tr>
<td>p NS</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>E-wave deceleration</td>
<td>r 0.04</td>
<td>0.48</td>
<td>0.27</td>
<td>0.53</td>
<td>-0.19</td>
</tr>
<tr>
<td>p NS</td>
<td>&lt;0.0001</td>
<td>&lt;0.01</td>
<td>&lt;0.0001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Peak A velocity</td>
<td>r 0.09</td>
<td>0.45</td>
<td>0.30</td>
<td>0.63</td>
<td>-0.06</td>
</tr>
<tr>
<td>p NS</td>
<td>&lt;0.001</td>
<td>&lt;0.006</td>
<td>&lt;0.0001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>A-wave VTI</td>
<td>r 0.04</td>
<td>0.40</td>
<td>0.26</td>
<td>0.53</td>
<td>-0.09</td>
</tr>
<tr>
<td>p NS</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>&lt;0.0001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Total VTI</td>
<td>r -0.04</td>
<td>0.46</td>
<td>0.22</td>
<td>0.56</td>
<td>-0.28</td>
</tr>
<tr>
<td>p NS</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Peak E:A velocity ratio</td>
<td>r -0.01</td>
<td>-0.05</td>
<td>-0.16</td>
<td>-0.12</td>
<td>-0.35</td>
</tr>
<tr>
<td>A-wave VTI ratio</td>
<td>r 0.17</td>
<td>0.05</td>
<td>0.18</td>
<td>0.06</td>
<td>0.30</td>
</tr>
<tr>
<td>total VTI ratio</td>
<td>r 0.17</td>
<td>0.05</td>
<td>0.18</td>
<td>0.06</td>
<td>0.30</td>
</tr>
<tr>
<td>First third VTI</td>
<td>r -0.01</td>
<td>-0.10</td>
<td>-0.20</td>
<td>-0.16</td>
<td>-0.48</td>
</tr>
<tr>
<td>total VTI ratio</td>
<td>r -0.01</td>
<td>-0.10</td>
<td>-0.20</td>
<td>-0.16</td>
<td>-0.48</td>
</tr>
</tbody>
</table>

**Analyses of Other Doppler Parameters of Filling**

The E-wave velocity-time integral, deceleration rate of the E wave, peak A-wave velocity, A-wave velocity-time integral, peak E-wave velocity, peak A-wave velocity ratio, A-wave velocity-time integral : total velocity-time integral ratio (atrial contribution to filling), and the first third velocity-time integral ratio (the proportion of the total velocity-time integral occurring in the first one third of the diastolic filling period) were individually analyzed to determine their hemodynamic correlates. Univariate correlations with data pooled from all dogs are summarized in Table 1.

Analyses of pooled data with multiple stepwise linear regression are shown in Table 2. The E-wave velocity-time integral and E-wave deceleration rate were similar to the peak E-wave velocity in that both correlated most significantly with left atrial V-wave pressure, followed by T_{L} and left ventricular systolic pressure. The multiple correlation coefficients obtained were similar to those found for the peak E-wave velocity.

The peak A-wave velocity and A-wave velocity-time integral correlated positively with left atrial V-wave pressure and negatively with T_{L}, demonstrating the susceptibility of the A wave to initial filling pressure as well as to relaxation rate, despite both hemodynamic events occurring during early diastole. The effects of T_{L}, however, were relatively weak.

The peak E-wave velocity:peak A-wave velocity ratio and the first third velocity-time integral:total velocity-time integral ratio correlated negatively with T_{L}, while the A-wave velocity-time integral:total
TABLE 2. Results of Multiple Stepwise Linear Regression Analyses Relating Individual Doppler Parameters With Multiple Hemodynamic Factors (n=82)

