Influence of Preload Reserve on Stroke Volume Response to Exercise in Patients With Left Ventricular Systolic Dysfunction: A Doppler Echocardiographic Study

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Objectives. This study evaluated the role of preload reserve in the stroke volume response to exercise in patients with left ventricular systolic dysfunction by assessing the relation between stroke volume and late left ventricular diastolic filling during exercise.

Background. In patients with left ventricular diastolic dysfunction, the absence of left ventricular distension is the fundamental mechanism explaining the nonaugmentation of stroke volume during exercise.

Methods. In 32 patients with left ventricular systolic dysfunction and 16 healthy control subjects, mitral and aortic velocities were recorded by Doppler echocardiography at rest and during submaximal supine bicycle exercise. Stroke volume, peak early (E) and late (A) mitral velocities, E/A ratio and end-diastolic filling were measured at rest and during exercise.

Results. Stroke volume increased significantly in control subjects but did not change in patients. Peak early mitral velocity increased significantly and to the same extent in both groups, whereas peak late mitral velocity and end-diastolic filling increased significantly in both groups but more so in control subjects; the E/A ratio increased significantly in control subjects but did not change in patients. In addition, stroke volume correlated significantly with peak late mitral velocity during exercise in patients (r = 0.72, p < 0.001).

Conclusions. Compared with control subjects, patients with left ventricular systolic dysfunction exhibited limited increases in both stroke volume and late left ventricular filling during exercise. Furthermore, their stroke volume response correlated with the capacity of the left ventricle to increase late diastolic filling, that is, preload reserve.

(J Am Coll Cardiol 1995;25:680–6)

In patients with heart failure, cardiac output response during exercise is a major determinant of functional status (1). The change in stroke volume is especially dependent on the level of afterload and on the recruitment of both contractile and preload reserve (2). In particular, an abnormal preload reserve was recognized as the critical determinant of the stroke volume response in patients with left ventricular diastolic dysfunction (3). It was recently suggested (4) that the same abnormality could also be involved in the abnormal exercise response of patients with left ventricular systolic dysfunction combined with two conventional mechanisms: a decrease in contractile reserve and an increase in afterload. Preload reserve, defined as the capacity of the left ventricle to distend, is difficult to assess because it requires left ventricular volume measurement during exercise (3–5). Preload reserve may also be quantified by the magnitude of the augmentation during exercise of the left ventricular late diastolic filling or, more simply, late mitral velocity using pulsed wave Doppler and mitral velocity recordings (6,7).

We postulated that stroke volume response to exercise depends on the change in left ventricular late diastolic filling in patients with left ventricular systolic dysfunction. To test this hypothesis, we studied stroke volume and mitral velocities by Doppler echocardiography at rest and during exercise in normal subjects and in patients with left ventricular systolic dysfunction.

Methods

Study patients. Patients were recruited according to the following criteria: at least one nonrecent episode of congestive decompensation (>1 month), age between 20 and 75 years and presence of echocardiographic left ventricular systolic dysfunction defined by a left ventricular end-diastolic diameter >55 mm, with a shortening fraction <25% and an ejection fraction <50%. Left ventricular diameters and the shortening fraction were measured by M-mode echocardiography and ejection fraction by two-dimensional echocardiography by application of a length–area method to an apical four-chamber view, according to American Society of Echocardiography recommendations (8). Each patient was in sinus rhythm, with

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0735-1097/95/$9.50
0735-1097(94)00449-Z
a PR interval of <0.20 s and no ventricular arrhythmia. Patients with valvular disease more than mild mitral regurgitation, pulmonary disease or acute myocardial infarction within 3 months were excluded. Also, visually normal angiographic coronary anatomy in the noninfarcted myocardium (n = 16) or the absence of myocardial redistribution during an exercise thallium-201 tomography (n = 20), or both, were required to exclude the possible presence of an active myocardial ischemic process. Each patient had a systolic blood pressure between 90 and 160 mm Hg and a diastolic blood pressure <95 mm Hg, measured by a mercury sphygmomanometer, and a cardiothoracic anatomy allowing satisfactory and reproducible Doppler–echocardiographic examination.

