PATHOPHYSIOLOGY AND NATURAL HISTORY
CORONARY ARTERY DISEASE

Dynamics of left ventricular filling at rest and during exercise

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ABSTRACT Left ventricular filling dynamics were examined at rest and during supine bicycle exercise in 33 patients at cardiac catheterization; 23 had coronary artery disease (ischemia group), five with prior infarction had an akinetic area at rest (scar group), and five had minimal cardiovascular disease (control). Peak filling rate and mean filling rate during the first half and second half of diastole were assessed by biplane angiography. Simultaneous micromanometer pressures were used to compute the time constant of isovolumic pressure decay (T). Peak filling rate and mean filling rate during the first half of diastole increased with exercise in all groups (from 615 to 1050 and 358 to 681 ml/sec in controls and comparably in the scar group and from 697 to 1035 and 347 to 768 ml/sec in the ischemia group). However, T was greater (reduced rate of pressure decay) with exercise in the ischemia group (38 vs 26 msec in controls; p < .05). Changes in the atrial driving pressure for filling appeared to counterbalance the difference in T. Mean filling rate during the second half of diastole increased with exercise in controls and in the scar group but only modestly in the ischemia group (from 202 to 349 ml/sec). The reduction in late diastolic filling during exercise-induced ischemia was associated with increased filling in early diastole, with a mid-diastolic volume increase from 160 to 186 ml and an upward shift in the diastolic pressure-volume relation. Thus left ventricular filling is not impaired at rest in patients with coronary artery disease who have normal ejection fractions. Furthermore, the augmentation of early filling induced by exercise is not blunted but is maintained during ischemia, apparently at the expense of elevated left atrial pressure. However, late filling is restricted with ischemia by an increase in impedance.


LEFT VENTRICULAR FILLING is a dynamic process involving the interaction of active and passive properties of the atria and ventricles. The rate of left ventricular pressure decay and the atrial-ventricular pressure gradient are major influences on ventricular filling in the early stages, and the operative stiffness of the left ventricle becomes increasingly important as filling progresses. Finally, the strength and timing of atrial contraction provide the end-diastolic "kick" to ventricular filling, which is frequently of importance in disease states.

During exercise and ischemia, cardiovascular function alters substantially. Ventricular filling must occur in an abbreviated diastole. During exercise, the rate of pressure decay in the normal ventricle increases significantly and filling pressures remain unaltered, whereas pressure decay is abnormal and filling pressures are grossly elevated in the ischemic ventricle. A major question must therefore be answered: What effects on ventricular filling are caused by relaxation abnormalities in patients with coronary artery disease? Some data have suggested that early filling rates are limited both at rest and during exercise in patients with coronary artery disease, yet simultaneous accurate measurements of ventricular volume and pressure have not been previously reported.

We have recently presented data on the abnormalities of ventricular pressure decay and their influence on diastolic pressures during exercise-induced ischemia in man. In this part of our study, we focus on the alterations in ventricular filling in three groups of patients: coronary patients with exercise-induced ischemia, patients with prior infarction but no ischemia with exercise, and control subjects. In addition, we provide data on the influence of left ventricular pressure decay, the driving pressure for filling, and the inflow impedance of the left ventricle on filling.
Methods

Patients. Thirty-three patients (32 men and one woman) were evaluated by right and left heart catheterization and biplane cineangiography at rest and during supine bicycle exercise. Five patients were classified as the control group and had minimal or no cardiovascular disease (two with no abnormalities, two with minimal coronary artery disease, and one with minimal mitral valve prolapse). Twenty-three patients, classified as the ischemia group, had significant coronary artery disease (greater than 50% diameter narrowing; 15 with three-vessel, five with two-vessel, and three with one-vessel disease) and exercise-induced regional wall motion abnormalities (14 had accompanying angina) with a fall in ejection fraction. Of this group, 16 had minimal or no regional hypokinesia at rest and seven with prior infarction had hypokinensis or akinesis (ejection fraction was ≥55% in 21/23). Five patients with prior infarction had a single large akinetic/dyskinetic area with reduced ejection fraction as revealed by resting angiogram but no new regional wall motion abnormality with exercise (scar group). None had angina, two had normal coronary arteries, and three had one-vessel disease of the coronary artery appropriate to the site of prior infarction.

