Determinants of Ejection Performance in Aortic Stenosis

DOMINIK HUBER, M.D., JOERG GRIMM, PH.D., ROSEMARIE KOCH, AND HANS P. KRAYENBUELH, M.D.

SUMMARY The cause of reduced ejection performance in patients with aortic stenosis is controversial. The relative contribution of afterload and contractility was evaluated in 76 patients with pure or predominant valvular aortic stenosis studied by left ventricular micromanometry and quantitative cineangiography. Thirteen patients without detectable heart disease served as controls. The ejection performance was assessed in terms of the mean normalized systolic ejection rate (MNSER, normal ≥ 2.0 end-diastolic volumes (EDV)/sec), contractility by total pressure Vmax (normal ≥ 1.47 muscle lengths/sec) and/or peak measured velocity of shortening (normal ≥ 1.14 muscle lengths/sec) and afterload by peak systolic circumferential wall stress (normal < 460 dyn · 10⁹/cm²).

The patients were divided into four groups according to the level of isovolumic contractility and peak systolic wall stress. In group 1, contractility and wall stress were normal. In group 2, contractility was normal and wall stress was increased. Wall stress was normal in group 3 and increased in group 4; in both groups, the isovolumic contractile indexes were depressed. At normal (groups 1 and 3) or increased (groups 2 and 4) wall stress, MNSER was significantly (p < 0.01) smaller in patients with reduced isovolumic contractility (1.72 EDV/sec in group 3 and 1.48 EDV/sec in group 4) than in the corresponding groups with normal contractility (2.34 EDV/sec in group 1 and 2.13 EDV/sec in group 2). Conversely, with a normal (control group and groups 1 and 2) or depressed (groups 3 and 4) contractile state, there was a significant inverse linear relationship between MNSER and systolic wall stress. The slopes of the two curves were almost identical, but the intercept on the y-axis (MNSER) was significantly (p < 0.001) smaller in patients with depressed contractility (3.09 EDV/sec) than in those with normal contractility (2.59 EDV/sec). Thus, both altered contractility and increased afterload are operative in depressing left ventricular ejection performance.

The observation that contractile state can be normal or impaired at normal and increased systolic wall stress is evidence for nonuniform myocardial quality in adequate as well as inadequate hypertrophy. The significantly higher left ventricular angiographic muscle mass in groups 3 and 4 than in groups 1 and 2 is consistent with the concept that whether or not hypertrophy is adequate or inadequate in terms of maintaining normal systolic stress, advanced myocardial hypertrophy leads to depression of contractility.

THE NATURE of depressed left ventricular ejection performance in chronic pressure-overload hypertrophy due to aortic stenosis is controversial. Whereas excess afterload accompanied by inadequate hypertrophy of normally functioning cardiac muscle has been suggested as the cause of impaired left ventricular shortening,¹ intrinsic depression of contractility of the hypertrophied myocardium has also been considered, at least in part, to be the cause of altered ejection performance.²ushing We studied 76 patients with aortic stenosis using high-fidelity micromanometry and quantitative cineangiography and found evidence that both altered contractility and increased afterload are operative in depressing left ventricular ejection performance. Depression of contractile state occurred not only in a subset of patients with inadequate hypertrophy,³ but also in a subset of patients with adequate hypertrophy, suggesting a nonuniform quality of the myocardium in pressure-overload hypertrophy.

Material and Methods

Patients

Seventy-six patients (17 females and 59 males) with pure or predominant aortic stenosis were studied by right- and left-heart catheterization and cineangiography. Premedication consisted of 10 mg of oral Librium. After the diagnostic part of the catheterization, a micromanometer catheter (Statham SF-1 or Millar) was introduced transseptally into the left ventricle.¹ Informed consent was obtained for this study. Fifty-four of the 76 patients had pure or almost pure aortic stenosis of varying severity, with an aortic regurgitation fraction of 0.20 or less by thermodilution (table 1). The remaining 22 patients had predominant aortic stenosis with aortic regurgitation fractions of 0.22–0.68. No patient had an aortic valve area greater than 1.0 cm². One patient had a small ventricular septal defect and another had a patent ductus arteriosus with a small left-to-right shunt. Selective coronary arteriography was carried out in 62 of the 76 patients. Significant arterial narrowing was absent in all but one patient, who had a 60% stenosis of the right coronary artery. The left ventricular cineangiogram showed no localized wall motion abnormality. The remaining 14 patients (two females and 12 males) had no clinical symptoms of coronary artery disease and none was older than 45 years (mean age 29 years, range 17–45 years).

