Relation between phasic mitral flow and the echocardiogram of the mitral valve in man

PAUL A. VIGNOLA, HARRIET J. WALKER, GERALD M. POHOST, AND LEONARD M. ZIR

From the Department of Medicine (Cardiac Unit), Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, U.S.A.

Ten patients without valvular disease were studied by ventriculography, and the rate and pattern of phasic blood flow into the left ventricle were determined by ventricular volume determinations at intervals of 33 ms during a single diastolic filling period. The derived left ventricular inflow patterns were then compared with the echocardiographic mitral EF slope obtained no more than 25 minutes before left ventriculography. The steepness of the EF slope was found to be inversely correlated with the time required to reach peak inflow velocity \( r = -0.80, P < 0.01 \) and directly correlated with the peak left ventricular inflow velocity divided by the time required to reach peak velocity \( r = 0.72, P < 0.05 \). No correlation was found between mean flow velocity into the left ventricle and the EF slope \( r = 0.40, P = NS \). A significant inverse correlation was found between the EF slope and the fraction of the diastolic filling period elapsed when 50 per cent of the filling volume had entered the left ventricle \( r = -0.85, P < 0.01 \). These findings suggest that the time required to reach left ventricular peak inflow velocity is one of the determinants of the mitral EF slope.

The echocardiographic diastolic closure slope of the anterior mitral valve leaflet (EF slope) has become an important measurement in clinical cardiology. Several disorders of left ventricular function have been associated with lessening of the steepness of this slope in the absence of intrinsic mitral valve pathology (Schattenberg, 1968; Popp and Harrison, 1969; Shah et al., 1971; McLaurin et al., 1973), in particular abnormalities in the rate of left ventricular filling (Zaky et al., 1968; DeMaria et al., 1976) and left ventricular compliance (Quinones et al., 1974). Though instantaneous mitral flow velocity throughout diastole has recently been measured in man (Kalmanson et al., 1975a, b), the relation between the patterns of flow observed and echocardiographic motion of the anterior mitral leaflet was not examined. The present study was undertaken to examine this relation and define those levels of mitral flow important in determining the echocardiographic diastolic closure slope.

Methods

The study population consisted of 10 subjects (mean age 51 years) selected from a group of patients undergoing diagnostic left ventriculography and coronary cineangiography as part of an evaluation of chest pain thought to be angina pectoris. Patients with mitral and aortic valve disease and patients with intracardiac shunts were excluded. Patients were catheterised in the postabsorptive state after light sedation with oral diazepam. Intracardiac pressures were measured with Statham P23Db transducers. The zero pressure reference level was 5 cm posterior to the sternum with the patient supine. Left ventricular end-diastolic pressure was taken at a point 40 ms from the beginning of the QRS complex if a discrete A wave was not recorded. Before coronary angiography single plane left ventriculography was performed in the 30 degrees right anterior oblique projection using the brachial or femoral artery approach. Meglumine diatrizoate, 50 ml (Renografin 76), was injected into the cavity of the left ventricle at rates of 9 to 12 ml/s using a Viamonte-Hobbs power injector. The left ventriculograms were recorded at 60 frames/second on
Echo and phasic mitral flow

35 mm film using either a Philips 6 in or a Siemens 7 in caesium iodide image intensifier. Correction factors for magnification and distortion were obtained for each patient using a standard 1 cm$^2$ angiocardiographic grid filmed at the level of the centre of the left ventricle (Dodge, 1971). The resolution of our cineangiocardiographic system was determined to be 3-7 line pairs per millimetre. Each ventriculogram was then viewed on a Vanguard XR-35 projector. Only those angiocardiograms with no ventricular irritability early in the injection were studied. A single complete diastolic filling period, usually the second or the third after the initiation of contrast medium injection, was then chosen for detailed analysis. The onset of diastole was identified by the ventriculographic frame first showing entrance of unopacified blood into the left ventricle. End diastole was identified by the frame with the greatest ventricular volume before the onset of left ventricular contraction. The ventricular outlines of alternate frames were traced throughout diastole. The outer margins of the ventricular silhouettes were defined by the outline of contrast medium between trabeculations. The papillary muscles were not excluded. The volume for every traced left ventricular silhouette was then calculated using the area-length method of Sandler and Dodge (1968) employing a computer assisted Graf-Pen system. The intraobserver reproducibility of the volume analysis was determined. Differences were found to be less than 1 per cent.