<table>
<thead>
<tr>
<th>Doppler parameters</th>
<th>Hemodynamic variables selected*</th>
<th>Multiple</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak E-wave velocity</td>
<td>LA V-wave pressure (3.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$T_L$ (-1.1)</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>LV systolic pressure (-0.3)</td>
<td></td>
</tr>
<tr>
<td>E-wave VTI</td>
<td>LA V-wave pressure (0.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$T_L$ (-0.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LV systolic pressure (-0.03)</td>
<td></td>
</tr>
<tr>
<td>E-wave deceleration</td>
<td>LA V-wave pressure (0.54)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$T_L$ (-0.09)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LV systolic pressure (-0.03)</td>
<td></td>
</tr>
<tr>
<td>Peak A-wave velocity</td>
<td>LA V-wave pressure (2.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$T_L$ (-0.6)</td>
<td>0.81</td>
</tr>
<tr>
<td>A-wave VTI</td>
<td>LA V-wave pressure (0.14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$T_L$ (-0.04)</td>
<td>0.74</td>
</tr>
<tr>
<td>Total VTI</td>
<td>LA V-wave pressure (0.50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$T_L$ (-0.16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LV systolic pressure (-0.05)</td>
<td>0.85</td>
</tr>
<tr>
<td>Peak E:A-wave velocity ratio</td>
<td>$T_L$ (-0.02)</td>
<td>0.60</td>
</tr>
<tr>
<td>A-wave VTI: total VTI ratio</td>
<td>$T_L$ (0.003)</td>
<td>0.51</td>
</tr>
<tr>
<td>First third VTI: total VTI ratio</td>
<td>$T_L$ (-0.004)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

$r$, $p$, SD

*Footnote: Hemodynamic variables tested were left atrial V wave pressure, left ventricular systolic pressure, left ventricular minimal pressure, left ventricular end-diastolic pressure and $T_L$.

The variables chosen by stepwise analysis are listed in order of decreasing strength of correlation. Coefficients for each of the hemodynamic factors are shown in parentheses against the factors.

LA, left atrial; LV, left ventricular; $T_L$, time constant of isovolumic relaxation; VTI, velocity-time integral.

velocity-time integral ratio correlated positively with $T_L$. Although the peak E-wave velocity:peak A-wave velocity ratio correlated very weakly with left atrial V-wave pressure by univariate analysis, all three Doppler parameters were independent of left atrial V-wave pressure with multivariate analysis.

Discussion

The results of this study demonstrate several points. The velocity of blood flow across the mitral valve is controlled simultaneously by multiple factors. Therefore, the simple correlation of one Doppler parameter with a single hemodynamic measurement is often poor because of spontaneous variations in the other codeterminant factors. Multivariate analysis, which accounted for the effects of multiple independent variables at the same time, revealed the highly significant influence of these factors on the pattern of transmirtal blood flow. Univariate correlations between the peak E-wave velocity and single hemodynamic measurements were substantially improved when the values of other codeterminant factors were constrained. Stronger multivariate correlations were found within individual dogs compared with correlations obtained with data pooled from all dogs, suggesting that there were important unidentified factors in the pooled data that differed among dogs.

This study is unique in that it is the first to simultaneously relate ventricular loading conditions and diastolic properties to Doppler measurements of transmirtal blood flow. The results demonstrate that left atrial V-wave pressure (the crossover pressure between the left atrium and ventricle), $T_L$, and left ventricular systolic pressure are important codeterminants of the Doppler transmirtal velocity profile. While they confirm a conceptual basis for using Doppler parameters of filling to evaluate left ventricular diastolic function, they also caution that conditions of ventricular preload and to a lesser extent, afterload, must also be carefully considered when these Doppler parameters are used to represent diastolic function.

We have previously reported in patients that a reduction in left atrial pressure by nitroglycerin reduced the peak velocity and velocity-time integral of the E wave and altered the Doppler velocity profile in a way that mimicked a worsening of diastolic function. Others have found similar results with different techniques to alter left atrial pressure, such as lower body negative pressure and balloon inflation in the inferior vena cava. These studies agree with earlier reports in dogs that the peak transmirtal flow rate, measured by electromagnetic flow probes, varied with left atrial pressure. The results of the present study add to this information by demonstrating that the relation between the peak E-wave velocity and crossover pressure is roughly
linear over the entire physiological range of left atrial pressures that were studied and that this relation is shifted by changes in values of $T_L$.

