Left ventricular filling dynamics: influence of left ventricular relaxation and left atrial pressure

YOSHIo IISHIDA, M.D., JAY S. MEISNER, PH.D., KATSUHIKO TSUIJOA, M.D., JOSE I. GALLOW, M.D., CHAIM YORAN, M.D., ROBERT W. M. FRATER, M.D., AND EDWARD L. YELLIN, PH.D.

ABSTRACT Peak rapid filling rate (PRFR) is often used clinically as an index of left ventricular relaxation, i.e., of early diastolic function. This study tests the hypothesis that early filling rate is a function of the atroioventricular pressure difference and hence is influenced by the left atrial pressure as well as by the rate of left ventricular relaxation. As indexes, we chose the left atrial pressure at the atroioventricular pressure crossover (PCO), and the time constant (T) of an assumed exponential decline in left ventricular pressure. We accurately determined the magnitude and timing of filling parameters in conscious dogs by direct measurement of phasic mitral flow (electromagnetically) and high-fidelity chamber pressures. To obtain a diverse hemodynamic data base, loading conditions were changed by infusions of volume and angiotensin II. The latter was administered to produce a change in left ventricular pressure of less than 35% (A-1) or a change in peak left ventricular pressure of greater than 35% (A-2). PRFR increased with volume loading, was unchanged with A-1, and was decreased with A-2; T and PCO increased in all three groups (p < .005 for all changes). PRFR correlated strongly with the diastolic atroioventricular pressure difference at the time of PRFR (r = .899, p < .001) and weakly with both T (r = .669, p < .01) and PCO (r = .601, p < .001). The correlation improved significantly when T and PCO were both included in the multivariate regression (r = .797, p < .0001). PRFR is thus determined by both the left atrial pressure and the left ventricular relaxation rate and should be used with caution as an index of left ventricular diastolic function.


RELAXATION ABNORMALITIES are one of the earliest manifestations of cardiac dysfunction and frequently precede systolic dysfunction in many disease states. Early filling function has been evaluated in a variety of diseases, e.g., coronary artery disease, hypertrophic cardiomyopathy, hypertensive heart disease, aortic valve disease, and congestive cardiomyopathy. Since its introduction by Weiss et al., the time constant (T) of an assumed exponential isovolumetric pressure decline has been accepted as a good indicator of early cardiac function and is now frequently measured during cardiac catheterization to evaluate left ventricular relaxation. Because this direct index of isovolumetric relaxation requires an invasive measurement of left ventricular pressure, many investigators assume that left ventricular relaxation can be assessed indirectly by estimating early diastolic filling. For example, peak rapid filling rate (PRFR) has been derived from radionuclide angiography, peak rates of chamber or wall dimension change have been measured from M mode echocardiograms, and peak rapid filling velocity has been determined with Doppler ultrasound.

These approaches are based on the principle that the falling ventricular pressure contributes to the generation of the atrioventricular pressure difference that accelerates the blood across the mitral valve. Fioretti et al. and Magorien et al. have shown a statistically significant, but weak, correlation between the time constant of relaxation and the rapid filling rate. Further clarification of the physiology of transmural blood flow, based on invasive animal experiments, would be helpful in the interpretation of data obtained by noninvasive means in the clinical setting.

We have shown that the transmural pressure-flow relationship can be described qualitatively by the following equation of motion:

$$\Delta P = (A)d(MiF)/dt + (B)(MiF)$$
where $\Delta P$ is the instantaneous atrioventricular pressure difference, $MiF$ is mitral flow, and (A) and (B) are inertial and resistive coefficients, respectively. At the time of peak flow, the rate of change of flow, $d(MiF)/dt$, is zero, and therefore $\Delta P$, i.e., the atrioventricular pressure difference at the time of peak flow $[(LAP - LVP)_{\text{max}}$, where LAP is left atrial pressure and LVP is left ventricular pressure], is proportional to the maximum flow rate, i.e., to the PRFR. We may thus speculate that factors other than the left ventricular relaxation rate, in particular the left atrial pressure at the time of mitral valve opening (pressure crossover or PCO), must contribute to early filling dynamics. (PCO was chosen as an index of the contribution of left atrial pressure to the gradient because it is frequently estimated by a wedge pressure, and it can also be estimated from an angiogram.) This study was designed to analyze early filling dynamics in the conscious dog, focusing on the role of left ventricular relaxation and left atrial pressure. The pressure-flow relationships were varied by changing the loading conditions on the heart.