Catheterization and cineangiography. Informed consent was obtained from all patients. Premedication consisted of 10 mg of chloralhydrate given orally 1 hr before catheterization. Cardiovascular medications were withheld for 12 to 24 hr before the study. Left ventricular pressure was measured with a Millar pigtail angiographic micromanometer introduced from the femoral artery. Pressures were recorded at a paper speed of 250 mm/sec (Electronics for Medicine, VR16), along with the first derivative of pressure (dP/dt), (dP/dt)/P, and an intracardiac electrocardiogram from the right-side catheter. Before both resting and exercise recordings the pressure was calibrated against a fluid-filled system.

Biplane left ventricular cineangiography was performed in the right anterior oblique (30 degrees) and left anterior oblique (60 degrees) projections at a filming rate of 50 frames/sec. Volumes were calculated by the area-length method. Each angiographic frame had a digital time corresponding to time marks on the pressure recordings.

Exercise protocol. All patients underwent precatheterization bicycle exercise testing to determine achieved work load and exercise limitations. At catheterization, pressures were recorded before and after the patients’ feet were strapped to the bicycle device. All resting data presented here are from the first angiogram, with patients’ legs in this elevated position; this accounts, in part, for the elevation in end-diastolic pressures. After the resting angiogram and a subsequent 12 to 15 min pause, exercise was begun at a low level. Patients underwent progressively higher work loads until either angina or other limiting symptoms occurred or until they achieved a submaximal heart rate predicted according to sex, height, and age. At the point of peak exercise, pressures were again recorded and simultaneous cineangiography was completed. Coronary arteriography was performed after exercise by means of the Judkins technique.

Data analysis. Resting and exercise data were derived from sinus beats selected during simultaneous pressure measurement and left ventricular cineangiography. Each beat analyzed was well opacified and occurred within 5 sec of the start of contrast injection. Postextrasystolic beats were excluded. Resting beats were from midinspiration and exercise beats were averaged if any respiratory-related pressure changes were noted. No patient had significant mitral regurgitation at rest or with exercise.

Ventricular filling was quantitated with frame-by-frame angiographic volumes from mitral valve opening to end-diastole. The time of mitral valve opening was noted as 20 msec before the time of the first frame showing the entry of unopacified blood into the left ventricle. The time of end-diastole was noted by the beginning of the rapid rise in left ventricular pressure immediately after the onset of the QRS complex. The time from mitral valve opening to end-diastole was referred to as the left ventricular filling time. This filling time was divided into a first and second half, the middle of which was middiastole. The average filling rates were calculated for the first and second half of diastole both at rest and during exercise. In addition, instantaneous filling rate was calculated every two frames after mitral valve opening by dividing the change in volume by 40 msec. The greatest value was termed the peak filling rate (figures 1 and 2). The distribution of filling was quantitated by calculating the percentage of total filling volume occurring in the first and second half of diastole. End-diastolic volume index, end-systolic volume index, and ejection fraction were calculated in the usual fashion. The filling volume was taken as the volume entering the ventricle between mitral valve opening and end-diastole. The volume immediately before mitral valve opening was used rather than end-systolic volume because of the known volume and shape changes occurring during the isovolumic relaxation period (an average increase of 5.2 ml in our patients).16

Pressure tracings were digitized for an entire cardiac cycle by an electronic digitizer (Numonics Corp.) interfaced with a Digital computer (PDP 11/10). A previously described program produced a printout of pressure and dP/dt values with a time interval between 3 and 10 msec depending on the heart rate (each cycle divided into 130 time intervals).17 The time constant of isovolumic pressure decay (T) was calculated as the negative reciprocal of the slope of the linear regression of pressure and dP/dt coordinates.15 These coordinates were taken from the isovolumic period, which occurred from immediately after maximum negative dP/dt until the time pressure had fallen to 5 mm Hg above the left ventricular end-diastolic pressure.

Left atrial pressure is a major determinant of left ventricular filling. Since left atrial pressure was not measured, we recorded the pressure at the time at which unopacified blood first entered the ventricle. This pressure is termed the opening pressure and is an index of the left atrial pressure responsible for mitral valve opening.

