Association between the exercise ejection fraction response and systolic wall stress in patients with chronic aortic insufficiency

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With the technical assistance of Debra Loge, B.S., Debra Cox, B.S., Chris Anderson, B.A., Rex Solin, B.A., and Rob McDonald, B.A.

ABSTRACT We studied the exercise ejection fraction response in 56 patients with chronic aortic insufficiency. All had left ventricular dilatation but preserved resting ejection fraction and minimal or no symptoms. The exercise ejection fraction increased by 0.05 units or greater in 18 (32%) patients (group I), remained within 0.05 units of the resting value in 18 (32%) patients (group II), and fell by 0.05 units or greater in 20 (36%) patients (group III). There were no significant differences among the groups in left ventricular end-diastolic dimension, end-systolic dimension, or fractional shortening by echocardiography or in resting left ventricular volumes and ejection fraction by radionuclide angiography. Left ventricular end-systolic wall stress was significantly higher in group III than in either group I or group II (89 ± 20 vs 70 ± 18 and 69 ± 17 × 10^3 dyne/cm²; p < .005). At peak exercise there were no differences among groups in systolic blood pressure. However, end-systolic volume increased from 65 ± 28 to 77 ± 36 ml/m² in group III and fell from 50 ± 21 to 28 ± 18 ml/m² in group I during exercise. Thus, at peak exercise end-systolic volume was nearly three times greater in group III than in group I. Although stress could not be determined directly during exercise, the directional changes in its determinants suggest that it also would have been higher in group III patients. A highly significant inverse correlation was present between the ejection fraction response and the change in end-systolic volume (r = −.87, p < .0001). Exercise capacity was significantly lower in group III than in groups I and II. These data demonstrate that patients with chronic aortic insufficiency whose ejection fraction falls during exercise have elevated resting left ventricular systolic wall stress, suggesting that left ventricular hypertrophy has not been adequate. Although these patients have a normal resting ejection fraction, left ventricular systolic pump performance cannot be sustained during exercise when wall stress rises further.


UNLIKE normal subjects who usually respond to exercise with an increase in left ventricular ejection fraction,1,2 patients with chronic aortic insufficiency demonstrate more variable changes.3-11 Although some demonstrate an increase in ejection fraction, many others show little change or even a reduction during exercise. It has been suggested that failure to increase ejection fraction during exercise is an abnormal response that may be an early indicator of left ventricular dysfunction.3,4,9 However, many factors that affect ejection fraction, such as left ventricular loading conditions, may change during exercise. At present the mechanism responsible for the variable exercise ejection fraction response in patients with aortic insufficiency is uncertain.

Recently, several investigators have suggested that in patients with chronic aortic insufficiency, deterioration of left ventricular performance may be detected at an early stage by noninvasive means. Measurements of left ventricular chamber dimensions, fractional shortening, and wall stress by M mode echocardiography...
have been used for that purpose.  

This study was undertaken to investigate the mechanism responsible for the changes in ejection fraction in patients with chronic aortic insufficiency and to assess the association between echocardiographic measurements and the ejection fraction response. The population evaluated included only asymptomatic or minimally symptomatic patients with evidence of left ventricular dilatation and preserved resting ejection fraction, since it is in such patients that early detection of left ventricular dysfunction would be of greatest clinical value.

Methods

Study population. The study population consisted of 56 consecutive patients who fulfilled the entry criteria listed below. They were part of a larger group undergoing evaluation during the recruitment phase of a clinical trial designed to assess the long-term effects of vasodilator therapy on the natural history of patients with aortic insufficiency. This collaborative study involves research teams at the Oregon Health Sciences University and the University of California in San Francisco. Data from the study are stored and analyzed at the Oregon State University. A study protocol has been submitted to and approved by the human research committee at each of the participating institutions. Informed consent was obtained from all patients.