To determine definitively the magnitude and timing of the PRFR, we used the highly invasive, but highly accurate, method of electromagnetic measurement of transmitral flow. To analyze the effect of changes in one parameter when all other parameters were held constant (an approach that is difficult if not impossible in the conscious dog), we have included as an Appendix a series of computational studies using a lumped-parameter electric analog of early filling dynamics.

**Methods**

**Animal preparation.** Eight large mongrel dogs, 25 to 30 kg, were anesthetized with sodium pentobarbital (30 mg/kg iv) and artificially ventilated with a mixture of room air and oxygen. After a left thoracotomy in the fifth intercostal space under sterile conditions, the pericardium was opened and the heart was supported in a pericardial cradle. During cardiopulmonary bypass, the left atrium was opened at the appendage and a circular electromagnetic flow probe (Carolina Medical Electronics) with a Teflon sewing ring was sutured to the mitral annulus with special care taken to avoid interference with cusps and ring motion, as previously described. High-fidelity micromanometers (Koenigsberg P-6.5) were inserted into the left ventricle and atrium via the apex and appendage, respectively. After the chest was closed, the wires and connectors were exteriorized in the intrascapular region. The dogs were permitted to recover for a minimum of 1 week and were trained to lie quietly on the experimental table. Antibiotics, analgesics, electrolytes, and anticoagulants were administered as required.

Hemodynamic data and the electrocardiogram were recorded on an oscillographic recorder (Electronics for Medicine DR-12) at a paper speed of 100 mm/sec. The rate of rise of left ventricular pressure ($dP/dt$) and the phonocardiogram were derived from the micromanometer signal. Phasic mitral flow was measured with a square-wave electromagnetic flowmeter (Carolina Medical Electronics 501). Zero level for mitral flow was determined during systole and long diastoles (figure 1). Both pressures were set for equal sensitivity and were adjusted to a common baseline by matching them during long diastoles (figure 1). Pressure zero was assumed to be at minimum left ventricular pressure at end-inspiration in dogs in the resting state at the onset of the study. Thus, although the amplitude of the pressures may have slightly in error, the atrioventricular pressure difference was accurate, and the purpose of this study was not compromised.

**Protocol.** Experiments were performed at least 1 week postoperatively while the unsedated, or mildly sedated (approximately 4 mg morphine sc), dogs were resting quietly on the table. The following interventions were chosen to change left ventricular relaxation rate and left atrial pressure by changing left ventricular loading conditions: (1) Volume loading was accomplished with 200 to 400 ml of normal saline that was rapidly infused (approximately 50 ml/min) to increase the end-diastolic pressure to approximately 13 mm Hg. (2) Pressure loading was induced with 2.3 to 9.6 $\mu$g angiotensin II injected as a bolus. The initial injection was adjusted to produce an increase of less than 35% in peak left ventricular pressure (A-1). After return to a new control hemodynamic state, the injected dose was increased to produce a greater than 35% increase in peak left ventricular pressure (A-2).

**Data processing and analysis.** The oscillographic records were digitized and analyzed with a sonic digitizer (Science Instruments, Palo Alto, Calif.).

**FIGURE 1.** Oscillographic record from a conscious dog illustrating the hemodynamic effects of volume loading (VL) on early left ventricular filling dynamics, and defining the diastolic parameters derived from the measurement of phasic transmitral flow (MiF), left ventricular pressure (LVP), and left atrial pressure (LAP). DFP = diastolic filling period from atrioventricular PCO to cessation of MiF; ECG = lead II electrocardiogram; $LVP_{\text{min}}$ = minimum LVP; $LVEDP$ = left ventricular end-diastolic pressure; PCG = intracardiac phonocardiogram derived from micromanometer. Asterisk and vertical line through $LVP_{\text{min}}$ indicate atrioventricular pressure difference. (LAP-LVP)$_{\text{max}}$, at time of PRFR. Rate of left ventricular relaxation is calculated from the time constant (T) of an assumed exponential fall in LVP from minimum $dP/dt$ to PCO (the isovolumetric period). After volume infusion, peak LVP increased from 121 to 135 mm Hg, $LVEDP$ increased from 6 to 16 mm Hg, and RR interval decreased from 598 to 534 msec. Despite an increase in T from 28 to 32 msec, PRFR increased from 178 to 220 ml/sec associated with an increase in (LAP-LVP)$_{\text{max}}$ from 6 to 8 mm Hg.
Accessories Corp. GP-7) coupled to a microcomputer (IBM-PC). Figure 1, left, illustrates a typical control cardiac cycle and the measured parameters. The time course of the fall in left ventricular pressure from minimum \( dP/\text{d} t \) to the atrioventricular PCO, i.e., the time of mitral valve opening, was characterized by the time constant \( T \) of an assumed exponential decay to zero pressure, \( P = P_0 \exp(-t/T) \). PRFR, atrioventricular pressure difference at the time of PRFR \( (LAP-LVP)_{\text{max}} \), time from minimum \( dP/\text{d} t \) to PRFR (t-PRFR), filling volume to PRFR (FV-PRFR), and total filling volume (FV) were determined from the digitized mitral flow curve (figure 1).