The ventriculographic stroke volume was taken as the difference between the end-diastolic and end-systolic volumes. Changes in ventricular volume between alternate cine frames of the diastolic filling period chosen for study were then determined. Since the time interval between alternate frames is 33 ms, the velocity of blood flow into the left ventricle was calculated for each 33 ms increment of the diastolic filling period and plotted as a function of time (Fig. 1). In this manner the pattern and rate of blood flow into the left ventricle could be graphically represented for each patient. From these plots the following values of diastolic left ventricular (LV) filling were calculated:

(a) mean LV inflow velocity (ml/s) = \[
\frac{\text{angiographic stroke volume}}{\text{diastolic filling period}}
\]

(b) initial peak inflow velocity (ml/s) = \[
\text{point Y of Fig. 1}
\]

(c) time to the development of peak inflow velocity (s)

(d) \[
\text{time to development of peak inflow velocity} \times \frac{\text{initial peak inflow velocity}}{\text{(ml/s per s)}}
\]

i.e. the slope of line X-Y (Fig. 1).

The pattern of blood flow into the left ventricle was displayed graphically in integral form by plotting the percentage of the diastolic filling time that had elapsed versus the percentage of total left ventricular filling that had been completed. For example, in case 3, 14 ml blood (i.e. 18% of the eventual filling volume) entered the left ventricular cavity by 33 ms (i.e. 8% of the eventual diastolic filling period). In like manner 46 per cent of the eventual filling volume entered the left ventricular cavity by 19 per cent of the eventual diastolic filling period, and so on. In this way the percentage of total diastolic flow into the left ventricle occurring with each 33 ms interval was plotted against the percentage of the total diastolic filling time elapsed (Fig. 2). Such graphs were plotted for each patient.

---

Fig. 1 Graph of phasic mitral flow during diastole for case 3. The onset of left ventricular filling is marked by point X; initial peak inflow by point Y; late diastolic inflow associated with atrial contraction by point Z.

Fig. 2 The percentage of left ventricular filling volume versus the percentage of diastolic filling period elapsed for case 3. Fifty per cent of the blood flow into the left ventricle has occurred during the first 22 per cent of the diastolic filling period.
From these graphs the percentage of the diastolic filling time that had elapsed when 50 per cent of left ventricular filling had been completed could be identified for each patient.

Each patient underwent echocardiography in the supine position in the cardiac catheterisation laboratory no more than 25 minutes before left ventriculography. All echocardiograms were obtained with an Ekoline 20 Smith-Kline ultrasonoscope using 7·5 or 10 cm focused transducers held perpendicularly to the chest wall in the 3rd to 5th left intercostal spaces. Recordings of the anterior mitral valve leaflet were made with a Honeywell 1856 strip chart recorder at both 50 and 100 mm/s paper speed. Care was taken to record the mitral anterior cusp echo which had the maximal excursion and a monophasic diastolic closure slope (Rodger and Sumner, 1975). The diastolic closure slope (EF slope) of 10 consecutive beats was calculated and an average value obtained for each patient. The heart rate at the time of echocardiography was 6 beats/minute faster than at the time of left ventriculography.

The mitral valve EF slope was then compared with the ventriculographic measures of left ventricular filling using standard regression analysis (Keeping, 1962). Correlation coefficients were determined for each; a significant relation was considered to exist when $P < 0.05$.