As part of the initial evaluation, patients underwent complete medical history and physical examination, 12-lead electrocardiogram, chest roentgenogram, M mode echocardiogram, and radionuclide angiogram. On the basis of these data, patients who fulfilled the following criteria were included in the analysis: clinical findings of aortic insufficiency, including the characteristic diastolic murmur and a pulse pressure of 60 mm Hg or greater; both left ventricular end-diastolic volume 100 ml/m2 or greater and preserved left ventricular ejection fraction (e.g., ≥0.50) by radionuclide angiography; ability to perform supine bicycle exercise; and the presence of at most mild, nonlimiting symptoms of fatigue and/or exertional dyspnea. Cardiac catheterization, which confirmed the diagnosis of aortic insufficiency, had been performed previously in 23 of the patients. Patients who had other possible causes of cardiomegaly, atrial fibrillation, a diastolic blood pressure of 90 mm Hg or greater, and those with noncardiovascular limitations to exercise were excluded. Patients with a history of angina or myocardial infarction, pathologic q waves on their electrocardiograms, or segmental wall motion abnormalities by radionuclide angiography were also excluded. In addition, significant coronary artery disease was ruled out in 20 patients (including 10 of 20 patients over 60 years old) who had undergone coronary angiography. Patients with physical findings or results of noninvasive tests suggesting additional significant valvular involvement were excluded from the study unless this was ruled out by cardiac catheterization and angiography. Patients with a transvalvular gradient of 25 mm Hg or greater across the aortic valve, those with a mitral valve area of 2.0 cm2 or less, or more than trivial mitral regurgitation, were excluded from the analysis.

The 56 patients who were included in this study averaged 47 years of age (range 19 to 83). There were 46 men and 10 women. The etiology of aortic insufficiency was believed to be rheumatic valvular disease in 12 (21%), congenital abnormality in 21 (38%), remote aortic valve endocarditis in five (9%), insufficiency as a consequence of valve commissurotomy for congenital aortic stenosis in one (2%), and unknown in 17 (30%). All patients had been aware of the presence of a heart murmur for at least 6 months and the known duration of disease for the group was 15.1 ± 12.3 years (mean ± SD). By New York Heart Association criteria all patients were in functional class I or II and in no instance had there been any change in symptoms within the 3 month period preceding study.

Tests. Radionuclide angiography was performed with a Technicare Series 400 Gamma Camera equipped with a 25 degree slant-hole collimator in San Francisco and a Searle Pho Gamma IV and parallel-hole collimator in Portland. Identical acquisition and exercise protocols and nuclear medicine analysis systems (MDS A2) were used. The blood pool was labeled with 20 to 25 mCi of technetium-99m siren pertechnetate by the red blood cell technique in vivo. At rest, equilibrium blood pool scintigrams were collected in both the anterior and the left anterior oblique projections, resulting in optimal separation of left and right ventricles and ventricles from atria. For the initial scintigrams the cardiac cycle was divided into 28 frames with a minimum of 300,000 counts/frame. Scintigrams were then collected with the patient at rest with legs elevated and during exercise. For these studies, all of which were obtained in the left anterior oblique projection, the cardiac cycle was divided into 20 frames and imaging was continued for 3 min. After a scinti-gram was obtained with the legs elevated, patients began supine exercise at 200 kpm and the workload was increased by 100 to 200 kpm every 4 min until exhaustion. Blood pressure was measured by palpation at the mid portion of each stage, with the fourth Korotkoff sound used to define diastole. A 5 ml blood sample was obtained by means of an indwelling venous catheter at the mid portion of the resting scintigrams and during even-numbered exercise stages. Patients exercised to a maximal workload of 587 kpm/min (range 150 to 1600 kpm/min). Exercise was terminated because of fatigue or breathlessness in all instances. No patient complained of chest pain.

Left ventricular ejection fraction was determined by standard technique, and left ventricular volumes were calculated by a counts-based, nongeometric method that has previously been reported from our laboratories and elsewhere.  

Left ventricular regions of interest were generated by a semiautomatic, second-derivative algorithm. These were manually adjusted when necessary. A time activity curve was then generated after subtraction of a parasternal background value. Ventricular volumes were calculated from the radionuclide activity normalized for the radionuclide activity per milliliter of blood corrected for the acquisition time per frame and decay of radioisotope. No attenuation correction was made, since the primary goal of the nuclear volume determinations was to assess changes during exercise in individual patients. The absolute volume measurements by this technique may therefore be in error in patients at the extremes of body habitus and in women with large breasts.