We examined several mechanisms by which late diastolic filling could be changed during ischemia. Alterations in chamber compliance could alter filling, and we constructed diastolic pressure-volume relations for resting and exercise data from all three groups. Three diastolic pressure-volume coordinates were used, including the early diastolic pressure nadir, middiastole, and end-diastole. Values from patients within each group were averaged and the mean pressure-volume coordinates were displayed graphically.

An additional influence on late diastolic filling is the extent to which the ventricle has already filled during early diastole. As the ventricle fills, operative compliance decreases because the rate of pressure increase is progressively greater than the rate of volume increase.2 In turn, ventricular filling would be expected to be increasingly limited. We arbitrarily chose the middiastolic time point to observe to what extent the ventricle had filled. Middiastolic volumes were computed at rest and during exercise.

Statistics. Rest and exercise data within groups were tested for significant changes by the paired t test. Differences between groups were tested by a one-way analysis of variance, and significant differences were located by Scheffe’s test.

Results

Examples of filling curves derived from frame-by-frame volume measurement are shown in figure 1.

CIRCULATION
Filling rates from the same two patients are presented in figure 2.

Resting and exercise volume data are given in table 1. During exercise, the control group had no significant change in end-diastolic volume (96 to 102 ml/m²) whereas end-systolic volume was reduced (35 to 28 ml/m²; p < .05) and ejection fraction increased (64% to 73%; p < .01). In the ischemia group, end-diastolic volume increased (104 to 115 ml/m²; p < .001) as did end-systolic volume (40 to 57/ml²; p < .001), and ejection fraction fell (62% to 50%; p < .001). During exercise in the scar group, end-diastolic volume did not change significantly (111 to 116 ml/m²). End-systolic volume (57 to 56 ml/m²) and ejection fraction (49% to 52%) were also unchanged. The control group had significantly (p < .05) greater exercise ejection fractions and smaller end-systolic volumes than those of the other two groups.

Left ventricular filling rates and parameters are presented in tables 2 and 3. As heart rate increased with exercise, the time available for filling decreased in all groups. There were no significant differences at rest or during exercise in filling time or heart rate between the patient groups. The total filling volume increased during exercise in the control group (104 to 126 ml; p < .05) and in the scar group (97 to 117 ml; p < .05) but fell in the ischemia group (118 to 101 ml; p < .001) (figure 3).

The peak filling rate was significantly augmented in all groups during exercise. In the control group, peak filling increased from 615 to 1050 ml/sec (p < .05), and a similar increase was observed in the ischemia group (697 to 1035 ml/sec; p < .001). The scar group also had increased peak filling rate (590 to 1185 ml/sec; p < .01) and there were no significant differences in peak filling rates between the different groups when we controlled for rest vs exercise. Similarly the mean filling rate for the first half of diastole was augmented in the control group (358 to 681 ml/sec; p < .05), the ischemia group (347 to 768 ml/sec; p < .001), and the scar group (303 to 808 ml/sec; p < .001). Again, no significant differences between groups was present at rest or during exercise. The mean filling rate during the second half of diastole also increased in the control group (119 to 649 ml/sec; p < .02) and the scar group (176 to 719 ml/sec; p < .005), but this increase was less substantial in the ischemia group (202 to 349 ml/sec; p < .001). During exercise the ischemia group

FIGURE 2. Instantaneous filling rate for the same two patients as in figure 1 was calculated every 40 msec from mitral valve opening to end-diastole. At rest both patients displayed the typical early rapid filling, followed by diastasis, which ended by the atrial contraction. During exercise, filling became a monophasic pattern of augmented peak filling rate in both patients. Restricted filling in the second half of diastole during exercise-induced ischemia is suggested by the rapid fall in filling rate to low levels.
TABLE 1  
Left ventricular volumes at rest and during exercise (mean ± 1 SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Ejection fraction (%)</th>
<th>EDV (ml/m²)</th>
<th>ESV (ml/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td>Rest</td>
</tr>
<tr>
<td>Control (n = 5)</td>
<td>64 ± 3</td>
<td>73 ± 4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>96 ± 6</td>
</tr>
<tr>
<td>Ischemia (n = 23)</td>
<td>62 ± 6</td>
<td>50 ± 7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>104 ± 12</td>
</tr>
<tr>
<td>Scar (n = 5)</td>
<td>49 ± 3</td>
<td>52 ± 7</td>
<td>111 ± 16</td>
</tr>
</tbody>
</table>