The study group comprised 32 patients (28 men, 4 women; mean [±SD] age 51 ± 14 years, range 15 to 71) with a body surface area of 1.85 ± 0.19 m². The cause of heart failure was either idiopathic dilated cardiomyopathy (n = 21) or coronary artery disease (n = 11). According to a modified New York Heart Association classification, 4, 17, 7 and 4 patients were, respectively, in functional classes I (capacity to climb four floors of the institution or more), II (from two up to four floors), III (from one up to two floors) and IV (less than one floor). Left ventricular end-diastolic diameter ranged from 59 to 100 mm (mean 73 ± 12), shortening fraction from 8% to 24% (mean 13 ± 5%) and ejection fraction from 10% to 48% (mean 25 ± 10%). Rest systolic pulmonary artery pressure measured by continuous wave Doppler (9) in the 30 patients with tricuspid regurgitation ranged from 22 to 60 mm Hg (mean 38 ± 10). Before the study, all patients were under treatment with angiotensin-converting enzyme inhibitors in addition to diuretic drugs (n = 15), nitrates (n = 16) and digitalis (n = 10). All drug therapy was discontinued 24 h before the study.

The control group comprised 16 healthy subjects (14 men, 2 women; mean age 45 ± 14 years, range 23 to 69) with a body surface area of 1.86 ± 0.18 m². Age, gender ratio and body surface area were not significantly different in the two groups. Written informed consent to participate in the study was obtained from each patient.

Exercise protocol. All patients performed submaximal supine exercise on a bicycle ergometer (Gauthier or Monark type). The initial work load of 30 W was progressively increased by 10 W/min until it reached 60% of the predicted maximal heart rate. This submaximal level of exercise was maintained at a plateau for 3 min to allow exercise Doppler measurements. Blood pressure was recorded at 1-min intervals at rest and during exercise by an oscillometric dinamap system. The electrocardiogram was also continuously monitored.

Doppler echocardiographic examination. A commercially available Doppler echocardiographic system (Advanced Technology Laboratory, Ultramark 9) was used with a 3-MHz phased-area transducer for two-dimensional echocardiographic and pulsed wave Doppler examination and a 2.25-MHz nonimaging transducer for continuous wave Doppler examination. Hard copies of the Doppler velocity tracings were obtained at a paper speed of 50 mm/s. Wall filters were set at 400 Hz. All recordings were videotaped.

Aortic velocities were measured by continuous wave Doppler in either an apical or a suprasternal view (10), and mitral velocities by pulsed wave Doppler in an apical four-chamber view with a sample volume localized on the tip of the mitral leaflets (11). Aortic diameter was measured in a two-dimensional parasternal long-axis view just below the aortic orifice from inner to inner echo at rest only because it is thought to remain constant during exercise (12).

The following variables were obtained at rest and during exercise: 1) stroke volume \((\pi/4 \times [\text{Aortic diameter}]^2 \times [\text{Aortic velocity–time integral}])\); 2) peak early (E) and late (A) diastolic mitral velocity and the A/E ratio; 3) velocity–time integral of the mitral velocity curve; 4) mitral valve area, by applying the continuity equation as the ratio of stroke volume to the mitral velocity–time integral; and 5) end-diastolic filling (Peak late mitral velocity × Mitral valve area), assuming that the area given by the continuity equation represents an average of instantaneous values throughout diastole. For each variable, three to five successive measurements were averaged. All recordings were performed by the same investigator and read by another expert who was unaware of the patients’ clinical data.

Validation and day-to-day intraobserver reproducibility of Doppler echocardiographic measurements. Doppler measurement of exercise stroke volume at the aortic orifice has been previously validated by comparison with thermodilution (10). Furthermore, in a subgroup of eight current subjects, four normal control subjects and four patients with heart failure, the same echocardiographic examination was repeated for each person, both at rest and during submaximal exercise, on two occasions separated by a 24-h interval. Intraobserver variability was calculated as the absolute difference between the paired measurements (SD) for each Doppler echocardiographic variable (Table 1).