End-diastolic and end-systolic volumes were then converted to volumes according to regression equations relating the nuclear measurements to contrast ventriculograms generated in each of the two laboratories. In San Francisco the correlation coefficient between nuclear counts and ventricular volumes by contrast angiography was .98 with a standard error of the estimate (SEE) of 18 ml; in Portland the correlation coefficient was .99 with an SEE of 13 ml. As a means of further assessing the compatibility of the data obtained from the two laboratories, unprocessed data from studies performed in Portland were analyzed in San Francisco. Results from this analysis showed an excellent correlation for ejection fraction (r = .96), left ventricular end-diastolic volume (r = .97), and end-systolic volume (r = .98) at the two institutions.  

A left-to-right ventricular stroke count ratio was determined with the method described by Bough et al.  

On the basis of the change in ejection fraction from the "legs-
up" resting scintigram to the maximal exercise study, patients were divided into three groups. Patients whose ejection fraction rose by 0.05 units or more were assigned to group I. Patients whose ejection fraction changed by less than 0.05 units in either direction were assigned to group II. Those whose ejection fraction decreased by 0.05 units or greater were assigned to group III.

M mode echocardiograms were obtained on the same day as the radionuclide studies. Standard techniques for data acquisition were used at each institution. Blood pressure was obtained with a sphygmanometer while the left ventricular cavity was being imaged. The left ventricular end-diastolic dimension (LVED), left ventricular end-systolic dimension (LVES), percent fractional shortening (%) FS, left ventricular posterior wall thickness at end-diastole (PWTd) and end-systole (PWTs), and interventricular septum thickness at end-diastole (IVSd) were measured in the manner suggested by the Joint International Society and Federation of Cardiology/World Health Organization Task Force.

From these measurements left ventricular end-systolic stress (ESS) was calculated according to the method of Grossman et al. and Reichek et al.

ESS (dyne/cm²) = 1.33 x 10⁵ SBP x LVED/4PWT³ [1 + PWT/LVES]

where SBP = systolic blood pressure by cuff measurement and the constant 1.33 x 10⁵ converts millimeters of mercury to dynes per square centimeter.

Left ventricular mass was calculated as follows:

mass (g) = 1.04[(LVED + PWTd + IVSd)³ - LVED³] - 14

Statistical analysis. Patients were divided into three groups based on the ejection fraction response, as outlined above. Analyses of variance were performed to determine whether measurements performed both at rest and during exercise identified separate populations. If analysis suggested that the groups differed significantly from one another (p < .05), multiple range testing comparing individual groups to one another was performed; p values less than .05 were considered significant.

When the relationship between variables was considered to be continuous, linear regression analysis was performed.

Results

The mean and SD for variables measured by radionuclide angiography at rest and during maximal exercise are shown in table 1. For the entire group of 56 patients there was a 15% fall in left ventricular end-diastolic volume index (EDVI) and an 8% decline in end-systolic volume index (ESVI) with exercise. No significant change in ejection fraction, which was 0.65 ± 0.09 at rest and 0.64 ± 0.14 at exercise, occurred.

The ejection fraction response to exercise was heterogeneous, increasing by at least 0.05 units in 18 patients (group I), increasing or decreasing by less than 0.05 units in 18 patients (group II), and decreasing by 0.05 units or more in 20 patients (group III). The measurements obtained at rest and during exercise for the three groups are summarized in tables 2 and 3. Significant differences in the ages of the patients were

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rest</th>
<th>Maximal exercise</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>66 ± 9</td>
<td>124 ± 24</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>146 ± 20</td>
<td>197 ± 32</td>
<td>&lt;.001</td>
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<tr>
<td>DBP (mm Hg)</td>
<td>69 ± 13</td>
<td>83 ± 20</td>
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<tr>
<td>PP (mm Hg)</td>
<td>77 ± 22</td>
<td>114 ± 34</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EDVI (ml/m²)</td>
<td>158 ± 46</td>
<td>137 ± 39</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ESVI (ml/m²)</td>
<td>56 ± 24</td>
<td>52 ± 33</td>
<td>&lt;.02</td>
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<tr>
<td>SCR</td>
<td>4.2 ± 1.7</td>
<td>2.5 ± 0.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EF</td>
<td>0.65 ± 0.09</td>
<td>0.64 ± 0.14</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal workload</td>
<td>(kpm/min)</td>
<td>—</td>
<td>587 ± 294</td>
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</table>

Data expressed as mean ± SD.