EDV = end-diastolic volume; ESV = end-systolic volume.  
Statistical comparisons (rest vs exercise): <sup>a</sup>p < .05; <sup>b</sup>p < .01; <sup>c</sup>p < .001.

had a significantly (p < .05) slower mean filling rate for the second half of diastole than those in the control and scar groups (figure 4).

The distribution of filling volume between the first and second half of diastole at rest and during exercise is shown in figure 5. In all groups at rest, approximately two thirds of filling took place in the first half of diastole and the remaining one third during the second half. With exercise the control group had a more even distribution of filling, with the percentage of filling in the second half of diastole increasing from 33 ± 4% to 48 ± 9% (p < .025). The scar group had a similar trend (36 ± 9% to 47 ± 6%; NS). In contradistinction, the ischemia group had a tendency for the percentage of filling taking place in the second half of diastole to be reduced (36 ± 13% to 31 ± 10%; NS). This reduced percentage was significantly lower than the exercise percentages in the control and scar groups (p < .05). Therefore, the filling rate and percentage of filling in the second half of diastole during exercise are lower in the ischemia group compared with the other groups.

Data for the factors that influence filling are given for all groups at rest and during exercise in table 4. The time constant of pressure decay (T) decreased in all groups during exercise, although lower values were achieved in the control group (48 to 26 msec; p < .02) than in the ischemia group (54 to 38 msec; p < .001) and the scar group (66 to 37 msec; p < .01). The left ventricular pressure at mitral valve opening, as an index of left atrial pressure, did not change with exercise in the control group (12 to 14 mm Hg; p < .001), increased insignificantly in the scar group (13 to 21 mm Hg) (figure 6), and greatly increased in the ischemia group (14 to 35 mm Hg; p < .001).

All patients in the ischemia group had an upward shift in the diastolic pressure-volume relation. Figure 7 shows the mean data from each of the three groups at rest and during exercise. The control group had a slight downward shift in the early diastolic pressure-volume relation and the scar group had no pressure-volume shifts. The ischemia group had an increase in end-diastolic pressure of 22 to 38 mm Hg (p < .001) while end-diastolic volume increased from 104 to 115 ml/m² (p < .001). The upward shift in diastolic pressure-volume relation was further characterized by an increase in mid-diastolic pressure from 11 to 28 mm Hg (p < .001), which was greater than that expected by the volume increase (figure 7). The control and scar groups had no significant increase in either end-diastolic pressure or volume (tables 1 and 4).

The left ventricle in ischemia group patients during exercise had filled to a greater extent by mid-diastole, with the mid-diastolic volume increasing from 160 to 186 ml (p < .001). The left ventricle was not filled to a greater extent at mid-diastole during exercise in the scar group (182 to 178 ml; NS) or in the control group (133 to 121 ml; NS).

TABLE 2  
Heart rate, filling time, and filling volume at rest and during exercise (mean ± 1 SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Heart rate (bpm)</th>
<th>Filling time (msec)</th>
<th>Filling volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td>Rest</td>
</tr>
<tr>
<td>Control (n = 5)</td>
<td>70 ± 18</td>
<td>120 ± 21&lt;sup&gt;b&lt;/sup&gt;</td>
<td>430 ± 150</td>
</tr>
<tr>
<td>Ischemia (n = 23)</td>
<td>68 ± 15</td>
<td>120 ± 14&lt;sup&gt;c&lt;/sup&gt;</td>
<td>470 ± 150</td>
</tr>
<tr>
<td>Scar (n = 5)</td>
<td>74 ± 16</td>
<td>138 ± 20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>440 ± 180</td>
</tr>
</tbody>
</table>