### Results

The basic haemodynamic and ventriculographic data of the 10 patients studied are summarised in Table 1. Two patients had normal coronary arteries. Four had single vessel, 3 had double vessel and 1 had triple vessel coronary artery disease as manifested by a reduction in vessel diameter of 75 per cent or more. Three subjects had either akinetic or dyskinetic left ventricular wall segments. The left ventricular end-diastolic pressure and left ventricular end-diastolic volume ranged from 2 to 25 mmHg (mean 8 ± 2 mmHg) and 48 to 387 ml (mean 160 ± 28 ml), respectively. The ejection fraction ranged from 0.31 to 0.74 (mean 0.60 ± 0.04). There was no significant correlation between these haemodynamic measurements and the echocardiographic mitral EF slope.

### Table 1 Basic haemodynamic and ventriculographic data for 10 study subjects

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Heart rate (beat/min)</th>
<th>LVEDP (mmHg)</th>
<th>LVEDV (ml)</th>
<th>SV (ml/beat)</th>
<th>Ejection fraction</th>
<th>CAD</th>
<th>Akinetic or dyskinetic LV wall motion abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>58</td>
<td>25</td>
<td>387</td>
<td>120</td>
<td>0.31</td>
<td>1 Yes</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>65</td>
<td>6</td>
<td>105</td>
<td>58</td>
<td>0.55</td>
<td>2 0</td>
</tr>
<tr>
<td>3</td>
<td>67</td>
<td>65</td>
<td>9</td>
<td>138</td>
<td>80</td>
<td>0.58</td>
<td>1 0</td>
</tr>
<tr>
<td>4</td>
<td>71</td>
<td>70</td>
<td>5</td>
<td>157</td>
<td>110</td>
<td>0.70</td>
<td>2 0</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>60</td>
<td>2</td>
<td>48</td>
<td>32</td>
<td>0.67</td>
<td>0 0</td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>64</td>
<td>5</td>
<td>126</td>
<td>88</td>
<td>0.70</td>
<td>1 0</td>
</tr>
<tr>
<td>7</td>
<td>53</td>
<td>62</td>
<td>18</td>
<td>198</td>
<td>119</td>
<td>0.60</td>
<td>3 Yes</td>
</tr>
<tr>
<td>8</td>
<td>54</td>
<td>66</td>
<td>5</td>
<td>120</td>
<td>53</td>
<td>0.44</td>
<td>2 Yes</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
<td>65</td>
<td>6</td>
<td>168</td>
<td>123</td>
<td>0.73</td>
<td>0 0</td>
</tr>
<tr>
<td>10</td>
<td>62</td>
<td>72</td>
<td>6</td>
<td>151</td>
<td>112</td>
<td>0.74</td>
<td>1 0</td>
</tr>
<tr>
<td>Mean ± standard error</td>
<td>62.2 ± 2.4</td>
<td>68 ± 2.5</td>
<td>8 ± 2</td>
<td>160 ± 28</td>
<td>90 ± 10</td>
<td>0.60 ± 0.04</td>
<td></td>
</tr>
</tbody>
</table>

LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; SV, stroke volume; CAD, number of major coronary arteries with a 75 per cent or greater reduction in diameter; LV, left ventricle.

