SUMMARY Transmirtal blood flow was measured in man by numerical differentiation of left ventricular volume as a function of time in 11 patients undergoing cardiac catheterization. Using this technique, transmirtal blood flow may be studied in a variety of pathologic states without the need for surgically introduced flowmeters. Just before left ventriculography, echocardiography of the mitral valve was performed. The pattern of transmirtal blood flow was strikingly similar to the diastolic movement of the anterior mitral leaflet. At any equivalent diastolic filling time, the percent of the integrated area beneath the curve inscribed by the diastolic anterior mitral leaflet echoes closely approximated the percent of stroke volume which had entered the left ventricle. This observation supports the hypothesis that mitral leaflet motion accurately reflects transmirtal flow. Consequently, at a given time during diastole, the relative velocity of transmirtal flow and the percent of the stroke volume which has entered the left ventricle may be approximated noninvasively from the anterior mitral leaflet echogram.

THE DIASTOLIC MOVEMENTS of the anterior leaflet of the mitral valve can be recorded noninvasively in most subjects by M-mode echocardiography. Correlation of these movements with changes in left ventricular pressure and intracardiac blood flow could increase the diagnostic information available from the echocardiogram. Efforts have been made to relate movements of the anterior leaflet during portions of diastole to altered left ventricular compliance, cardiac output, and left ventricular diastolic pressure. However, relatively little information relates anterior leaflet movement throughout diastole to hemodynamic parameters. Studies in experimental animals have shown a qualitative similarity between the patterns of transmirtal blood flow shown by electromagnetic flowmeters sutured to the mitral anulus or left atrium, and the diastolic motion of the anterior leaflet.4, 5 While there are theoretical problems involving the interpretation of flowmeter data, the results suggest that diastolic anterior leaflet movements may be proportional to the (volume) rate of transmirtal flow, with anterior and posterior movements indicating increasing and decreasing flow rates, respectively. A critical examination of this hypothesis in man requires a method which not only minimizes problems of instrumentation, but is relatively safe and applicable to a variety of states of altered transmirtal flow. In this report, we examine the relationship of transmirtal blood flow derived from frame-by-frame analysis of the cine left ventriculogram and echocardiographically determined anterior mitral leaflet motion. This technique is applicable at the time of cardiac catheterization to

human subjects with a variety of cardiac disorders affecting diastolic left ventricular filling and mitral leaflet motion.

Methods

Patients with mitral stenosis, mitral regurgitation, aortic regurgitation, or left ventricular aneurysm, and patients not in sinus rhythm, were excluded from the study. This was done to avoid pathologic states in which the normal response of the anterior mitral leaflet to transmirtal flow might a priori be disturbed, and states in which changes in left ventricular geometry would not allow accurate determination of left ventricular volume. Clinical and hemodynamic data are presented in table 1.

Echocardiograms, with special attention directed to the anterior mitral leaflet, were obtained just before left ventriculography. We used a commercially available ultrasonescope and chart recorder equipped with a four-channel multiplex system. The transducer was angulated to obtain diastolic anterior leaflet echoes of maximum amplitude using standard techniques. When possible, simultaneous left ventricular pressure was recorded with a high-fidelity micromanometer tipped catheter (Millar Mikro-Tip). Special care was taken to avoid confusion of catheter echoes with those of anterior mitral leaflet, and we removed or repositioned the catheter when necessary. In five patients, high right atrial pacing at a constant rate just exceeding the patient's sinus rate insured identical heart rates during the echocardiogram and the subsequent left ventriculogram. Data from patients in whom atrial pacing was not used were included only if the heart rates during the echocardiogram and left ventriculogram did not differ by more than 2 beats/min.