Statistical analysis. All data are expressed as mean value ± SD. A two-way analysis of variance was used. Statistical significance was defined as \(p < 0.05\). Moreover, the power of the study derived from the beta coefficient was used to interpret the nonsignificant results for the main comparisons. A power ≥80% was considered necessary to interpret a result as actually nonsignificant. Univariate linear regression analysis was also performed.
Table 2. Hemodynamic Response (mean ± SD) to Submaximal Supine Bicycle Exercise

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>SBP (mm Hg)</th>
<th>SV (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>H</td>
<td>C</td>
</tr>
<tr>
<td>Rest</td>
<td>67 ± 8</td>
<td>p &lt; 0.05</td>
<td>122 ± 10</td>
</tr>
<tr>
<td></td>
<td>73 ± 9</td>
<td></td>
<td>15 ± 18</td>
</tr>
<tr>
<td>Exercise</td>
<td>101 ± 4*</td>
<td>p = 0.15</td>
<td>138 ± 12*</td>
</tr>
<tr>
<td></td>
<td>98 ± 8*</td>
<td></td>
<td>130 ± 21*</td>
</tr>
</tbody>
</table>

*p < 0.001, rest versus exercise. C = healthy control subjects; H = patients with heart failure; HR = heart rate; SBP = systolic blood pressure; SV = stroke volume.

Results

Rest and exercise stroke volume. At rest, stroke volume was slightly but significantly lower in patients than control subjects (Table 2), and heart rate slightly but significantly higher, whereas systolic blood pressure was not different in the two groups. During submaximal exercise, heart rate and systolic blood pressure increased significantly and to the same extent in the two groups, whereas stroke volume increased significantly in control subjects but did not change in patients (+28 ± 13% in control subjects vs. +2 ± 14% in patients, p < 0.001).

Rest and exercise mitral flow variables. At rest, peak early and late mitral velocities, the A/E ratio (Table 3), velocity-time integral of the mitral curve, mitral valve area and end-diastolic filling (Table 4) were not significantly different in patients and control subjects. During exercise, peak early mitral velocity increased significantly and to the same extent in the two groups (+28 ± 25% in patients vs. +35 ± 23% in control subjects, p = 0.32, power 80%), whereas peak late mitral velocity increased significantly in the two groups but significantly less in patients (+18 ± 28% in patients vs. +74 ± 39% in control subjects, p < 0.001). The A/E ratio, velocity-time integral of the mitral curve and mitral valve area increased slightly but significantly in control subjects but did not change in patients. End-diastolic filling increased significantly in the two groups, but the increase was significantly larger in control subjects (+93 ± 46% in control subjects vs. 28 ± 44% in patients, p < 0.001). Finally, the mitral flow profile at the submaximal exercise plateau differed significantly for both groups, with similar peak early velocity but significantly higher peak late velocity and A/E ratio in control subjects than patients (Fig. 1). In addition, despite the wide range of responses to exercise in both groups, peak late mitral velocity increased by ≥25% in all 16 control subjects and in only 13 of 32 patients who comprised group 1, whereas it decreased, did not change or increased by <25% in the other 19 patients who comprised group 2.