### Table 2 Measures of diastolic LV inflow velocity

<table>
<thead>
<tr>
<th>Case No.</th>
<th>EF slope (mm/s)</th>
<th>Mean flow velocity (ml/s)</th>
<th>Peak flow velocity (ml/s)</th>
<th>Time to peak flow (s)</th>
<th>XY slope (ml/s per s)</th>
<th>% of elapsed dfp at which 50 per cent flow has occurred</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>109</td>
<td>520</td>
<td>780</td>
<td>0.16</td>
<td>5200</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>320</td>
<td>780</td>
<td>0.16</td>
<td>4700</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>198</td>
<td>190</td>
<td>690</td>
<td>0.066</td>
<td>10 400</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>165</td>
<td>220</td>
<td>570</td>
<td>0.099</td>
<td>5700</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>204</td>
<td>50</td>
<td>210</td>
<td>0.033</td>
<td>6300</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>130</td>
<td>190</td>
<td>420</td>
<td>0.13</td>
<td>3200</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>120</td>
<td>225</td>
<td>780</td>
<td>0.13</td>
<td>5900</td>
<td>26</td>
</tr>
<tr>
<td>8</td>
<td>85</td>
<td>80</td>
<td>210</td>
<td>0.099</td>
<td>2100</td>
<td>56</td>
</tr>
<tr>
<td>9</td>
<td>150</td>
<td>200</td>
<td>690</td>
<td>0.099</td>
<td>6900</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td>110</td>
<td>260</td>
<td>510</td>
<td>0.099</td>
<td>5100</td>
<td>42</td>
</tr>
<tr>
<td>Mean ± standard error</td>
<td>135 ± 14</td>
<td>230 ± 40</td>
<td>505 ± 70</td>
<td>0.108 ± 0.013</td>
<td>5550 ± 703</td>
<td>36.6 ± 4.1</td>
</tr>
</tbody>
</table>

EF slope early diastolic closure slope of the anterior mitral valve leaflet echo; dfp, diastolic filling period; XY slope, slope of line between points X and Y on the phasic mitral flow plot, i.e. peak inflow velocity/time to peak inflow velocity in seconds.
Fig. 1 illustrates the pattern of blood flow into the left ventricle during diastole for case 3. With the opening of the mitral valve (X) the velocity of blood flow into the left ventricle increases rapidly until it peaks at (Y). After this point the inflow velocity falls off rapidly only to increase again with atrial contraction (Z).

The percentage of total diastolic flow into the left ventricle against elapsed time expressed as a percentage of the diastolic filling period for case 3 is plotted in Fig. 2. Fifty per cent of the eventual blood flow into the left ventricle has occurred during the first 22 per cent of the total diastolic filling period.

Table 2 summarises the derived measures of the velocity of blood flow into the left ventricle in early diastole and the echocardiographic EF slope. The EF slope ranged from 78 to 204 mm/s with a mean of 135 ± 14. The mean and initial peak blood flow velocity into the left ventricle were 230 ± 40 ml/s and 70 ± 70 ml/s, respectively.

Fig. 3A, B, and C illustrate the patterns of phasic blood flow velocity into the left ventricle for 3 of the patients with differing echocardiographic mitral valve EF slopes. With the steeper EF slope the peak mitral inflow velocity (Y) tends to be greater. Though the correlation between the EF slope and the initial peak inflow velocity did not reach statistical significance, there was a good negative correlation of the EF slope with the time required to reach peak flow velocity (r = -0.80, P < 0.01) (Fig. 4). In addition there was a statistically significant correlation between the echocardiographic EF slope and initial peak inflow velocity divided by the time to the development of peak inflow velocity for each patient (r = 0.72, P < 0.05) (Fig. 5). There was no significant relation between the EF slope and the
The percentage of left ventricular filling volume versus the percentage of the diastolic filling period elapsed for 3 patients with differing echocardiographic mitral EF slopes. With steeper EF slopes the curves are shifted to the left as a greater portion of the blood flow enters the ventricle earlier in diastole.

When the percentage of total diastolic flow occurring with each 33 ms increment of time is plotted against the percentage of the diastolic filling period elapsed for each patient, a series of curves is generated (Fig. 6). The curve is shifted to the left as a greater portion of the blood flow enters the ventricle earlier in diastole. For case 4 with an EF slope of 165 mm/s, 50 per cent of the left ventricular filling volume enters the ventricle during the initial 29 per cent of the diastolic filling period. For case 6 with an EF slope of 130 mm/s, 50 per cent flow has occurred by 50 per cent of the diastolic filling period. For case 8 with an EF slope of 85 mm/s, the 50 per cent flow point occurs at 56 per cent of the diastolic filling period. For the 10 study patients there was a statistically significant negative correlation between the echocardiographic EF slope and the percentage of the elapsed diastolic filling period at which 50 per cent flow occurred ($r = -0.85, P < 0.01$) (Fig. 7).