Immediately after the echocardiogram, biplane (eight patients) or right anterior oblique (three patients) left ventriculograms were exposed at 58–60 frames/sec during quiet respiration using meglumine diatrizoate, Phillips 9-inch cesium iodide image intensifiers, and Arriflex cameras. Correction factors for
magnification and distortion were obtained for each patient using a grid filmed at the angiographic center of the left ventricle in the projections. When present, premature ventricular complexes and the first beat following them were rejected, and the earliest well-opacified acceptable beat was used for frame-by-frame analysis. This beat was always among the first five beats after injection of contrast material. Individual frames were identified using cine pulse markers, and the ventricular silhouettes were digitized using a sonic pen system. A digital computer (Tektronics 4051) was used to calculate and plot ventricular volume frame by frame, as a function of time, from biplane or single plane formulas. A 7.5 Hz digital filter was used to smooth the raw data points. Numerical differentiation of the smoothed data with a sliding Lagrange polynomial was then performed (fig. 1). The derivative of left ventricular volume with respect to time, or dV/dt, represents the rate of transmural blood flow in the absence of aortic regurgitation.

If anterior leaflet motion not only resembles dV/dt

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**Figure 1.** Flow data and mitral echogram from a patient with a recent myocardial infarction but normal coronary arteriograms. The raw volumetric data points are shown in the right panel. A curve is drawn through the smoothed data points (see text). The instantaneous rate of transmorial flow, dV/dt, is displayed from end-systole to end-diastole, and the ECG is shown at the lower portion of the panel. The curve depicting dV/dt as a function of time is seen to be biphasic, with maximum flow rates in early diastole. The mitral echogram from the same patient is shown in the left panel, with a simultaneous high-fidelity pressure tracing. The diastolic anterior leaflet echoes appear in a biphasic pattern, with the initial opening amplitude exceeding that of the opening during atrial systole. This pattern closely resembles the biphasic dV/dt curve in the right panel. LV = left ventricular.

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**Table 1.** Description of Patients—Clinical and Hemodynamic Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Age (years)</th>
<th>LVEDP (mm Hg)</th>
<th>EF</th>
<th>LVEDVI (L/min/m²)</th>
<th>HR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>Atypical chest pain</td>
<td>49</td>
<td>3</td>
<td>0.76</td>
<td>55</td>
<td>95</td>
</tr>
<tr>
<td>CP</td>
<td>Coronary artery disease</td>
<td>55</td>
<td>7</td>
<td>0.75</td>
<td>51</td>
<td>71</td>
</tr>
<tr>
<td>MS</td>
<td>Hypertrophic cardiomyopathy</td>
<td>60</td>
<td>48</td>
<td>0.80</td>
<td>63</td>
<td>85</td>
</tr>
<tr>
<td>JS</td>
<td>Aortic stenosis</td>
<td>72</td>
<td>20</td>
<td>0.94</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>NC</td>
<td>Coronary artery disease</td>
<td>58</td>
<td>13</td>
<td>0.63</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>WR</td>
<td>Coronary artery disease</td>
<td>56</td>
<td>7</td>
<td>0.32</td>
<td>165</td>
<td>83</td>
</tr>
<tr>
<td>JH</td>
<td>Coronary artery disease</td>
<td>58</td>
<td>13</td>
<td>0.42</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>HR</td>
<td>Congestive cardiomyopathy</td>
<td>42</td>
<td>36</td>
<td>0.21</td>
<td>102</td>
<td>95</td>
</tr>
<tr>
<td>MR</td>
<td>Myocardial infarction, normal coronaries</td>
<td>40</td>
<td>15</td>
<td>0.59</td>
<td>62</td>
<td>72</td>
</tr>
<tr>
<td>JM</td>
<td>Coronary artery disease</td>
<td>55</td>
<td>20</td>
<td>0.29</td>
<td>148</td>
<td>83</td>
</tr>
<tr>
<td>RJ</td>
<td>Aortic stenosis</td>
<td>58</td>
<td>18</td>
<td>0.73</td>
<td>100</td>
<td>60</td>
</tr>
</tbody>
</table>

Abbreviations: LVEDP = left ventricular end-diastolic pressure; EF = ejection fraction; LVEDVI = left ventricular end-diastolic volume index; HR = heart rate.
qualitatively, but is proportional to it throughout diastole, the fraction of stroke volume which enters the left ventricle via the mitral valve at any time will equal the fraction of the total area beneath the curve inscribed by the anterior mitral leaflet at the corresponding time. \( E(t) \) represents the amplitude of mitral valve excursion above the baseline drawn through the D point of the echocardiogram (fig. 2).