All patients were in sinus rhythm and the duration

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of the QRS did not exceed 0.11 second. Thirty-two of the 76 patients with aortic stenosis were on maintenance digitalis at the time of catheterization. Thirteen patients (five females and eight males) without detectable heart disease were investigated by the same methods and served as controls (table 1). Six were studied because of atypical chest pain and seven had a systolic murmur found to be functional in origin. The mean age was significantly lower in the controls than in the 76 patients with aortic stenosis (34 vs 48 years, \( p < 0.001 \)).

Calculations

Left ventricular volumes and ejection fraction (EF) were determined from the cineangiogram obtained in the right anterior oblique projection at a film speed of 50 or 75 frames/sec. The area-length method was used for the calculations. In 48 patients, an additional cineventriculogram was carried out in the antero-posterior projection to determine the end-diastolic thickness of the left ventricular free wall. In the remaining patients, wall thickness was measured in the middle third of the anterior contour of the right anterior oblique ventriculogram. Left ventricular muscle mass was calculated according to the method of Rackley and co-workers.\(^{15}\)

To assess left ventricular ejection performance, we calculated the mean rate of ventricular volume reduction during systole (mean normalized systolic ejection rate [MNSER]) by dividing the left ventricular EF by the ejection time.\(^{11}\) We chose this variable because it has been shown to be particularly sensitive for detecting abnormal ejection performance\(^{14}\) and because it appeared appropriate in analogy to the classic force-velocity relationship to oppose a velocity variable rather than a pure shortening variable (as EF) to afterload. As a measure of left ventricular afterload, circumferential peak systolic wall stress \( (S_{\text{peak}}) \) was calculated according to the technique of Gaasch and co-workers.\(^{12}\) Although this method is based on the determination of end-diastolic and end-systolic left ventricular dimensions, wall thickness and peak systolic pressure and requires several assumptions, the values of peak stress calculated in patients with aortic valve disease compare favorably \( (r = 0.95) \) with max-

| TABLE 1. Hemodynamic Data Characterizing Aortic Valvular Obstruction |
|-----------------------------|----------------|------------------|------------------|
|                            | Age \( (\text{years}) \) | MSPG \( (\text{mm Hg}) \) | fao \( (\text{systolic pressure gradient}) \) |
| Controls \( (n = 13) \)     | 34              | (19-48)          |                          |
| Aortic stenosis \( (n = 76) \) | 48             | (17-73)         | 0.15                      |
| Pure \( (n = 54) \)          | 47             | (17-69)         | 0.05                      |
| Predominant \( (n = 22) \)   | 48             | (29-73)         | 0.39                      |
|                            |                | (36-126)        | 0.76                      |

Mean values are given with ranges in parentheses.

Abbreviations: AVA = aortic valve area; fao = aortic regurgitant fraction; MSPG = mean systolic pressure gradient across the aortic valves.
shortening extrapolated linearly to zero pressure (Vmax), 8,19 Total pressure indexes were given preference to developed pressure indexes because the former have been shown to be more reliable in detecting a reduced contractility in patients with unequivocally depressed left ventricular function. 11 With a series elasticity constant of 28, the normal range in our laboratory is for Vpm 1.14–1.96 muscle lengths (ML)/sec and for Vmax, 1.47–2.39 ML/sec. 8 The assumption of an identical series elasticity constant in normal and in hypertrophied left ventricular myocardium appears justified because, in a study of patients with pressure and volume overload hypertrophy, 26 the series elastic stiffness constant was not significantly different in patients with aortic stenosis, aortic insufficiency and controls, whereas patients with congestive cardiomyopathy had a significantly increased stiffness constant.