One control cycle and one intervention cycle, each at end-inspiration, were analyzed for each intervention. In some cases the same intervention was performed in the same dog on different days, and not every intervention provided data suitable for analysis in each dog. To partition out variance due to differing responses among dogs, and due to the fact that there was more than one data point for some dogs, multiple linear regression was performed with \( n - 1 \) dummy variables, where \( n \) equals the number of dogs.

Because the value of the resistive coefficient \( B \) in the equation of motion is different for each dog, we used the ratios of paired data, intervention divided by control \( i/c \), henceforth called normalized values, to eliminate interindividual differences in mitral valve impedance. This approach also removed possible errors in flow probe calibration. For example, \( \text{PRFR} i/c \) was correlated with \( (LAP-LVP)_{\text{max}} i/c \). Control and intervention data are presented as mean \( \pm \) SD and were tested for significant changes by paired \( t \) test. Changes in data and correlation coefficients were accepted as significant at the \( p < .05 \) level.

**Results**

**Effect of augmented ventricular loading on early filling dynamics**

*Increased blood volume.* Representative original oscillographic records illustrating the hemodynamic effects of volume infusion are shown in figure 1. Peak left ventricular pressure, left ventricular end-diastolic pressure, and left atrial pressure all increased substantially, as did \( T \) and heart rate. Despite the slowing of relaxation, PRFR increased in association with the increase in the atrioventricular pressure difference. This was due to an increase in left atrial pressure at the moment of mitral valve opening (PCO), which was larger than the small increase in minimum left ventricular pressure.

*Increased afterload.* Typical responses to angiotensin II injections are shown in figures 2 and 3. With moderate increases in peak left ventricular pressure and left ventricular end-diastolic pressure (figure 2), \( T \) increased, but PRFR did not change because minimum left ventricular pressure and PCO increased equally, thereby maintaining the atrioventricular pressure difference. With large increases in peak left ventricular pressure and left ventricular end-diastolic pressure (figure 3), PRFR decreased significantly in association with a decrease in the atrioventricular pressure difference that was caused by minimum left ventricular pres- sure increasing more than PCO. The increase in \( T \) was larger in this case than in the former. A reflex decrease in heart rate in response to the elevated systemic pressure was observed in both cases.

**FIGURE 2.** Oscillographic records illustrating the effect of a moderate increase in afterload induced by angiotensin II injection on left ventricular early filling dynamics. Peak left ventricular pressure (LVP) increased from 142 to 159 mm Hg, left ventricular end-diastolic pressure (LVEDP) increased from 11 to 13 mm Hg, and RR interval increased from 572 to 642 msec. Despite an increase in \( T \) (27 to 36 msec), PRFR and \( (LAP-LVP)_{\text{max}} \) showed no significant changes. Remaining abbreviations are as in figure 1.

**FIGURE 3.** Oscillographic records illustrating the effect of a large increase in afterload induced by angiotensin II injection on left ventricular filling dynamics. Peak left ventricular pressure increased from 136 to 204 mm Hg, left ventricular end-diastolic pressure (LVEDP) increased from 12 to 22 mm Hg, and RR interval increased from 602 to 756 msec. \( T \) greatly increased from 32 to 42 msec and PRFR decreased from 160 to 127 ml/sec associated with a decrease in \( (LAP-LVP)_{\text{max}} \) (9 to 6 mm Hg). Remaining abbreviations are as in figure 1.
**TABLE 1**