If anterior leaflet excursion is proportional to \( dV/dt \), then

\[
k \frac{E(t)}{dV/dt} = k \frac{dV}{dt}
\]

where \( k \) is a proportionality constant. Integrating both sides of equation 1 between time zero (end-systole) and any time \( \tau \) during diastole gives

\[
k A(\tau) = V(\tau) - V(0)
\]

FIGURE 2. Determination of the area beneath the curve inscribed by the diastolic echoes of the mitral leaflet in a patient with hypertrophic cardiomyopathy. A line is drawn through the D point parallel to the edge of the recording paper until the terminal diastolic anterior leaflet echoes are intersected. This point of intersection, taken to represent end-diastole, is located within 5–10 msec of the peak of the R wave of the ECG, and coincides with the onset of mechanical systole, as shown by the simultaneous high fidelity pressure tracing. Fifty to 60 parallel lines were then drawn to the leading edge of the anterior leaflet echoes (the number is reduced here for clarity) and numerical integration performed by the trapezoidal rule. LV = left ventricular.

A \( (\tau) \) represents the area beneath the echoes of the anterior mitral leaflet at time \( \tau \). \( V (\tau) \) is the left ventricular diastolic volume at time \( \tau \) and \( V(0) \) is the end-systolic volume. Similarly,

\[
k A(T) = V(T) - V(0) = SV
\]

where time \( T \) signifies end-diastole and \( SV \) is the stroke volume. \( A(T) \) represents the total area beneath the curve inscribed by the anterior mitral leaflet echoes during diastole. Dividing equation 2 by equation 3 yields

\[
\frac{A(\tau)}{A(T)} = \frac{|V(\tau) - V(0)|}{SV}
\]

The left side of equation 4 is determined by dividing the area beneath the anterior leaflet echoes at any time \( \tau \) by the total area beneath the leaflet echoes during diastole. The right side is readily obtained from ventriculographic data and offers the advantage of using the actual volumes rather than \( dV/dt \). In view of the above identity, a plot of the percent of the area inscribed by the anterior leaflet echoes vs the percent of stroke volume which has entered the left ventricle at an equivalent time should be linear with a slope of unity and an intercept of zero.

For this study, end-systole and end-diastole on the left ventriculogram were selected to correspond to the points of zero transmural flow, using a plot of \( dV/dt \) vs time (fig. 1). The frames thus chosen were no more than two frames distant from the frames with the smallest (end-systolic) and the largest (end-diastolic) ventricular silhouettes. On the echocardiogram (fig. 2), end-diastole was taken at the D point and end-diastole at the point of intersection of the terminal diastolic portion of the curve describing anterior leaflet motion and a line drawn through the D point parallel to the base of the recording paper. This placed end-diastole within 5–10 msec of the peak of the R wave on the ECG and generally coincided with the onset of mechanical systole, as judged from simultaneous high fidelity micromanometer pressure tracings. Although the baseline thus defined for numerical integration is somewhat arbitrary, variations of several millimeters did not significantly affect the results, which depend on a ratio of areas, \( A(\tau)/A(T) \). After enlarging the echocardiogram eight-to-10-fold with an opaque projector, the area under the anterior leaflet echoes was obtained by application of the trapezoidal rule over 50–60 points.

Ideally, the echocardiogram and left ventriculogram should be recorded simultaneously to obtain values for the quantities in equation 4. However, it is technically difficult to perform these procedures simultaneously. Even if this were possible, phase lags between transmural blood flow and mitral valve opening movements have been reported. To avoid these problems, echocardiograms and left ventriculograms were compared at equal percentages of the diastolic filling time for each technique. For example, if we assume equation 4 is valid and 60% of the stroke volume has entered the left ventricle at 40% of the total diastolic filling time determined from the left ventriculogram, 60% of the area beneath the anterior mitral leaflet should be inscribed at 40% of the
diastolic filling time determined from the echocardiogram.