Patients with Aortic Stenosis

The 76 patients with aortic stenosis were divided into four groups based on their level of isovolumic contractility and afterload (fig. 1). In groups 1 and 2, Vpm (≥ 1.14 ML/sec) and Vmax (≥ 1.47 ML/sec) were normal. Afterload as estimated from Speak was normal in group 1 (< 460 dyn · 10^3/cm^2) and increased in group 2 (≥ 460 dyn · 10^3/cm^2). In groups 3 and 4, the isovolumic contractile indexes were depressed (Vpm < 1.14 and Vmax < 1.47 ML/sec). The Speak was normal in group 3 and elevated in group 4. To make sure that the classification of patients with normal and depressed contractility based on Vpm and Vmax was not accidental, left ventricular contractility was also evaluated by means of a “ventricular function” diagram with two independent variables not used in the previously described grouping of the 76 patients. Figure 2 shows the relationship between the maximal rate of rise of left ventricular pressure (dP/dt max) and the end-diastolic circumferential wall stress. The mean values in groups 3 and 4 were clearly shifted to the right as compared with those of groups 1 and 2 and the control patients. The left ventricular circumferential wall stress at dP/dt max was not significantly different in groups 1 and 3 (205 vs 198 · 10^3 dyn/cm^2) or in groups 2 and 4 (252 vs 268 · 10^3 dyn/cm^2). In control patients, stress at dP/dt max was 262 · 10^3 dyn/cm^2. Thus, under similar loading conditions, the rightward and downward shift of group 3 with respect to group 1 and of group 4 with respect to

FIGURE 1. Grouping of the 76 patients into four groups (I–IV) based on peak measured velocity of contractile elements (Vpm) and/or total pressure Vmax (measures of myocardial contractility) and on peak systolic wall stress (measure of left ventricular afterload).

FIGURE 2. Relationship between the maximal rate of rise of left ventricular pressure (max DP/dt) and end-diastolic circumferential wall stress. In this ventricular function diagram, the two groups in which depressed left ventricular contractility was postulated based on the isovolumic contractile measures Vpm and Vmax (groups 3 and 4) were clearly shifted to the right as compared with groups 1 and 2 and the control group (C). This rightward shift confirms the reduced contractile state in groups 3 and 4.
group 2 in dP/dt max plotted against end-diastolic stress confirms the reduced contractile state in groups 3 and 4 that was postulated on the basis of Vpm and total pressure Vmax.

Statistics

For intergroup comparisons, the SPSS one-way computer program was used.21 If the analysis of variance was significant, p values were obtained by the least significant difference procedure; otherwise, the Scheffe procedure was applied. For the comparison of two regression lines, covariance regression analysis was used.22

Results

The hemodynamic and angiographic data of the control patients and of the four groups with aortic stenosis are summarized in tables 2 and 3. In the patients with increased peak systolic wall stress (groups 2 and 4), the severity of the aortic stenosis as estimated from the aortic valve area was somewhat more marked than in those with similar inotropic state but normal peak wall stress (groups 1 and 3). The size of the aortic valve orifice was significantly different in groups 1 and 2 (p < 0.05).

According to the mode of grouping, the isovolumic contractile indexes Vpm and Vmax were normal in groups 1 and 2 and depressed in groups 3 and 4. S\textsubscript{peak} was increased in groups 2 and 4 as compared with groups 1 and 3 and the controls. There was no difference of S\textsubscript{peak} in groups 1 and 3 or in groups 2 and 4.

Left ventricular ejection performance as estimated by the MNSER varied considerably in the four groups. With either normal (groups 1 and 2) or depressed (groups 3 and 4) contractile state, an increased systolic wall stress or afterload (groups 2 and 4) tended to be associated with a smaller MNSER. Conversely, with either normal (groups 1 and 3) or increased (groups 2 and 4) systolic wall stress, MNSER was significantly smaller in patients with impaired isovolumic contractility (groups 3 and 4) than in patients with normal contractility (groups 1 and 2). A linear regression analysis of MNSER vs S\textsubscript{peak} in the patients with normal contractility and those with depressed isovolumic contractility (fig. 3) showed a significant linear inverse relationship between MNSER and S\textsubscript{peak} for both groups. Comparison of the two curves by covariance regression analysis showed no significant difference of the slopes of the curves, which were almost parallel. The intercept on the y-axis was significantly (p < 0.001) smaller in the patients with depressed than in those with normal contractility. Thus, ejection performance (MNSER) was inversely related to afterload (S\textsubscript{peak}), and this relationship was modulated by the level of the contractile state.