Statistical comparisons (rest vs exercise): <sup>a</sup>p < .05; <sup>b</sup>p < .01; <sup>c</sup>p < .001.
TABLE 3
Left ventricular filling rates at rest and during exercise (mean ± 1 SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>PFR (ml/sec)</th>
<th>MFR1 (ml/sec)</th>
<th>MFR2 (ml/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td>Rest</td>
</tr>
<tr>
<td>Control (n = 5)</td>
<td>615 ± 163</td>
<td>1050 ± 318A</td>
<td>358 ± 104</td>
</tr>
<tr>
<td>Ischemia (n = 23)</td>
<td>697 ± 219</td>
<td>1035 ± 309C</td>
<td>347 ± 140</td>
</tr>
<tr>
<td>Scar (n = 5)</td>
<td>590 ± 209</td>
<td>1185 ± 161B</td>
<td>303 ± 88</td>
</tr>
</tbody>
</table>

PFR = peak filling rate; MFR1 = mean filling rate in first half of diastole; MFR2 = mean filling rate in second half of diastole.

Statistical comparisons (rest vs exercise): *p < .05; **p < .01; ***p < .001.

Discussion

At rest, the ventricular filling pattern is characterized by a biphasic pattern. An initial rapid inflow of blood is separated from the late atrial contribution by a period of diastasis, during which little filling occurs. As heart rate increases, diastasis is increasingly reduced in duration until fusion of the early and late components of filling. During exercise the accompanying alterations in rate of pressure decay, left atrial mean pressure, and the strength of atrial contraction may promote a monophasic inflow pattern of augmented rate. The characteristics of this monophasic inflow pattern were quantitated in this study and there were apparent similarities and differences between groups. The rate of inflow of blood during early diastole appeared remarkably similar in patients with ischemia during exercise to that in control patients despite clear differences in systolic performance and the rate of isovolumic pressure decay. It did not matter whether the peak rate of inflow or the mean rate during the first half of diastole were examined. Patients with prior infarction, reduced ejection fraction at rest, and no ischemia with exercise had a similar augmentation of filling. An analysis of filling during the second half of diastole revealed a clear difference between the ischemia group and the other two groups. While the controls and the scar group patients were able to continue ventricular filling at a rate threefold above resting values, the patients with ischemia had a rapid reduction in filling rate. The mean rate of filling during the second half of diastole was increased from rest, but the relative restriction to filling was readily apparent (figures 1 and 2). The filling rate data are further supported by the changes in the distribution of filling. During ischemia there was a reduced percentage of blood entering during the second half of diastole, compared with that at rest and with that of the other groups during exercise. From these observations two key questions are raised. First, why is filling during the first half of diastole equally augmented in patients with ischemia and in control patients during exercise despite impaired pressure decay in the former? Second, what accounts for the restriction on filling in the second half of diastole during exercise-induced ischemia?

The rate of pressure decay in the left ventricle has been characterized by the time constant of isovolumic pressure decay, T. Numerous investigators have focused attention on the multiple mechanical, hemodynamic, humoral, and pharmacologic influences on

FIGURE 3. Left, The mean filling volume declined in the ischemia group during exercise but increased in the other groups. Right, Filling time (from mitral valve opening to end-diastole) decreased with exercise in all groups.
It has been suggested that T, in turn, may be an important determinant of left ventricular filling, but only limited data have been presented from animal and human studies. The reduction of T during exercise was accompanied by an increase in the mean filling rate during the first half of diastole in our study. In the control patients T was reduced to the lowest levels, yet the early filling rates were no greater than those in the patients developing ischemia who had a limited reduction in T. Our explanation for this apparent lack of relation between filling and T is that another important determinant of filling, i.e., the atrial driving pressure, was altered. Yellin et al. have proposed that filling is proportional to the magnitude of atrial-ventricular pressure difference and the rate at which this difference develops. Simultaneous atrial and ventricular pressure measurements were not possible in this study, but we did have a reasonable estimate of atrial driving pressure from the pressure at mitral valve opening. This opening pressure did not change during exercise in the control group but increased moderately in the scar group and increased greatly in the ischemia group (figure 6). We believe that the combination of T and the opening pressure allows an attractive explanation for the mean filling rates during the first half of diastole. The elevated opening pressure during ischemia overshadows the inadequately reduced T to produce a filling pattern indistinguishable from that of controls during the first half of diastole. Indeed, the fastest filling rates, either peak or mean during the first half of diastole, were seen in those patients with ischemia who had an elevated opening pressure, and T reduced to a low value close to that of controls.