Hemodynamic data before and after interventions

<table>
<thead>
<tr>
<th></th>
<th>VL</th>
<th></th>
<th>A-1</th>
<th></th>
<th>A-2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C (n = 24)</td>
<td>I (n = 24)</td>
<td>C (n = 22)</td>
<td>I (n = 22)</td>
<td>C (n = 12)</td>
<td>I (n = 12)</td>
</tr>
<tr>
<td>RR (msec)</td>
<td>551 ± 94</td>
<td>462 ± 75&lt;sup&gt;a&lt;/sup&gt;</td>
<td>464 ± 73</td>
<td>614 ± 188&lt;sup&gt;a&lt;/sup&gt;</td>
<td>548 ± 95</td>
<td>761 ± 239&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>FV (ml)</td>
<td>31.2 ± 4.0</td>
<td>33.9 ± 3.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>27.3 ± 5.6</td>
<td>27.7 ± 5.7</td>
<td>31.8 ± 4.1</td>
<td>24.5 ± 2.0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PLVP (mm Hg)</td>
<td>118 ± 10</td>
<td>127 ± 11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>122 ± 12</td>
<td>150 ± 15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>124 ± 13</td>
<td>181 ± 15&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>9.4 ± 3.4</td>
<td>13.3 ± 4.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.7 ± 3.4</td>
<td>17.0 ± 4.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11.3 ± 1.9</td>
<td>19.3 ± 2.0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>dP/dt max (mm Hg/sec)</td>
<td>2087 ± 196</td>
<td>2339 ± 381&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2343 ± 557</td>
<td>2148 ± 490&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2237 ± 291</td>
<td>2053 ± 354&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>dP/dt min (mm Hg/sec)</td>
<td>1824 ± 344</td>
<td>1985 ± 507&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2002 ± 417</td>
<td>2291 ± 404&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2220 ± 310</td>
<td>2335 ± 199</td>
</tr>
<tr>
<td>IVRP (msec)</td>
<td>40.7 ± 7.9</td>
<td>34.9 ± 10.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>42.5 ± 11</td>
<td>50 ± 14&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44.8 ± 9.5</td>
<td>66.5 ± 11.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>MLAP (mm Hg)</td>
<td>8.7 ± 1.7</td>
<td>16.5 ± 5.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.7 ± 2.5</td>
<td>14.7 ± 4.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.2 ± 1.4</td>
<td>18.2 ± 2.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>(LAP - LVpmax (mm Hg)</td>
<td>7.7 ± 1.6</td>
<td>12.1 ± 3.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.5 ± 1.5</td>
<td>7.0 ± 1.6</td>
<td>9.6 ± 1.7</td>
<td>7.4 ± 1.5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>LVpmin (mm Hg)</td>
<td>2.6 ± 0.7</td>
<td>5.1 ± 3.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.9 ± 2.8</td>
<td>7.3 ± 2.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.1 ± 0.9</td>
<td>10.5 ± 2.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>T (msec)</td>
<td>25.3 ± 2.7</td>
<td>28.0 ± 4.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>25.3 ± 4.8</td>
<td>31.6 ± 5.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28.7 ± 4.3</td>
<td>39.0 ± 5.1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PRF (ml/sec)</td>
<td>11.7 ± 1.5</td>
<td>21.5 ± 6.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.1 ± 3.8</td>
<td>20.1 ± 7.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14.6 ± 2.5</td>
<td>21.9 ± 2.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>t-PRFR (msec)</td>
<td>157 ± 15</td>
<td>194 ± 18&lt;sup&gt;a&lt;/sup&gt;</td>
<td>160 ± 33</td>
<td>158 ± 40</td>
<td>161 ± 20</td>
<td>137 ± 19&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PCO-PFPR (msec)</td>
<td>84 ± 10</td>
<td>77.6 ± 8.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>87.4 ± 12.2</td>
<td>92.5 ± 14.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>90.6 ± 8.6</td>
<td>106 ± 10.1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>FV-PFPR (ml)</td>
<td>4.7 ± 0.7</td>
<td>5.9 ± 1.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.1 ± 1.1</td>
<td>4.7 ± 1.1</td>
<td>5.4 ± 0.7</td>
<td>3.8 ± 0.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

- n = number of cycles analyzed; VL = volume loading; C = control; I = intervention; RR = RR interval on electrocardiogram; PLVP = peak left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; dP/dt max = maximum dP/dt; dP/dt min = minimum dP/dt; IVRP = isovolumetric relaxation period; MLAP = mean left atrial pressure; LVP min = minimum left ventricular pressure.

- <sup>a</sup>p < .001; <sup>b</sup>p < .01; <sup>c</sup>p < .02, by paired t test.

**Mean hemodynamic data.** The mean hemodynamic data before and after the interventions are summarized in table 1 and illustrated in figure 4. In volume infusion studies, T increased significantly (11%), despite an increase in heart rate and probable increase in contractility due to parasympathetic withdrawal. Minimum left ventricular pressure increased more than PCO, leading to a significant increase in the maximum atrio-

**FIGURE 4.** PRFR, T, and PCO before and after the intervention in volume loading (VL). A-1, and A-2 groups. Despite increases in T in all three groups, PRFR increased in the VL group, remained the same after A-1, and decreased after A-2. The change in T was different among the groups, but the change in PCO was almost the same in each group.
ventricular pressure difference (57%). Thus, PRFR increased 24%, FV-PRFR increased 26%, and t-PRFR decreased 8%.