Despite theoretical predictions and empirical practical application, preliminary reports have found disappointingly weak or absent relations in vivo between Doppler filling parameters and hemodynamic properties of diastolic function. Corresponding information in the radionuclide literature is sparse. In a unique study, Magorien et al found a modest inverse correlation ($r = -0.49$, $p$ not given) between the normalized peak filling rate measured by radionuclide ventriculography and $T_L$ in 28 patients with various heart diseases. Using measurements of transmural flow in dogs obtained from electromagnetic flow probes, Ishida et al found a weak correlation ($r = -0.37$, $p < 0.01$) between proportional change in $T_L$ and proportional change in the peak filling rate.

In this study, the peak E-wave velocity (the Doppler equivalent of the peak filling rate) correlated negatively with $T_L$. The univariate correlation in the

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**Figure 4:** Plots of three Doppler transmitral velocity profiles taken from one dog illustrating the effects of changes in left atrial V-wave pressure (LA) at similar time constant of relaxation ($T$). An increase in the peak velocity of the early filling or E wave with an increase in left atrial V-wave pressure is clearly evident. More detailed descriptions of the other effects are given in the text.

**Figure 5:** Plots of three Doppler transmitral velocity profiles taken from one of the dogs, illustrating the effects of changes in the time constant of relaxation ($T$) at constant left atrial V-wave pressure (LA). A decrease in the peak velocity of the early filling or E wave with an increase in the time constant of relaxation is clearly evident. More detailed descriptions of the other effects are given in the text.
FIGURE 6. Plot of univariate correlation of peak E-wave velocity with left atrial V-wave pressure in pooled data from all dogs with only those experimental stages with left ventricular systolic pressures that were not markedly high or low (between 90 and 110 mm Hg) and values of \( T_L \) that were not greatly elevated (<45 msec). Peak E-wave velocities were corrected for interdog differences. Regression line was fitted through the origin. A strongly positive correlation was found between peak E-wave velocity and left atrial V-wave pressure (\( y = 5.11x, r = 0.83, p < 0.0001, SD = 10 \) cm/sec, \( n = 35 \)). Correlation coefficient was improved compared with that obtained with all 82 stages of the pooled data (\( r = 0.58 \)).

Pooled data between the peak E wave velocity and \( T_L \) was slightly lower than those found by Magorien and Ishida. In addition to inherent differences between the peak E-wave velocity and the peak filling rate, the present analysis also differed from the other two in containing much larger numbers of data points and differed from that of Ishida et al in the use of absolute values rather than proportional changes in the variables. When the range of left atrial pressures was reduced, the correlation between the peak E-wave velocity and \( T_L \) improved. By stratifying left atrial pressure into three separate ranges, the inverse linear relation between the peak E-wave velocity and \( T_L \) could be shown to shift upward with increasing crossover pressure and downward with decreasing crossover pressure.

Although \( T_L \) was not altered as a primary hemodynamic endpoint during the experiments, variation in values of \( T_L \) may have occurred for a variety of reasons. An increase in ventricular systolic pressure may have slowed relaxation rate. Previous reports have suggested that \( T_L \) varies directly with left ventricular end-systolic pressure and myocardial fiber length. Muscle twitch experiments have also indicated that an increase in afterload early in systole both delays the onset and slows the rate of relaxation. The changes in \( T_L \) could not always be directly attributed to changes in left ventricular systolic pressure, and other factors must also have contributed to these changes. Although attempts were made to prevent this, spontaneous fluctuations in myocardial temperature, blood gases, and pH may also have altered the rate of relaxation.

The negative relation between left ventricular systolic pressure and the peak velocity of the E wave was relatively weak compared with the more dominant influence of crossover pressure and \( T_L \). This

FIGURE 7. Plot of univariate correlation of peak E-wave velocity with \( T_L \) in pooled data from all dogs with only those experimental stages in which left atrial V-wave pressures were not elevated (≤14 mm Hg). Peak E-wave velocities were corrected for interdog differences. A negative correlation was found between peak E-wave velocity and \( T_L \). Regression line was \( y = -1.16x + 87, r = -0.54, p < 0.0001, SD = 12 \) cm/sec, \( n = 76 \)). Correlation coefficient was improved compared with that obtained with all 82 stages of the pooled data (\( r = -0.32 \)).