Relations between stroke volume and mitral flow variables in patients with heart failure. In patients with left ventricular systolic dysfunction, stroke volume was not significantly correlated with peak early mitral velocity either at rest or during exercise. Furthermore, the relative change in stroke volume induced by exercise was not significantly correlated with the change in peak early mitral velocity. In contrast, stroke volume was significantly correlated with peak late mitral velocity at rest (r = 0.46, p < 0.01) and especially during exercise (r = 0.72, p < 0.001, Fig. 2). In addition, the relative change in stroke volume was also significantly correlated with that in peak late mitral velocity (r = 0.52, p < 0.01). Thus, during exercise, stroke volume response seems to be determined by the change in peak late mitral velocity. To identify the hemodynamic determinants of the exercise-induced change in peak late mitral velocity, we compared the two groups of patients (those with a 25% increase and those with a smaller increase, a decrease or no change in peak late mitral velocity). As expected, stroke volume increased significantly in group 1 but did not change in group 2 (9 ± 12% in group 1 vs. 2 ± 13% in group 2, p < 0.01). Age, cause of heart failure, severity of left ventricular dysfunction (assessed by left ventricular volume and mass and ejection fraction), rest heart rate, arterial systolic blood pressure and pulmonary artery pressure did not differ significantly in the two groups. By contrast, the functional class was significantly higher (2.5 ± 0.8 in group 2 vs. 1.9 ± 0.8 in group 1, p < 0.05) and rest A/E ratio significantly lower (0.55 ± 0.28 in group 2 vs. 0.83 ± 0.40 in group 1, p < 0.05) in group 2 than in group 1.

Table 3. Rest and Exercise Mitral Flow Variables (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>E (cm/s)</th>
<th>A (cm/s)</th>
<th>A/E</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C (cm/s)</td>
<td>H (cm/s)</td>
<td>C</td>
</tr>
<tr>
<td>Rest</td>
<td>73 ± 21</td>
<td>80 ± 18</td>
<td>56 ± 20</td>
</tr>
<tr>
<td></td>
<td>p = 0.23 (33%)</td>
<td></td>
<td>p = 0.24 (28%)</td>
</tr>
<tr>
<td>Exercise</td>
<td>101 ± 21*</td>
<td>99 ± 15*</td>
<td>93 ± 21*</td>
</tr>
<tr>
<td></td>
<td>p = 0.20 (36%)</td>
<td></td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
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*p < 0.001 and #p < 0.05, rest versus exercise. Power of the study is shown in parentheses. Abbreviations as in Tables 1 and 2.
Table 4. Rest and Exercise Mitral Variables (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>VTIM (cm)</th>
<th>MVA (cm²)</th>
<th>EDF (ml·s⁻¹)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>H</td>
<td>C</td>
</tr>
<tr>
<td>Rest</td>
<td>13.3 ± 3.5</td>
<td>11.5 ± 3.1</td>
<td>5.6 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>p = 0.07</td>
<td></td>
<td>p = 0.45</td>
</tr>
<tr>
<td>Exercise</td>
<td>15.3 ± 2.9*</td>
<td>11.3 ± 3.3</td>
<td>6.3 ± 1.3*</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.001</td>
<td></td>
<td>p = 0.90</td>
</tr>
</tbody>
</table>

*p < 0.01 and †p < 0.001, rest versus exercise. EDF = end-diastolic filling; MVA = mitral valve area. Other abbreviations as in Tables 1 and 2.

**Discussion**

Left ventricular filling changes induced by submaximal supine bicycle exercise were significantly different between patients with left ventricular systolic dysfunction and healthy control subjects. Stroke volume increased significantly in the control subjects but did not change in patients. Early diastolic filling increased similarly in the two groups, whereas late diastolic filling (and end-diastolic filling) increased more in the control subjects, thus increasing the A/E ratio in control subjects but in patients. Furthermore, in patients exercise change in stroke volume seems to be determined by the change in late diastolic filling. The capacity to increase late left ventricular filling during exercise, which represents the preload reserve, was not related to age, etiology of heart failure, severity of echocardiographic left ventricular dysfunction, rest pulmonary artery pressure, heart rate or systolic blood pressure but was significantly reduced in patients with a high functional class and a rest mitral flow profile of the restrictive type.