**Discussion**

Using standard ventriculographic and haemodynamic techniques we have derived the pattern of phasic left ventricular inflow velocity throughout diastole in selected patients with coronary artery disease and related the patterns derived to the echocardiographic motion of the anterior mitral valve leaflet. In these patients the echocardiographic EF slope was found to be significantly correlated with the time required to reach peak inflow velocity and with the initial peak left ventricular velocity divided by the time required to reach peak velocity, i.e. the rate of rise of flow velocity to peak inflow velocity. No correlation was found between overall mean flow velocity into the left ventricle and the EF slope. Finally, a significant negative correlation was found between the EF slope and the fraction of the diastolic filling period elapsed when 50 per cent of the filling volume had entered the left ventricle. These data suggest that the rate of early left ventricular filling, as manifested by the time required to reach initial peak inflow velocity, is one of the major determinants of the mitral EF slope.

Nolan et al. (1969) were among the first to examine the pattern of transmitral flow using electromagnetic flow transducers sewn to the left atrial wall of normal calves. Though they could distinguish 6 separate phases of diastolic transmitral flow they observed that left ventricular filling had two major components, a rapid passive early phase followed by an active late diastolic phase mediated by atrial contraction. More recently, Laniado et al. (1975), using a similar experimental model, reported a significant correlation between cardiac output and the echocardiographic mitral early diastolic closure slope in anaesthetised open chest dogs. The effect of changes in the rate of early diastolic filling on this slope was not examined directly. Kalmanson and colleagues have recently developed a technique for recording instantaneous mitral valve flow velocity in
man by means of a directional Doppler ultrasound catheter positioned in the left atrium via the transseptal route (Kalmanson et al., 1975a). Though the authors reported on the range of normal flow velocity patterns using this technique (Kalmanson et al., 1975b) mitral valve echocardiograms were not examined.

In the present study, using standard ventriculographic techniques and equipment, phasic mitral valve flow was derived for each study subject and compared with the echocardiographic EF slope of the anterior leaflet of the mitral valve. The validity of such a frame-by-frame analysis of ventricular volumes to derive left ventricular phasic inflow velocity has been recently presented (Hammermeister et al., 1974; Hammermeister and Warbasse, 1974). The patterns of left ventricular inflow derived using this method are quite similar to those previously observed, as mentioned above, in the experimental animal (Nolan et al., 1969; Laniado et al., 1975) and in man using the transseptal Doppler catheter (Kalmanson et al., 1975a, b). Though the latter provides information only about the pattern of left ventricular inflow velocity and not flow volume (ml/s), the conversion of flow velocity to flow volume requires that the mitral orifice area be known throughout the diastolic filling period.

DeMaria and colleagues (1976) have recently examined the relation between the echocardiographic mitral diastolic closure slope and transmitral flow. By dividing diastole into three equal parts they were able to show a significant correlation between the EF slope and mitral flow during the initial third of diastole. The results of the present study confirm this finding. In addition we have extended the analysis by dividing diastole into 33 ms increments and by so doing have derived the pattern of phasic mitral flow for each study patient. Such an analysis has allowed us to determine that for patients with coronary artery disease the time required to reach peak inflow velocity may be a more important determinant of the steepness of the mitral EF slope than the peak inflow velocity itself.