FIGURE 8. Plot of univariate correlation of peak E-wave velocity with left atrial V-wave pressure in all stages pooled from all dogs, stratified according to whether \( T_L \) was less than 35 msec (shown by the crosses) or equal to or more than 35 msec (squares). Peak E-wave velocities were corrected for interdog differences. Regression lines were fitted through the origin. Slope of the relation between peak E-wave velocity and left atrial V-wave pressure was shifted downward by higher values of \( T_L \). For \( T_L \leq 35 \) msec, \( y = 5.39x, r = 0.78, p < 0.001, SD = 9 \) cm/sec, \( n = 57 \). For \( T_L \geq 35 \) msec, \( y = 3.76x, r = 0.72, p < 0.001, SD = 13 \) cm/sec, \( n = 25 \).
The relation was completely obscured in the pooled data when univariate analysis was used and was recognized only after the effects of both crossover pressure and TL were removed by stepwise analysis. In individual dogs, this relation was evident only when experimental stages with similar left atrial pressures were selected for analysis. Similarly, in pooled data, the univariate relation between left ventricular systolic pressure and the peak E-wave velocity could be demonstrated only after values of crossover pressure and TL were restricted to narrower limits.

The selection of left ventricular systolic pressure by stepwise multiple regression analysis after TL had been already selected suggested that left ventricular systolic pressure may have exerted its effects on the peak E-wave velocity through mechanisms other than TL alone. It is possible that the increase in aortic diastolic pressure that necessarily accompanied the increase in left ventricular systolic pressure increased coronary turgor and, hence, ventricular stiffness in diastole.25

Data analysis in the present study concentrated primarily on the peak velocity of the E wave, as this parameter is more easily understood from basic hydrodynamic principles and, further, is the Doppler equivalent of the peak filling rate, which is used traditionally by other imaging techniques as the primary index of diastolic function.4,5 Other Doppler characteristics of the E wave, such as the velocity-time integral and the deceleration rate, were similar to the peak E-wave velocity in correlating positively with crossover pressure and negatively with TL.

Unlike our previous findings and others,17-19 the peak velocity and velocity-time integral of the A wave correlated significantly with the crossover pressure. Although these Doppler and hemodynamic events are not simultaneous, a change in the crossover pressure produced a directionally similar change in left atrial pressure just before atrial contraction. Through the operation of Starling's Law, a decrease in left atrial pressure and volume may be expected to reduce the peak velocity of the A wave.26 The discrepancy between the current findings and those observed previously in patients17-19 may be explained by the large changes in left atrial pressure in these dogs, compared with the relatively small changes in the patients.

Because of the dependence of the A-wave velocities on left atrial pressure, the peak E-wave velocity:peak A-wave velocity ratio was relatively independent of the crossover pressure but corre-
lated modestly with $T_L$. Similarly, the A-wave velocity-time integral:total velocity-time integral ratio and the first third velocity-time integral:total velocity-time integral ratio were relatively independent of the crossover pressure but correlated significantly with $T_L$ in the multivariate analysis. These results suggest that Doppler parameters that are based on proportions within the Doppler velocity profile rather than absolute values are less dependent on filling pressure and may, therefore, be more specific indexes of ventricular diastolic properties. The correlations of these parameters with $T_L$, however, were weak, and the clinical implications of these findings require further evaluation.

Theoretical Considerations

The factors that determine the velocity of blood flow across the mitral valve can be more clearly understood by examining the basic hydrodynamic principles that govern this process. The velocity of blood flow across the mitral valve is determined principally by the pressure gradient across the valve. The process is described by the Bernoulli equation, which relates pressure gradient to convective acceleration, flow acceleration, and viscous friction. Theoretical considerations predict that the velocity of transmirtal blood flow during the early filling phase of the ventricle depends on the complex and continuous interaction of multiple factors, which include the pressure of the left atrium and left ventricle at mitral valve opening, left ventricular compliance and relaxation rate, left atrial compliance, and mitral orifice area. The situation during the atrial contraction phase is more complex still. Passive ventricular compliance, atrial preload at the onset of contraction, atrial contractility, and mitral orifice area are expected to exert important effects here.