Other investigators have noted an inverse relationship between filling rates and relaxation parameters in coronary artery disease patients at rest and in patients with hypertrophic cardiomyopathy. Fioretti et al. reported that T decreased slightly and filling rates increased during pacing tachycardia. These data and ours suggest that the rate of left ventricular pressure decay is a determinant of ventricular filling.

The decrease in end-systolic volume in exercise has been suggested as a mechanism for augmentation of filling during exercise by the production of diastolic suction. The alterations in end-systolic volume in this study were opposite in those in the control group and the ischemia group, but no difference in filling rates in the first half of diastole was apparent. Yet the changes in driving pressure for filling may counterbalance the alterations in end-systolic volume, as it appears to do for changes in T. End-systolic volume may also influence T, and it is not currently possible to study the separate effect of end-systolic volume on filling.
TABLE 4
Determinants of filling at rest and during exercise (mean ± 1 SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Opening pressure (mm Hg)</th>
<th>Middiastolic volume (ml)</th>
<th>Middiastolic pressure (mm Hg)</th>
<th>End-diastolic pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T (msec)</td>
<td>Rest Exercise</td>
<td>Rest Exercise</td>
<td>Rest Exercise</td>
</tr>
<tr>
<td>Control (n = 5)</td>
<td>48 ± 14</td>
<td>26 ± 6²</td>
<td>12 ± 7</td>
<td>14 ± 10</td>
</tr>
<tr>
<td>Ischemia (n = 23)</td>
<td>54 ± 10</td>
<td>38 ± 10⁸</td>
<td>14 ± 6</td>
<td>35 ± 9³</td>
</tr>
<tr>
<td>Scar (n = 5)</td>
<td>66 ± 10</td>
<td>37 ± 3⁴</td>
<td>13 ± 5</td>
<td>21 ± 13</td>
</tr>
</tbody>
</table>

Opening pressure = left ventricular pressure at angiographic mitral valve opening.

Statistical comparisons (rest vs exercise): ²p < .05; ³p < .001.

It is apparent that changes in end-systolic volume do influence filling by indicating where the ventricle begins to fill on the pressure-volume relation. In controls, the reduction in end-systolic volume during exercise allows filling to begin at a smaller volume and therefore allows augmented early filling at a lower intra-ventricular pressure. Filling can proceed on a relatively flat portion of the passive pressure-volume relation. Filling volume, and similarly stroke volume, can be augmented without an increase in end-diastolic volume and pressure. During ischemia the increased end-systolic volume places the ventricle on a rightward portion of the pressure-volume relation, and subsequent filling moves the ventricle rapidly to a steeper portion of the pressure-volume relation. Filling and stroke volumes are reduced despite an increase in end-diastolic volume.

The similarities in filling during the first half of diastole between patients with ischemia and control subjects during exercise do not imply an insignificant pressure decay abnormality in those with ischemia. The abnormal characteristics of isovolumic left ventricular pressure decay also affect diastolic pressures, as we have previously reported. These changes and others combine to produce gross elevations of intra-ventricular pressure. The resultant effects on wall tension and pulmonary capillary pressure place major limitations on the ability to exercise.

In addition, the similarities in early diastolic filling between our three groups do not imply a normal filling process. During ischemia, filling rates were probably maintained at the significant expense of elevated atrial pressure. Likewise, increased atrial pressures during exercise were abnormal in the scar group. This lends further support to the belief that characterization of the filling process requires more than flow measurements.

Our data show that late diastolic filling is abnormally slow during exercise-induced ischemia. Frequently, as in the example in figures 1 and 2, filling virtually stopped well before end-diastole. In addition to showing this new finding, our data suggest several possible explanations for this restricted filling pattern.