Because preliminary analysis indicated that the hemodynamic effect of increased afterload on early filling dynamics depended on the degree of the increase, as demonstrated in figures 2 and 3, we analyzed the responses to angiotensin by dividing the results into two groups: A-1 (peak left ventricular pressure increase < 35%) and A-2 (peak left ventricular pressure increase > 35%). The increased afterload caused a reflex decrease in heart rate and probably a decrease in contractility, because maximum dP/dt decreased despite the increase in peak left ventricular pressure. T increased significantly in both groups, but it was more pronounced after A-2 (36% vs 25%), reflecting the increase in ventricular load and decrease in contractility. Minimum left ventricular pressure increased in both groups, but the change was substantially greater after A-2. Because PCO increased equally in both groups, the maximum atrioventricular pressure difference and PRFR were maintained after A-1, but decreased after A-2. FV-PRFR followed the same pattern as PRFR in both groups, and t-PRFR increased in both groups (6% and 17%).

Thus, despite a prolongation of relaxation (increased T) under all three loading conditions, early filling dynamics (PRFR) showed different changes (table 1), indicating that PRFR is not solely determined by the left ventricular relaxation rate (T). Because left atrial pressure at the onset of filling (PCO) increased in all three groups, it may be postulated that the increase in PCO minimized or overcame the effect of slowed relaxation on PRFR.

**Determinants of PRFR.** As shown in figure 5, when the data were analyzed with the use of the normalized values (i/c), PRFR correlated strongly with (LAP-LVP)max (r = .899, p < .0001), thus proving the validity of our conceptual approach (see Methods). This excellent correlation also means that PRFR should be determined by the factors that determine the atrioventricular pressure difference at peak mitral flow.

The major determinants of the atrioventricular pressure difference during early diastole should be the rate and duration of left ventricular relaxation, passive left ventricular compliance, the end-systolic volume (characterized by minimum left ventricular pressure), the left atrial pressure at the onset of mitral inflow, and the compliance of the left atrium (determining the rate of fall of left atrial pressure). In our effort to make this study relevant to current clinical practices, we then analyzed the relationships between PRFR, T, and PCO using the statistical methods described above. There were weak but statistically significant correlations between PRFR and T (r = .369, p < .01) and between PRFR and PCO (r = .601, p < .001). When the normalized data were analyzed with both T and PCO in the regression against PRFR, the correlation improved considerably (r = .797, p < .0001). These results strongly suggest that PRFR is not solely determined by the left ventricular relaxation rate but that it is also influenced by the left atrial pressure at the onset of flow.

**t-PRFR and early filling volume.** Figure 6 shows the correlation between the normalized t-PRFR and T. There is a statistically significant and moderately strong correlation (r = .560, p < .001). Since t-PRFR encompasses the duration of isovolumetric relaxation as well as the time from onset of filling to PRFR, the large variance in the data is not surprising. When measured from the onset of filling (PCO-PRFR), the t-PRFR does not change with changes in loading conditions (table 1), and hence it is not a meaningful index of early filling dynamics.

It is also interesting to note that the early filling volume (FV-PRFR) correlated highly with PRFR (r = .801, p < .001) (figure 7), and that the average FV-PRFR/FV calculated from all the data (control and intervention) was 17.5 ± 4.2%, with no apparent differences among the six groups. Thus, approximately 18% of the FV enters the ventricle before peak flow is reached, and it varies little under hemodynamic conditions such as those used in this study.
FIGURE 6. Scatter plot showing the relationship between normalized t-PRFR and T. The correlation is significant and stronger than that between PRFR and T. VL equals volume loading.

Discussion

The measurement of early filling by contrast and radionuclide angiography and by ultrasonography has been used for the detection of diastolic dysfunction in patients with various heart diseases. Based on experimental and clinical evidence that the impairment of left ventricular relaxation may occur before systolic dysfunction in many disease states, and based on the assumption that the rate of ventricular relaxation is an important determinant of early diastolic filling, many clinicians have attempted to determine early abnormalities in left ventricular relaxation by estimating early filling function, and in particular, by using the PRFR as an index.

The loading interventions used in this study, increased preload and afterload, are known to change the rate of left ventricular relaxation in ways that are consistent with the results of this study (see Brutsaert et al. for reviews). However, we do not know what these interventions would do to diastolic function in the diseased heart, nor do we know how changes in the rate of isovolumetric relaxation will affect diastolic events after the onset of filling. Alterations in relaxation in patients with coronary artery disease, for example, have been shown to be accompanied by decreases in passive left ventricular compliance, presumably due to incomplete deactivation.