The pattern of blood flow into the left ventricle was further analysed by determining the percentage of total left ventricular filling which had occurred for each cumulative increment in diastolic filling time. By plotting the percentage of the left ventricular filling volume which had entered the ventricle against the percentage of the diastolic filling period elapsed for each 33 ms study point throughout diastole a curve could be plotted for each patient. The curves of the patients with the steeper EF slopes were shifted to the left while those with the more attenuated slopes were shifted to the right. A significant negative correlation existed between the EF slope and the percentage of the diastolic filling period elapsed at 50 per cent flow.

It should be noted that such an analysis is based on the assumption that small differences in heart rate alone do not significantly alter the rate at which the left ventricle fills in early diastole. Though the validity of this assumption cannot be determined directly from our data, the lack of a correlation between heart rate and peak mitral flow, the time to peak mitral flow, and the rate of rise to peak flow in the present study indirectly support this assumption. In addition the range of heart rates observed in our study population during ventriculography is narrow. Any independent effect of these small differences in heart rate upon peak mitral flow, the time to the development of peak mitral flow, and the rate of rise to peak flow if present would be expected to be small.

Although it is frequently stated that differences in left ventricular compliance play an important role in determining the echocardiographic mitral diastolic closure slope (Shah et al., 1969; Duchak et al., 1972; Bergeron et al., 1975), little direct evidence on this point is yet available. Layton et al. (1973) noted a significant relation while examining beat-to-beat variation in mechanically damped left ventricular end-diastolic pressure and simultaneously recorded mitral diastolic closure slope. Quinones et al. (1974) noted a significant correlation between the non-simultaneously recorded mitral EF slope and the calculated slope of the left ventricular log pressure-volume relation and the left ventricular end-diastolic distensibility index as derived from post a wave left ventricular end-diastolic pressure. The authors have correctly pointed out the potential limitations of such an approach (Quinones et al., 1974; Gaasch et al., 1975). DeMaria et al. (1976) were only able to show a general relation between the non-simultaneously recorded mitral EF slope and total left ventricular diastolic compliance (\(\Delta V/\Delta P\)) normalised for end-diastolic volume. These investigators concluded that the mitral EF slope did not provide an accurate assessment of total left ventricular compliance in individual patients. In the present study measures of ventricular compliance were not examined. Such an investigation would require the examination of simultaneously recorded mitral EF slopes with measures of early, as well as total, diastolic compliance using high fidelity pressure recordings and simultaneous biplane angiographic volumes (Gaasch et al., 1975)—techniques not available to us at the time of the study.

The subjects of the present study are a selected group of patients with varying degrees of coronary artery disease. Since patients with valvular heart
disease were excluded and patients with congestive and hypertrophic cardiomyopathy were not studied. The results of our analysis should not be extended to these disease states. Variation in vortex formation of the undersurface of the mitral leaflets and aberration in left ventricular geometry resulting in altered traction of papillary muscles on chordae tendineae may independently influence the echocardiographic mitral EF slope in these conditions (Madeira et al., 1974).

In summary, using standard ventriculographic and haemodynamic techniques we have derived the pattern of phasic left ventricular inflow velocity throughout diastole in selected patients with coronary artery disease and related the patterns derived to the echocardiographic mitral valve diastolic closure slope. Our data suggest that the time required to reach mitral peak left ventricular inflow velocity is a significant determinant of the mitral EF slope. The reason for this relation is unclear but may be related in part to the earlier and more rapid development of vortices on the undersurface of the mitral leaflets resulting in more rapid early diastolic closure. The exact role and relative importance of altered left ventricular compliance in altering this relation requires further study using simultaneous high fidelity echocardiographic, haemodynamic, and ventriculographic measurements.

The authors thank Drs. Robert A. Johnson, Robert E. Dinsmore, Laura F. Wexler, Gordon S. Myers, and Robert S. Lees for reviewing the manuscript.

References


Requests for reprints to Dr. Paul A. Vignola, Noninvasive Diagnostic Laboratory, Massachusetts General Hospital, Boston, Massachusetts 02114, U.S.A.