Impedance to filling of the left ventricle increases as the ventricle increases in size and pressure rises, since the instantaneous chamber compliance decreases. During exercise-induced ischemia the increase in end-systolic volume followed by a rapid filling early in diastole places the ventricle at a greater volume at middiastole. From this volume factor alone it is reasonable to conclude that the ventricle would be operat-

![FIGURE 6. Left. T (rate of isovolumic pressure decay) is shown at rest and exercise for the three groups. Pressure decay decreased during exercise in all but was abnormally slow in the ischemia and scar groups. Right. Left ventricular pressure at mitral valve opening is used as an index of the atrial driving pressure for filling. During exercise in the ischemia group there was a large increase in this index.](http://circ.ahajournals.org/Downloaded from http://circ.ahajournals.org/)
ing on a rightward, steeper portion of the pressure-volume relation.

The upward shift in the diastolic pressure-volume relation is a representation of reduced chamber compliance during ischemia. Mann et al. have reported similar data with pacing-induced angina in man. To what extent upward shifts in the diastolic pressure-volume relation impede ventricular filling remains to be shown in more controlled studies. In addition, the role of viscous effects is not clear from our data, although animal studies have not consistently shown significant viscous effects at the heart rates achieved in this study. It remains possible that with augmented filling rates and a partially relaxed ventricle, viscous effects may be significant.

Our choice of middiastole as the separation of early and late diastolic filling was based on several observations. With patients at rest, middiastole always occurred during diastasis, and we observed that peak filling typically occurred in the first half of diastole during exercise. In addition, patients in the ischemia group frequently had a rapid deceleration of filling in late diastole. To quantitate this observation, the middiastolic time was arbitrarily used to provide a filling rate for the second half of diastole.

Pressure decay and atrial driving pressures could influence filling past middiastole, and passive chamber properties could influence early diastolic filling. Filling dynamics are clearly complex and further data under more controlled conditions are necessary to clarify the relative influence of filling determinants throughout diastole.

Diastolic filling rates obtained by radionuclide methods have recently been reported for coronary artery disease patients at rest and during exercise. Abnormalities of early filling at rest have been described in patients with normal ejection fractions, but our data do not reveal significant resting abnormalities of filling in this group of coronary artery disease patients. Our ischemia group was chiefly composed of patients with normal resting ejection fractions, and their resting filling patterns were indistinguishable from those of controls. Patients from the scar group who had reduced ejection fractions had a tendency to have reduced peak and mean filling rates during the first half of diastole. This did not achieve statistical significance because of the relatively small number of patients in this group and the considerable variability of resting rates. Hammermeister and Warbasste, using contrast angiography, have shown reduced peak filling rates in a group of coronary artery patients at rest, with a reduced mean ejection fraction of 53%. Important differences exist between contrast ventriculography and radionuclide ventriculography. Filling rates with radionuclide methods are not true volume rates but quantitate filling by changes in the number of end-diastolic counts per unit of time. This not only has uncertain physiologic meaning but also biases data by making filling rates lower in those with larger end-diastolic volumes. A second major limitation of the radionuclide assessment of filling is its inability to identify physiologically important time points, i.e., mitral valve opening. By using the time between the smallest number of counts to the largest number of counts as the time of interest, radionuclide studies do not calculate changes of volume during the true filling period. This time includes the end of systole before the aortic valve closes and the isovolumic relaxation period, which is determined by the time of aortic valve closing, mitral valve opening, and the rate of pressure decay between the two. Pressure decay in coronary artery patients may be affected by medications, prior infarction, or asynchrony, which is very common even when the ejection fraction is normal. Thus radionuclide studies have several biases that would tend to underestimate filling in coronary artery disease patients. Crawford et al. has described an additional problem of data averaging by equilibrium radionuclide methods in acute ischemia. Finally, Bonow et al. have commented on the inability of first-pass tech-
niques to quantitate diastolic events because of the variable concentration of tracers in the inflowing blood.

Leg elevation clearly raised end-diastolic pressure and volume, as we have previously discussed. This could have influenced our results by causing alterations in atrial pressure. Contrast angiography does alter the hemodynamic state of the patient, but previous studies have shown this not to be important if the beat analyzed is soon after the beginning of the injection.

Exercise disproportionately reduces the duration of diastole and consequently filling changes are necessary. This study provides new data on filling changes during exercise in patients with and without coronary artery disease. It is increasingly apparent that left ventricular filling involves a complex interplay of multiple factors.

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