It is physically, indeed intuitively, clear from first principles that the transmitral flow rate is determined by the driving pressure difference and the impedance to flow. At the moment of peak flow there are no accelerative forces \( \frac{d(i/MF)}{dt} = 0 \) and the flow rate, i.e., the PRFR is proportional to the atrioventricular pressure difference at that time (figure 5). The sensitivity of the PRFR as an index of diastolic function is thus determined by the interaction of all the factors that determine the driving pressure gradient. Clearly, the rate of pressure fall will influence the rate at which the pressure difference is established. But the pressure difference is also determined by the magnitude of the left atrial pressure at the time of mitral valve opening and its fall as the atrium empties, and by the left ven-

FIGURE 7. Scatter plot showing the relationship between normalized FV-PRFR and PRFR. The correlation is strong; early filling rate is a good indicator of early filling volume. The insert shows the average percent filling volume to the time of peak flow (FV-PRFR/FV). VL equals volume loading.
tricular pressure minimum which is, in turn, determined by the end-systolic volume, the rate and duration of relaxation, and the passive viscoelastic properties of the myocardium during filling. Once the mitral valve opens and filling starts, the fall in ventricular pressure as well as the fall in atrial pressure are determined by the elastic properties of the chambers. The process of filling then interacts with the driving pressure gradient and none of the parameters discussed above are independent of each other.

Given such a complex situation, it is no wonder that the simple correlations of PRFR with T, and of PRFR with PCO, although statistically significant, have weak correlation coefficients (see also Fioretti et al. and Magorien et al.). Multiple regression of PRFR with T and PCO improved the goodness of fit (r^2 = .635), thereby demonstrating the combined effects of relaxation and filling pressure, but it also revealed that other factors must be considered.

One unknown, but probably small, source of variance is in measurement error: determining flow baseline, matching pressure baselines at relatively short diastolic filling periods, and the calculation of T from a rapidly changing waveform. The use of a simple exponential to calculate T may also introduce some variability. We and others have shown that isovolumetric left ventricular pressure does not decay exponentially. But we have also shown that the calculation of T based on the assumption of monoexponential decay to a zero asymptote is a reasonable approach to characterizing the rate of pressure fall. In particular, when the same method is used for all the calculations the effect is small and the results consistent.

Another source of variance is the use of the PCO as an index of maximum atrioventricular pressure difference. We have chosen PCO because it is a more clearly defined point than (LAP-LVP)max, and less subject to artifact, particularly in the clinical setting. Furthermore, the PCO can be estimated from the time at which unopacified blood enters the ventricle during left ventricular cineangiography with simultaneous measurement of left ventricular pressure.

This study was designed to change the loading conditions on the ventricle in ways that change the determinants of early filling and that also mimic changes occurring in cardiac disease. To our knowledge, except for a preliminary report from this laboratory, this is the first time this problem has been attacked by directly measuring phasic transmural blood flow and chamber pressures in the conscious dog.

In a narrow sense, we have demonstrated conclusively that the PRFR is determined by the driving atrioventricular pressure difference (figure 5), that changes in left atrial pressure can minimize or overcome the effects on early diastolic filling of changes in the rate of left ventricular relaxation, and that changes in the atrioventricular driving pressure difference can be estimated by changes in the left atrial pressure at mitral valve opening. We have also shown that the t-PRFR is a better predictor of relaxation rate (T) than the PRFR (r = .560 vs r = .369), and that the PRFR is a good predictor of early filling volume (figure 7).

In its broadest sense, this study clarifies the dynamic interaction of cardiac properties that are known to be affected by disease, i.e., rate of ventricular relaxation and left atrial pressure, and demonstrates their effects on the phasic waveforms of pressure and flow across the mitral valve (figures 1 to 3). We trust that these highly invasive studies from the experimental animal laboratory will clarify the physiologic dynamics of ventricular filling and thereby facilitate the interpretation of results obtained with less invasive methods in the clinical setting.

Despite the fact that we have demonstrated the interaction of relaxation and filling pressure in determining early filling dynamics, it is clear from the variance in the data that not all factors have been considered. Obviously, in the conscious dog it is not possible to control all parameters but one, and to study the effect of that one variable. Furthermore, physical properties, e.g., atrial compliance, may vary with changes in loading conditions, and we have not been able to consider such effects in this study. To solve these problems and to further clarify the physiology of early filling dynamics, we offer the following computational model as an Appendix.