**Results**

In each patient, the curve describing dV/dt from end-systole to end-diastole had a striking resemblance to the pattern of diastolic motion of the anterior mitral leaflet. Examples of a variety of flow patterns are shown in figures 1, 3, 4, 5 and 6. Figure 1 demonstrates the commonly encountered biphasic motion of diastolic anterior mitral leaflet echoes, with the E point slightly higher than the A point. The ventriculographic data reveal a biphasic pattern of diastolic transmitral blood flow, with the maximum rate of flow greater in early diastole than during atrial systole; the similarity to the echocardiographic anterior mitral leaflet motion is evident. Figure 3 presents data from a patient with normal hemodynamics during right atrial pacing. At a paced heart rate of 95, the mitral leaflet echoes have a monophasic pattern (at lower heart rates, after catheterization, a typical biphasic pattern of anterior leaflet echoes was noted). The curve describing transmitral blood flow obtained from the left ventriculogram during atrial pacing at an identical rate is also monophasic; this indicates that the anterior leaflet echoes reflect the pattern of transmitral blood flow. Figure 4 presents the findings in a patient with sinus bradycardia. The ventriculographic data show a small mid-diastolic increase in dV/dt. This is consistent with the echocardiographic finding of a transient mid-diastolic anterior movement of the anterior mitral leaflet.

Figure 5 shows data from a patient with car-

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Flow data and mitral echogram from a patient with atypical chest pain and heart rate of 95 beats/min (sinus rhythm). The format is identical to that of figure 1. Atrial pacing ensured identical heart rates during the left ventriculogram and echocardiogram. The right panel shows that the curve of dV/dt vs time is monophasic. The left panel shows the diastolic anterior leaflet echogram. The strong echoes above the leaflet originate from the catheter used to obtain the high-fidelity pressure tracing, also shown. Note that the curve inscribed by the anterior leaflet echoes is monophasic and resembles the rate of flow as a function of time. LV = left ventricular.
any time equals the percent of total area beneath the curve inscribed by the anterior mitral leaflet echoes at the equivalent time. Using equation 4, a plot of \( |V(\tau) - V(0)|/SV \) against \( A(\tau)/A(T) \) should have a slope of unity and intercept zero. To assess this, equation 4, expressed in percent, was applied; points from the echocardiographic and ventriculographic data were plotted at equal percentages of diastolic filling time at each 10% of diastolic filling time from zero to 90% of diastole. The pooled results for all patients are shown in figure 7, with the line of identity drawn through the points. The correlation coefficient is 0.98 and the least squares line best fitting these data is \( y = x - 2.2\% \), which does not differ significantly from \( y = x \) (\( p = 0.05 \)). The relationship for the individual patients is shown in table 2. High correlation was found for all

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**Figure 4.** Flow data and mitral echogram from a patient with aortic stenosis and sinus bradycardia. The format is the same as that of the previous figures. The \( dV/dt \) vs time, shown in the right panel, has a positive deflection in mid-diastole. The diastolic anterior leaflet echogram, shown in the left panel, shows a mid-diastolic opening motion and an overall pattern which closely resembles the \( dV/dt \) curve in the right panel.

**Figure 5.** Flow data and mitral echogram from a patient with coronary artery disease and congestive heart failure. The format is the same as in previous figures. With the exclusion of the BC interruption, the mitral valve echogram closely resembles the \( dV/dt \) curve in the right panel. Despite the large atrial contribution to left ventricular (LV) end-diastolic pressure (20 mm Hg), maximum flow rate, as well as maximum mitral opening excursion, occurs in early diastole.
patients ($r \geq 0.9$). The slopes and intercepts fell near one and zero, respectively, except in the case of one patient (JM) with intercept 15%. Thus, despite the limitations of quantifying the echocardiographic data, our results, using equation 4, suggest that the diastolic motion of the anterior mitral leaflet is proportional to transmitral flow in these patients.

**Discussion**

Previous studies which examined the relationship of transmitral blood flow to the anterior mitral leaflet echogram have used surgically implanted flowmeters, which limited the scope of investigation to experimental animals. While pulsed Doppler flow data may eventually be correlated with the echocardiogram, it should be noted that velocity of flow, in distance per unit time, is measured with this technique, as opposed to volume flow (dV/dt). With our method, measuring dV/dt requires knowledge of only left ventricular volume as a function of time during diastole. These data are readily available from left ventriculograms obtained during cardiac catheterization. The reliability of calculating dV/dt by numerical differentiation of left ventricular volume as a function of time has been demonstrated. Thus, in our study we have been able to compare anterior mitral echograms and derived diastolic flow data from patients with a variety of patterns of transmitral flow.