**Left ventricular filling during exercise.** The few studies devoted to the adaptation of left ventricular filling during exercise are in agreement with our findings. In an angiographic study, Caroll et al. (13) found that during supine bicycle exercise, early diastolic filling increased to the same extent in patients with left ventricular ischemic dysfunction and in control subjects, whereas late diastolic filling increased significantly in control subjects but did not change in patients. Hayashi et al. (6) recorded mitral flow velocity during isometric exercise in patients with an old myocardial infarction. In their patients with left ventricular dysfunction, defined by a left ventricular end-diastolic pressure >18 mm Hg, peak early

Figure 1. Examples of mitral flow velocity in a normal control subject (top) and a patient with left ventricular systolic dysfunction (bottom) at rest (R) and during submaximal exercise (E). Arrow = 100 cm·s⁻¹.
mitral velocity increased significantly, and both peak late mitral velocity and the A/E ratio decreased significantly. In their other patients, peak early mitral velocity decreased, and both peak late mitral velocity and the A/E ratio increased significantly. These two responses differed from those in normal subjects, whose increased A/E ratio resulted from an increased peak late mitral velocity with no change in peak early mitral velocity. Presti et al. (7) measured mitral flow velocity before and immediately after upright bicycle exercise in patients with coronary artery disease and in control subjects. Peak early and late mitral velocities increased significantly in both groups, although the ischemic group exhibited a larger increase in peak early mitral velocity and the control group a larger increase in peak late mitral velocity, resulting in a lower A/E ratio in the ischemic group and a higher A/E ratio in the control group. The slightly discordant results of the previous studies may be due to large differences in the type of exercise (isometric or dynamic), patient position during exercise, timing of measurements (during or immediately after exercise), mechanism of left ventricular failure (ischemic or nonischemic) and level of left atrial pressure.

Relation between stroke volume and left ventricular filling during exercise: role of preload reserve. In patients with left ventricular systolic dysfunction, the response of stroke volume to exercise was correlated significantly with the increase in late mitral velocity but not with that of early mitral velocity. Therefore, the capacity of the left ventricle to increase its end-diastolic filling, that is, preload reserve, seems to constitute a major determinant of the stroke volume response to exercise, not only in patients with left ventricular diastolic dysfunction, as previously demonstrated (3), but also in those with left ventricular systolic dysfunction. Using an isotopic methodology, Konstam et al. (4) noted that patients with left ventricular systolic dysfunction were unable to increase left ventricular end-diastolic volume or stroke volume during exercise. To interpret the weak correlation between exercise stroke volume and exercise peak late mitral velocity found in the present study (r = 0.72), two explanations may be proposed. First, stroke volume is a multifactorial variable. Second, our patients were heterogeneous, especially with respect to the etiology of heart failure as well as type of therapy before the study. Additionally, therapy was discontinued only 24 h before the study and may have affected the results.

Significance of exercise-induced changes in mitral flow velocity in control subjects and in patients with left ventricular systolic dysfunction. Peak early mitral velocity is determined by left ventricular relaxation, left atrial pressure at mitral opening, left ventricular end-systolic volume and heart rate (14,15). During exercise, the change in peak early mitral velocity is believed to be a function of the changes in each of these variables but chiefly in left ventricular relaxation and left atrial pressure. Thus, it was established that in normal subjects a large decrease in the constant time of relaxation (tau) during exercise, combined with no change in left atrial pressure, leads to an increase in early diastolic left ventricular filling. By contrast, in patients with ischemic left ventricular dysfunction, an increase in left atrial pressure combined with a small decrease in tau was responsible for an increase in early filling of a similar magnitude (13). In patients with restrictive left ventricular dysfunction after transplantation, the same determinants were involved, mainly with impairment of myocardial relaxation (16). It is likely that the large increase in peak early mitral velocity that we observed in patients with left ventricular systolic dysfunction results from the same abnormalities, that is, a significant and large increase in left atrial pressure combined with a limited reduction in tau. In addition, one experimental study (17) demonstrated in dogs that the progressive worsening of left ventricular systolic dysfunction was not accompanied by any decrease in peak early mitral velocity because left atrial pressure gradually increased until the later stages of heart failure, when peak early mitral velocity decreased (17).