Appendix

To understand the physiologic mechanisms involved in the dual-dependence of PRFR on T and PCO, we developed a lumped-parameter electric analog of the pulmonary bed–left atrium–left ventricle (figure 8). Since only diastole is modeled, there is no ventricular outflow tract, and atrial/ventricular systoles are not simulated. The components chosen were thought to be the minimum number required for the purpose of modeling early diastolic dynamics. Definitions of component values and their sources are given in table 2. Stepwise differentiation at 1 msec intervals was used to solve the following equations derived from figure 8:

\[
\frac{d\text{MiF}}{dt} = \frac{(P_{LA} - P_{LV} - R_m \cdot \text{MiF}^2)}{L_m}
\]

\[
P_f = \left(\frac{P_r - P_{LA}}{R_p}\right)
\]

\[
\frac{dV_f}{dt} = -P_f
\]

\[
\frac{dV_{LA}}{dt} = P_f - \text{MiF}
\]

\[
\frac{dV_{LV}}{dt} = \text{MiF}
\]

\[
P_{LV} = E_{LV \text{ max}} \cdot e^{rT} \cdot (V_{LV} - V_{LVO}) + A e^{rT} \cdot V_{LV} + R_m \cdot \text{MiF}
\]
Pp = PlA · (VLA - LAO)

The dependence of PRFR on T, PCO, and atrial compliance is illustrated in figure 9, where PRFR is plotted versus PCO for a large range of values of T. Atrial elastance is low in the top panel, normal in the middle panel, and high in the bottom panel. These were the only parameters varied in the simulation — all others remained at their normal values (table 2). This analysis verified that the primary determinants of PFR are T and PCO. However, left atrial elastance is also influential because of its effect on atrial reservoir function.27, 28

When elastance is low, left atrial pressure falls more slowly as the atrium empties. This results in a larger peak pressure gradient for filling, Pp, and a larger PRFR. Conversely, when elastance is high, left atrial pressure falls quickly with

**TABLE 2**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF</td>
<td>Pulmonary vein flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MiF</td>
<td>Mitral flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pp</td>
<td>Pulmonary pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PlA</td>
<td>LA pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pp</td>
<td>LV pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Pulmonary elastance</td>
<td>0.2</td>
<td>mm Hg/ml</td>
<td>29</td>
</tr>
<tr>
<td>R</td>
<td>Pulmonary resistance</td>
<td>0.2</td>
<td>mm Hg/ml/sec</td>
<td>30</td>
</tr>
<tr>
<td>ElA</td>
<td>LA elastance</td>
<td>0.7</td>
<td>mm Hg/ml</td>
<td>28</td>
</tr>
<tr>
<td>VLAo</td>
<td>LA unstrained volume</td>
<td>10.0</td>
<td>ml</td>
<td>28</td>
</tr>
<tr>
<td>A</td>
<td>LV passive elastance coefficient</td>
<td>0.4</td>
<td>mm Hg</td>
<td>31</td>
</tr>
<tr>
<td>α</td>
<td>LV passive elastance exponent</td>
<td>0.1</td>
<td>ml</td>
<td>31</td>
</tr>
<tr>
<td>RLV</td>
<td>LV wall viscosity</td>
<td>0.01</td>
<td>mm Hg/ml/sec</td>
<td>31</td>
</tr>
<tr>
<td>Emax</td>
<td>LV active elastance</td>
<td>5</td>
<td>mm Hg/ml</td>
<td>28</td>
</tr>
<tr>
<td>T</td>
<td>time constant</td>
<td>20</td>
<td>msec</td>
<td></td>
</tr>
<tr>
<td>Rm</td>
<td>Mitral resistance</td>
<td>0.0008</td>
<td>mm Hg/ml²/sec²</td>
<td>27</td>
</tr>
<tr>
<td>Im</td>
<td>Mitral inertance</td>
<td>0.002</td>
<td>mm Hg/ml²/sec²</td>
<td>27</td>
</tr>
</tbody>
</table>

No values are assigned to the pressures and flows because they depend on the system properties (values shown).

LA = left atrial; LV = left ventricular; LVESP = LV end-systolic pressure; ESV = end-systolic volume.