The results concerning the peak E-wave velocity in this in vivo study agree with computer models of early left ventricular filling, which predict a positive correlation of the peak transmitral flow rate with crossover pressure and a negative correlation with $T_L$. Unlike the curvilinear relation between peak E-wave velocity (or peak filling rate) and crossover pressure in the computer models, however, the relation in vivo appeared linear.

Limitations of the Study

Several limitations of the experimental model should be discussed. The peak V-wave of the left atrial pressure trace was used to represent the pressure at mitral valve opening. Although the crossover point between left atrial and left ventricular pressures would have been preferred as an index of the pressure at mitral valve opening, the recording of atrial and ventricular pressures on separate tracks of the strip chart recorder made its derivation difficult and unreliable. In the absence of mitral regurgitation, passive atrial filling from the pulmonary veins produces the V wave of the atrial pressure trace. When left ventricular pressure decreases below left atrial pressure during ventricular relaxation, the mitral valve opens, ventricular filling and atrial emptying are initiated, and left atrial pressure falls (the Y descent). Therefore, the peak of the V wave may be expected reasonably to reflect the pressure at which the mitral valve opens. As alterations in left atrial pressure were relatively large in these experiments, we do not feel that this limitation in our methodology significantly affected the overall relations that were observed.

Unlike normal pulmonary artery flow, which is pulsatile, roller pump flow into the pulmonary artery was continuous and therefore nonphysiological. The effects of this anomaly were probably minimal because the pattern of pulmonary venous flow is related primarily to events in the left atrium rather than to those in the pulmonary artery. Also, normal pulmonary capillary flow is minimally pulsatile or nonpulsatile so that any differences in the phasic pattern of pulmonary artery flow are minimized by the time flow reaches the capillaries. The normal phasic pattern of left atrial pressure in this study supports the above contentions.

The dogs were studied with the chest and pericardium open. This experimental model was deliberately chosen to allow strict control of hemodynamic conditions and optimal acquisition of echocardiographic data. Although an intact pericardium may influence the diastolic function of the ventricle, this effect is small with a normal pericardium. Whether the chest and pericardium are open or closed should not greatly alter the observed relations between the pattern of ventricular filling of the ventricle and diastolic properties and loading conditions because the effects of the chest and pericardium are themselves mediated through alterations in the diastolic properties of the ventricle. Nevertheless, it must be recognized that alterations in diastolic function through the open-chest condition and changes in ventricular interaction may alter the exact magnitude of these relations compared with the intact conscious animal. Furthermore, the data demonstrated in this study may not strictly represent the situation seen in diseased hearts, and care must be taken not to readily extrapolate these findings to those other situations.

A limitation of the data analysis was that it was not possible to evaluate all the potential factors that determined the velocity of transmirtal blood flow. For example, the compliance of the left ventricle and left atrium were not examined. For the purpose of this study, we were interested primarily in the influence of loading conditions and relaxation on the early filling velocities of the ventricle. The failure to consider the other possible determinants is probably an important reason why the multivariate correlations between the Doppler and hemodynamic measurements were not stronger. To try to account at least partly for unknown interdog differences, dog weight was introduced as an additional independent variable in all multiple regression analyses of pooled
data, but this maneuver failed to improve these correlations. It should be realized that this limitation does not negate the validity of the relations that were found nor any of the conclusions of this study.

Conclusion

The transmitted flow velocity profile is determined by multiple factors, which include loading conditions (filling pressure and, to a lesser extent, systolic pressure), as well as ventricular relaxation rate. The simple correlation of one Doppler parameter of filling with a single hemodynamic factor is often obscured by simultaneous variations in these multiple factors. The demonstration of a relation in vivo between Doppler parameters of filling and ventricular relaxation rate provides a basis for using Doppler filling parameters to evaluate diastolic function. More important, however, the results of this study urge the cautious use of these Doppler parameters for evaluating diastolic function because other factors are involved that relate to the loading conditions of the ventricle.

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