The physical determinants of peak late mitral velocity include left atrial contraction (18), pressure (19) and afterload, as reflected by left ventricular chamber distensibility (20). The change in peak late mitral velocity during exercise is a function of the change in each of these variables. To our knowledge, left atrial contractility, volume and compliance during exercise have not been assessed in patients. However, left ventricular chamber distensibility was studied by Carroll et al. (13), who established that in normal subjects, the diastolic left ventricular pressure-volume relation does not change during exercise, whereas in patients with ischemic left ventricular dysfunction, it shifts upward and to the left. This worsening of left ventricular distensibility during exercise might lead to a decrease in peak mitral velocity during atrial contraction after the limits of both contractile and preload reserve of the left atrium have been reached. This atrial afterload mismatch might be involved in patients with left ventricular systolic dysfunction during exercise. In the present study, we assessed the effect of some fundamental clinical and hemodynamic variables on the exercise response in left ventricular filling. Only a high functional class and rest mitral velocity profile of a restrictive type...
resulted in an abnormal exercise response with no augmentation in peak late mitral velocity. Nevertheless, other important potential determinants of left ventricular filling, such as right ventricular dimension and respiration, were not studied.

**Methodologic limitations of the study.** For exercise stroke volume measurement by Doppler echocardiography, many technical possibilities are available. We chose to combine subaortic diameter measurement by two-dimensional echocardiography with aortic velocity recording by continuous wave Doppler. This method has been previously validated (10). In addition, it has been established that intrapatient variability was better when continuous Doppler was used rather than pulsed Doppler, particularly for stroke volume monitoring during therapeutic or physiologic interventions, such as exercise (21).

Accurate measurement of exercise mitral velocity by pulsed Doppler is technically difficult because of the instability of the sample volume in the mitral orifice. To limit the effect of this problem, only the higher mitral velocities were selected here. With this reservation, the intrapatient variability that we obtained for mitral velocity measurements, separated by a 24-h interval, was acceptable.

End-diastolic filling was characterized in the present study by measurements of velocity and flow (end-diastolic filling) at atrial contraction rather than by the velocity-time integral of the A wave because this integral is usually difficult to obtain during exercise, as the A and E waves tend to merge as a result of tachycardia, whereas the A wave is measured easily and consistently.

We used a submaximal rather than maximal exercise capacity for two reasons. First, exercise cardiac adaptation, with an increase in both left ventricular end-diastolic volume and stroke volume and a decrease in end-systolic volume, occurs early during exercise (at 40% of the peak oxygen uptake, VO\(_2\)). Above this submaximal exercise level, these left ventricular variables remain constant, and cardiac output increases as a function of heart rate (3,22). Second, mitral flow morphology cannot be adequately analyzed at a heart rate >120 beats/min.

Finally, the results we obtained during supine exercise cannot actually be extrapolated to upright exercise. Thus, the changes in stroke volume and left ventricular end-diastolic volume are larger during upright than supine exercise, and the contribution of the preload reserve is more important (23).

From a statistical point of view, because many of our results were nonsignificant, the power of the study was obtained for the main comparisons of the left ventricular filling variables. Thus, the power for intergroup comparisons of peak early mitral velocity both at rest (23%) and during exercise (36%), peak late mitral velocity at rest (28%) and the A/E ratio at rest (35%) was low. This finding indicates that the results of the present study should be interpreted with caution and require confirmation in a larger group of patients and subjects.

**Conclusions.** Exercise-induced changes in stroke volume and left ventricular filling are radically altered in patients with left ventricular systolic dysfunction compared with healthy subjects. Thus, stroke volume increased significantly in our control subjects but did not change in our patients. Both early and late left ventricular filling increased significantly in the two groups, but whereas the change in early filling was similar in both groups, the change in late filling was significantly smaller in patients than control subjects. Furthermore, in patients with left ventricular systolic dysfunction, 1) the stroke volume response to exercise correlated significantly with the change in peak late mitral velocity, which reflects preload reserve; and 2) the limited increase in this late mitral velocity was combined with a more severe stage of heart failure and a rest mitral flow profile of the restrictive type.

We thank Laurence Hennebert for help with manuscript preparation and Denise Martin for technical assistance.

**References**