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; SCR = stroke count ratio; EF = ejection fraction.

EDVI, ESVI, SCR, and EF all were measured by radionuclide angiography.

seen with a stepwise increase in age from group I to group III. Although there was trend toward larger resting left ventricular volumes and a slightly lower ejection fraction in group III patients, the differences among the groups were not significant.

At maximal exercise the groups did not differ significantly in their heart rate or blood pressure response, although both tended to be slightly higher in group I. There were significant differences among the groups for left ventricular volumes, with the lowest values for both end-diastolic and end-systolic volumes occurring in group I and the highest in group III. As expected by the definition of the groups, group I had a higher exercise ejection fraction than either group II or group III. The change in ejection fraction and left ventricular volumes from rest to exercise in the groups is shown in figure 1. All three groups demonstrated a reduction in end-diastolic volume during exercise, with the greatest change occurring in group I. Substantial intergroup differences in exercise-induced changes in end-systolic volume were present, with group I exhibiting an average decrease of 46%, group II showing essentially no change, and group III showing an increase of 18%. Although a modest inverse correlation was noted between the exercise ejection fraction response and the change in EDVI (r = -.35, SEE = 0.08 units, p < .005), a considerably stronger relationship was seen between changes in ejection fraction and ESVI (r = .87, SEE = 0.04 units, p < .00001) (figure 2).

As shown in table 3, exercise performance differed between the groups. Group I patients exercised longer and achieved a greater workload than did patients
whose ejection fraction decreased during exercise. When maximal workload was assessed as a function of the ejection fraction response, a modest but highly significant relationship was detected ($r = .47$, SEE = 262 kpm/min, p < .001).

The association between ejection fraction response and M mode echocardiographic variables is shown in table 4. A significant difference among the groups was seen only for end-systolic wall stress, with group III patients demonstrating significantly higher levels than either group I or group II patients. Examination of the intergroup differences in systolic blood pressure, wall thickness, and cavity dimensions, which are the determinants of wall stress, indicated that the differences were not caused by the influence of any single variable. Although group III tended to have a higher systolic pressure, larger dimensions at end-diastole, and a thinner posterior wall during diastole, the differences in each case were not significant.

**Discussion**

Within this large group of essentially asymptomatic patients with chronic aortic insufficiency, the ejection fraction response to supine bicycle exercise was quite variable. When patients were grouped according to ejection fraction response, no significant intergroup differences were present in resting left ventricular size and function as assessed by either nuclear or echocardiographic techniques. Although such heterogeneity in the ejection fraction response to exercise has been previously reported in patients with aortic insufficiency, this study is unique with regard to both the size and composition of the population. Prior investigations have included patients with normal left ventricular

### TABLE 2

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>ANOVA</th>
<th>Group I vs II</th>
<th>Group I vs III</th>
<th>Group II vs III</th>
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<td>Age (beats/min)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>HR (mm Hg)</td>
<td>37 ± 14</td>
<td>48 ± 15</td>
<td>56 ± 16</td>
<td>&lt;.003</td>
<td>&lt;.05</td>
<td>.001</td>
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<td>SBP (mm Hg)</td>
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<tr>
<td>DBP (mm Hg)</td>
<td>63 ± 18</td>
<td>60 ± 13</td>
<td>59 ± 11</td>
<td>NS</td>
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<tr>
<td>PP (mm Hg)</td>
<td>72 ± 24</td>
<td>76 ± 26</td>
<td>88 ± 33</td>
<td>NS</td>
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<td></td>
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<td>EDVI (ml/m²)</td>
<td>149 ± 33</td>
<td>149 ± 41</td>
<td>172 ± 57</td>
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<tr>
<td>ESVI (ml/m²)</td>
<td>50 ± 21</td>
<td>49 ± 20</td>
<td>65 ± 28</td>
<td>NS</td>
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<tr>
<td>SCR</td>
<td>4.2 ± 2.1</td>
<td>4.0 ± 1.4</td>
<td>4.5 ± 1.8</td>
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<tr>
<td>EF</td>
<td>0.66 ± 0.09</td>
<td>0.66 ± 0.09</td>
<td>0.62 ± 0.09</td>
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Data expressed as mean ± SD.
ANOVA = analysis of variance. Other abbreviations as in table 1.