![FIGURE 8](image-url)  
**FIGURE 8.** Electrical circuit analog of in vivo system. The pulmonary bed is simulated by a passive elastance, E, which empties through resistor, R, into the atrium. Atrial elastance is also passive (atrial systole is not simulated) and linear. Mitral flow, MiF, is through a diode (mitral valve), and a nonlinear resistance/inertance (mitral orifice). The ventricle is modeled as a nonlinear viscoelastance (see equation 6, Appendix). The elastance consists of an exponential time-varying term (to model relaxation) and an exponential volume-dependent term. The pressure component due to viscosity is assumed to be proportional to MiF. Initial conditions (at end-systole): Pp = PlA; MiF = 0; PF = 0; VLV = 20 ml.

![FIGURE 9](image-url)  
**FIGURE 9.** PRFR vs left atrial pressure at mitral valve opening (PCO). Data for a range of time constants of relaxation (T) are plotted in each panel. Top, Atrial elastance = 0.175 mm Hg/ml (compliance = 5.71 ml/mm Hg); middle, atrial elastance = 0.7 mm Hg/ml (compliance = 1.43 ml/mm Hg); bottom, atrial elastance = 2.8 mm Hg/ml (compliance = 0.356 ml/mm Hg). Note that at any PCO, PRFR increases as T decreases and as atrial elastance decreases (compliance increases). This type of plot is particularly useful for visualizing the interaction of PCO and T in determining PRFR. For example, at atrial elastance = 0.7 mm Hg/ml; PCO = 8 mm Hg; T = 20 msec, PRFR equals 78 ml/sec. If relaxation slows such that T = 40 msec, PRFR decreases to 67 ml/sec. However, PRFR can be restored to its original value by increasing PCO to 10 mm Hg.
FIGURE 10. Sensitivity of PRFR to changes in PCO ($\Delta$PRFR/$\Delta$PCO) vs PCO for a range of $T$ (10 to 80 msec). Sensitivity is greatest at a small PCO and large $T$.

FIGURE 11. Sensitivity of PRFR to changes in $T$ ($-\Delta$PRFR/$\Delta$PCO) vs $T$ for a range of values of PCO (2 to 22 mm Hg). Sensitivity is greatest at $T$ between 10 and 30 msec at any given PCO.
ventricular filling, and peak $P_{LA-PL}$ is earlier and smaller, as is PRFR. This type of plot (figure 9) is particularly useful for visualizing the interaction of PCO and T in determining PRFR. For example, PRFR = 91 mg/sec when atrial elastance = 0.7 mm Hg/ml; PCO = 10 mm Hg; T = 20 msec. If relaxation slows such that T = 40 msec, then PRFR decreases to 78 ml/sec. However, PRFR can be restored to its original value by increasing PCO to 12.5 mm Hg. Furthermore, at a PCO of 10 mm Hg, PRFR assumes values from 78 to 108 ml/sec when elastance is low (top panel) and from 39 to 76 ml/sec when elastance is high (bottom panel). Thus, the effects of changes in atrial compliance seen in various pathologic states should be taken into consideration before drawing conclusions about left ventricular diastolic function from measurements of PRFR.

The sensitivity of PRFR to changes in PCO is plotted versus PCO in figure 10. Atrial elastance is normal (0.7 mm Hg/ml). PRFR is most sensitive to changes in PCO when PCO is small. An increase in T decreased the sensitivity of PRFR to PCO at any given PCO. For example, at a PCO of 10 mm Hg, the rate of change in PRFR with respect to PCO is 6.6 at T = 10 msec and 4.2 at T = 80 msec. The sensitivity of PRFR to changes in T is plotted versus T for a range of values of PCO in figure 11. This sensitivity is more complex than the sensitivity to changes in PCO. When PCO is normal or high, PRFR is most sensitive to changes in T with maximum sensitivity occurring at T between 10 and 30 msec. This is consistent with the concept of regulation of early filling by rate of ventricular relaxation. When PCO is low, PRFR is far less sensitive to changes in T and sensitivity is less a function of T.

This work could not have been done without the skilled technical assistance of Messrs. A. Leon, P. Bon, and F. Rivera, and the typing of Ms. M. Olivera.

References
26. Ishida Y, Meisner JS, Tsujioka K, Gallo JJ, Yoran C, Frater RW, Yellin EL: Peak rapid filling rate may not reflect left ventricular relaxation properties when left atrial pressure compensates for changes in loading conditions. Circulation 70(suppl II): II-349, 1984 (abst)
27. Meisner JS: Left atrial role in left ventricular filling: dog and computer studies, thesis, Albert Einstein College of Medicine, 1986
Left ventricular filling dynamics: influence of left ventricular relaxation and left atrial pressure.
Y Ishida, J S Meisner, K Tsujioka, J I Gallo, C Yoran, R W Frater and E L Yellin

doi: 10.1161/01.CIR.74.1.187
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/74/1/187

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

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

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