Some of our results may be anticipated from previous work. Flowmeter studies in the dog have demonstrated a similarity between the normally encountered biphasic diastolic flow pattern, and anterior mitral leaflet motion, similar to that shown in figure 1.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Slope</th>
<th>Intercept in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR</td>
<td>0.99</td>
<td>-2.0</td>
</tr>
<tr>
<td>CP</td>
<td>0.87</td>
<td>+6.9</td>
</tr>
<tr>
<td>MS</td>
<td>0.93</td>
<td>+2.0</td>
</tr>
<tr>
<td>JS</td>
<td>0.9</td>
<td>-8.0</td>
</tr>
<tr>
<td>NC</td>
<td>0.91</td>
<td>+1.2</td>
</tr>
<tr>
<td>WR</td>
<td>0.94</td>
<td>0.0</td>
</tr>
<tr>
<td>JH</td>
<td>0.96</td>
<td>+7.0</td>
</tr>
<tr>
<td>HR</td>
<td>1.06</td>
<td>-7.4</td>
</tr>
<tr>
<td>MR</td>
<td>0.88</td>
<td>+8.0</td>
</tr>
<tr>
<td>JM</td>
<td>1.26</td>
<td>-15.0</td>
</tr>
<tr>
<td>RJ</td>
<td>0.95</td>
<td>-3.0</td>
</tr>
</tbody>
</table>
With increasing heart rates, the pattern of anterior mitral leaflet motion may become monophasic. Data obtained from flowmeter studies in animals, and from studies of transmitral blood flow in humans using methods similar to our own, have shown a monophasic pattern of transmitral blood flow as heart rate increases. These findings are consistent with the monophasic patterns of transmitral blood flow and anterior leaflet motion shown in figure 3. Flowmeter data on beats with long R-R intervals in the dog reveal a mid-diastolic increase in transmitral flow. Furthermore, it has been suggested that transmitral flow may oscillate in response to alterations in the atrio-ventricular pressure gradient. While the physical mechanism for this altered mid-diastolic flow pattern is not entirely understood, it appears both in the echocardiograms and dV/dt plots during sinus bradycardia (fig. 4). Patients with decreased left ventricular compliance may show decreased E-F slopes on the diastolic mitral echograms. While we have not yet investigated a large series of patients with decreased anterior mitral leaflet with E-F slopes, the data in figure 6 imply that our approach is applicable to such patients. The mitral echogram from the patient with severe isolated aortic stenosis and left ventricular hypertrophy shows a markedly attenuated E-F slope. This pattern is clearly reflected in the diastolic dV/dt curve also shown in figure 6. However, one of our observations not clearly anticipated from previous work is that left ventricular diastolic pressure alone may not have a dominant influence on the pattern of anterior leaflet motion (fig. 5), aside from its effect on transmitral flow, which depends on the atrio-ventricular pressure gradient.

By comparing the percent of the area beneath the diastolic anterior mitral leaflet echoes with the percent of stroke volume which has entered the left ventricle at equivalent times during diastole, we have demonstrated that anterior leaflet motion is proportional to transmitral flow. Consequently, the percent of stroke volume which has entered the left ventricle at various portions of diastole may be approximated noninvasively from the echocardiogram. This may have particular application to studies of left ventricular compliance, where information regarding diastolic ventricular volume changes is commonly obtained noninvasively using contrast ventriculography. However, we have not attempted to show that the area beneath the curve inscribed by the anterior leaflet echoes during diastole represents an absolute measure of stroke volume.

While the diastolic movements of the anterior mitral leaflet undoubtedly result from numerous factors, including intraventricular vortex systems and mitral ring motion, transmitral blood flow may be the most significant quantitatively. This observation should extend the application of the M-mode echocardiogram to the characterization of altered transmitral flow in several pathologic states.

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