### TABLE 3

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<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>ANOVA</th>
<th>Group I vs II</th>
<th>Group I vs III</th>
<th>Group II vs III</th>
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<td>18</td>
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<tr>
<td>HR (mm Hg)</td>
<td>133 ± 23</td>
<td>118 ± 24</td>
<td>118 ± 23</td>
<td>NS</td>
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<td>SBP (mm Hg)</td>
<td>209 ± 38</td>
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<td>193 ± 28</td>
<td>NS</td>
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<td></td>
<td></td>
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<tr>
<td>DBP (mm Hg)</td>
<td>88 ± 17</td>
<td>86 ± 15</td>
<td>76 ± 25</td>
<td>NS</td>
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<td>PP (mm Hg)</td>
<td>121 ± 33</td>
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<td>117 ± 40</td>
<td>NS</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>EDVI (ml/m²)</td>
<td>117 ± 32</td>
<td>135 ± 26</td>
<td>156 ± 45</td>
<td>&lt;.006</td>
<td>NS</td>
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<td>ESVI (ml/m²)</td>
<td>28 ± 18</td>
<td>45 ± 17</td>
<td>77 ± 36</td>
<td>&lt;.001</td>
<td>&lt;.01</td>
<td>&lt;.001</td>
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<tr>
<td>SCR</td>
<td>2.4 ± 0.8</td>
<td>2.7 ± 0.8</td>
<td>2.6 ± 0.7</td>
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<tr>
<td>EF</td>
<td>0.75 ± 0.10</td>
<td>0.66 ± 0.10</td>
<td>0.52 ± 0.11</td>
<td>&lt;.001</td>
<td>&lt;.01</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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<td>Ex stage³</td>
<td>3.8 ± 1.3</td>
<td>2.9 ± 1.0</td>
<td>2.1 ± 1.1</td>
<td>&lt;.001</td>
<td>&lt;.05</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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<tr>
<td>Maximal workload</td>
<td>744 ± 264</td>
<td>631 ± 308</td>
<td>405 ± 206</td>
<td>&lt;.001</td>
<td>NS</td>
<td>&lt;.001</td>
<td>&lt;.05</td>
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</table>

Data expressed as mean ± SD.
Abbreviations as in tables 1 and 2.
³At maximum workload.
Ejection Fraction

\[ p < 0.0001 \]

End-diastolic Volume

\[ p < 0.02 \]

End-systolic Volume

\[ p < 0.0001 \]

\[ T = \pm \text{S.D.} \]

FIGURE 1. Changes from rest to peak exercise in ejection fraction in the three groups, as well as changes in left ventricular EDVI and ESVI. Significance values for analysis of variance for the three groups are shown in the upper part of each panel and those for intergroup comparisons are bracketed below. See text for further discussion.

FIGURE 2. Top. Relationship between the change in EDVI and change in ejection fraction from rest to peak exercise in 56 patients with chronic aortic insufficiency. A weak inverse correlation is seen. Bottom. The relationship between the change in ESVI and change in ejection fraction from rest to peak exercise in the same group of patients. In this case the inverse correlation is highly significant.

size, thus raising the possibility of either acute or very mild disease.\(^4,7,9,11\) Others included patients with a depressed resting ejection fraction.\(^3,10,11\) The observation that ejection fraction is reduced even further during exercise in this group is of limited clinical value. All patients included in this study had enlarged left ventricles and preserved resting ejection fraction. Symptoms were minimal and most of these patients would not be considered for valve replacement by our current criteria. In patients such as these, the implications of a reduction in EF during exercise are of most interest, since it has been postulated that this response may be a harbinger of incipient myocardial dysfunction. Although an association between a reduction in ejection fraction during exercise and echocardiographic predictors of incipient left ventricular dysfunction has been reported,\(^15\) no such association was seen in this study, in which values for left ventricular dimensions and fractional shortening were similar for the three groups.

Factors that alter left ventricular loading conditions as well as those that change contractility will influence ejection fraction. When left ventricular preload is reduced or afterload is increased, ejection fraction may fall. Although preload, as estimated by EDVI, fell in all three groups, the reduction was significantly smaller in group III, suggesting that the ejection fraction responses were not determined by preload changes. At rest, end-systolic wall stress, which is a measure of left ventricular afterload, was considerably higher in group
TABLE 4
Echocardiographic indexes for the three groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>ANOVA Group I vs II</th>
<th>Group I vs III</th>
<th>Group II vs III</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>18</td>
<td>18</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>135±18</td>
<td>136±23</td>
<td>146±20</td>
<td>NS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EDD (mm)</td>
<td>64±5</td>
<td>63±16</td>
<td>68±8</td>
<td>NS</td>
<td>-</td>
<td>-</td>
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<td>ESD (mm)</td>
<td>40±6</td>
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<td>44±8</td>
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<tr>
<td>FS</td>
<td>0.37±0.07</td>
<td>0.39±0.06</td>
<td>0.35±0.07</td>
<td>NS</td>
<td>-</td>
<td>-</td>
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<tr>
<td>PWTd (mm)</td>
<td>12.1±1.6</td>
<td>12.4±1.5</td>
<td>11.6±1.2</td>
<td>NS</td>
<td>-</td>
<td>-</td>
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<tr>
<td>PWTs (mm)</td>
<td>18.1±2.2</td>
<td>18.7±0.8</td>
<td>18.1±2.6</td>
<td>NS</td>
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<td>EDD/2 PWTd</td>
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<td>2.9±0.4</td>
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<td>-</td>
<td>-</td>
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<td>ESS (\times 10^5) dyne/cm²</td>
<td>70±18</td>
<td>69±17</td>
<td>89±20</td>
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<td>NS</td>
<td>&lt;.01 &lt;.005</td>
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<tr>
<td>LV mass (g)</td>
<td>446±109</td>
<td>460±169</td>
<td>491±145</td>
<td>NS</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

Data expressed as mean ± SD.

EDD = end-diastolic dimension; ESD = end-diastolic pressure; FS = percent fractional shortening; PWTd = posterior wall thickness at diastole; PWTs = posterior wall thickness at systole; ESS = end-systolic stress; LV = left ventricular. Other abbreviations as in tables 1 and 2.

III patients than in group I or II. Although stress could not be measured during exercise, analysis of the variables used in the stress equation suggests that it rose considerably in group III patients. End-systolic wall stress varies directly with end-systolic pressure and volume and indirectly with wall thickness. All three groups had similar, elevated levels of systolic blood pressure during exercise. However, while ESVI fell in group I patients and showed essentially no change in group II patients, ESVI increased in group III. The only factor that could compensate for this would be a proportionately greater increase in wall thickness in group III patients during exercise. Since there were no significant differences in resting wall thickness among the groups and group III had decreased ejection fraction during exercise, it seems highly unlikely that this group had a greater increase in wall thickness than that in groups I and II. Thus the high levels of resting wall stress in group III patients and the strong inverse correlation between the ejection fraction response and changes in end-systolic volume strongly suggest an important role of afterload excess in the exercise ejection fraction response in our patients. The finding that ejection fraction was not reduced in group III patients at rest despite higher levels of wall stress suggests that reserve mechanisms were adequate to maintain cardiac function in the basal state but not when demands on the ventricle increased during exercise.

Grossman et al. have suggested that increased systolic wall stress is the stimulus for compensatory hypertrophy of the left ventricle. To maintain wall stress in the range of that in groups I and II, group III patients should have had larger values for wall thickness and left ventricular mass. Thus, in group III patients compensatory hypertrophy did not appear to have been adequate for the prevailing left ventricular loading conditions. Whether this imbalance between load and hypertrophy resulted from gradual failure to develop adequate hypertrophy or was a relatively recent phenomenon in response to a change in the severity of regurgitation or a reduction in myocardial contractility cannot be answered from the present data. Other workers have evaluated the importance of systolic wall stress in aortic insufficiency. Richar et al. noted that levels of end-systolic stress were similar in asymptomatic patients with aortic insufficiency who had a normal resting ejection fraction and a group of normal subjects. However, symptomatic patients with aortic insufficiency with a reduced ejection fraction had evidence of substantially higher levels of end-systolic stress. From these data the authors concluded that afterload excess had contributed to the reduction in ejection fraction. A similar conclusion was reached by Osbakken et al. who evaluated peak wall stress by means of left heart catheterization and angiography. Lewis et al. and Iskandrian et al. reported that estimates of peak systolic stress at rest were higher in patients with aortic regurgitation who had an abnormal exercise ejection fraction response than in patients with normal exercise reserve. Recently, both Kumparis et al. and Gaasch et al. have demonstrated that patients with chronic aortic insufficiency and evidence of abnormally high systolic wall stress preoperatively had a higher incidence of postoperative heart failure and were less likely to achieve substantial reduction in left ventricular size after surgery. Although data from this study do not directly address the prognostic significance of a decreasing ejection fraction exercise, we
did find that group III patients, who were otherwise similar to other patients, demonstrated significantly poorer exercise performance. Only a careful longitudinal follow-up of this group, which is currently under way, will determine whether these findings are of prognostic importance.

There are several limitations to the present study. Although the patient population was fairly homogeneous in that all had evidence of left ventricular dilatation, a preserved resting ejection fraction, and minimal or no symptoms, there were significant differences in age, with group III patients being older than those in groups I and II. This suggests that the impaired ejection fraction response and relatively insufficient degree of hypertrophy may be a function of the chronicity of the volume overload. It may also be an age-related phenomenon. Previous studies have shown that older subjects without evidence of heart disease tend to have a smaller increase in ejection fraction during exercise than younger patients. However, a reduction in ejection fraction of greater than 0.05 units in patients under 60 years of age was rare in these studies. Since 23 of our patients demonstrated a reduced ejection fraction and only 10 of these patients were older than 60, an age-related reduction in myocardial reserve alone cannot account for the abnormal responses seen in the majority of our patients. The presence of a greater number of older patients in group III raises the possibility that some of the differences may have been caused by undetected coronary disease. Although this cannot be excluded entirely, since not all patients underwent coronary angiography, the lack of clinical evidence of coronary disease, chest pain during exercise testing, or exercise-induced abnormalities in segmental wall motion all argue against the presence of significant coronary disease. In addition, none of the 20 patients who had undergone coronary angiography, including 10 of 20 group III subjects, had evidence of significant coronary disease.

In this study cuff systolic pressure rather than end-systolic pressure was used to calculate end-systolic wall stress. However, other investigators have shown that cuff systolic pressure correlates closely with end-systolic pressure in normal subjects and in patients with heart disease, including aortic insufficiency.

In addition, Reichek et al. have demonstrated a close correlation between end-systolic stress measured by the methods used in this study and by more precise invasive methods in patients with aortic insufficiency. We evaluated meridional wall stress in this study. Although this is usually representative of changes that develop in circumferential and radial wall stress, differences may exist depending on the geometry of the ventricle.

Clinical significance. The patients included in this analysis would not usually be considered as surgical candidates based on their lack of symptoms and the presence of preserved resting left ventricular function. However, it has been suggested that a reduction in ejection fraction during exercise is an early manifestation of deterioration in left ventricular systolic pump function. The observation that end-systolic wall stress is elevated at rest and that it appears to rise substantially during exercise in patients whose ejection fraction falls suggests that afterload in excess of available myocardial reserve is an important determinant of this response. Furthermore, lack of adequate hypertrophy to normalize wall stress raises the possibility that compensatory mechanisms are beginning to fail in patients who experience a reduction in ejection fraction during exercise. Whether or not this represents an intermediate phase between well-compensated aortic insufficiency and the onset of overt left ventricular dysfunction is still not known. If this is an intermediate stage, its duration and the consequences of prolonged observation on the ability of the left ventricle to respond favorably to valve replacement at a later time are also unknown. Therefore these data must be interpreted with caution. Recommendations for valve replacement should not be based on a reduction in exercise ejection fraction alone, but this finding probably identifies a group of patients who should be followed with extra caution.

The observations regarding afterload excess also raise interesting questions regarding the use of vasodilator drugs in the treatment of aortic insufficiency. There is evidence, at least in short-term studies, that arterial dilating agents will reduce both left ventricular volume and systolic arterial pressure. The expected result of such therapy would be a reduction in systolic wall stress. If afterload excess is an important cause for deterioration of left ventricular performance, the possibility exists that early intervention with an arterial dilating agent might prevent or delay this.

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