EF behaved in a manner similar to MNSER in the four groups with aortic stenosis (table 3). Again, EF was significantly smaller in the patients with impaired isovolumic contractility (groups 3 and 4) than in the patients with normal contractility (groups 1 and 2).

The use of the thick-walled formula23 to calculate wall stress instead of the Sandler-Dodge formula18 led only to minor changes in the classification of the patients with aortic stenosis (table 4). Using the control patients to establish the normal range of peak systolic stress (250–425 \times 10^4 \text{dyn/cm}^2), three of the former group 2 patients became group 1 patients, and two patients of group 4 shifted to group 3. Comparison of table 4 with table 3 shows that the mean values of MNSER and EF in groups 1 to 4 were similar and the p values were the same. Moreover, regression analysis between MNSER and S\textsubscript{peak} revealed two significant (p < 0.005 and p < 0.05) linear inverse relationships: the regression formula for the pooled data of groups 1 and 2 and controls was 

\[ y = 2.99 - 0.0017x \]

and for groups 3 and 4, \[ y = 2.49 - 0.0021x \]. The two regression lines were almost parallel; however, the intercept in the patients with normal isovolumic contractility was higher than in

![Figure 3. Relationship between mean normalized systolic ejection rate (MNSER) and peak systolic circumferential wall stress. Separate linear regression analysis was performed for the patients with normal contractility (closed symbols) and for the patients with depressed contractility (open symbols). Both regressions elicited a significant inverse relationship between MNSER and peak systolic wall stress. Comparison of the two lines by covariance regression analysis yielded no significant difference for the slopes but a significantly (p < 0.001) higher intercept in the patients with normal isovolumic contractility (3.09 end-diastolic volumes/sec) than in those with depressed contractility (2.59 end-diastolic volumes/sec). Thus, MNSER depended on both contractile state and afterload. CO = control patients.](image-url)
### Table 2. Hemodynamic Data

<table>
<thead>
<tr>
<th>Group</th>
<th>HR (beats/min)</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>MSPG (mm Hg)</th>
<th>AVA (cm²)</th>
<th>max dp/dt (mm Hg/sec)</th>
<th>Vpm (ML/sec)</th>
<th>Vmax (ML/sec)</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group C (n = 13)</td>
<td>76 ± 11 (63-104)</td>
<td>116 ± 12 (91-142)</td>
<td>8.6 ± 2.8 (3.2-12.4)</td>
<td>6.3 ± 2.4 (2.1-9.3)</td>
<td>0.79 ± 0.15 (0.3-1.1)</td>
<td>1670 ± 350 (1210-2270)</td>
<td>1.62 ± 0.32 (1.14-1.96)*</td>
<td>1.96 ± 0.37 (1.47-2.39)*</td>
<td>34 ± 10 (19-48)</td>
</tr>
<tr>
<td>Group 1 (n = 19)</td>
<td>72 ± 12 (52-98)</td>
<td>188 ± 39 (127-274)</td>
<td>13.6 ± 5.8 (6.0-27.0)</td>
<td>63 ± 27 (10-108)</td>
<td>0.79 ± 0.33 (0.3-1.5)</td>
<td>1840 ± 320 (1200-2410)</td>
<td>1.48 ± 0.26 (1.18-2.0)</td>
<td>1.90 ± 0.26 (1.48-2.52)</td>
<td>43 ± 15 (19-65)</td>
</tr>
<tr>
<td>Group 2 (n = 32)</td>
<td>74 ± 11 (53-97)</td>
<td>225 ± 38 (158-313)</td>
<td>16.9 ± 5.3 (8.3-28.0)</td>
<td>81 ± 25 (36-131)</td>
<td>0.64 ± 0.21 (0.3-1.05)</td>
<td>2270 ± 470 (1590-3120)</td>
<td>1.51 ± 0.24 (1.17-2.17)</td>
<td>1.95 ± 0.3 (1.56-2.93)</td>
<td>50 ± 13 (17-69)</td>
</tr>
<tr>
<td>Group 3 (n = 9)</td>
<td>75 ± 11 (57-128)</td>
<td>184 ± 24 (136-210)</td>
<td>28.6 ± 7.0 (16.1-37.4)</td>
<td>66 ± 16 (45-98)</td>
<td>0.75 ± 0.20 (0.45-1.0)</td>
<td>1470 ± 460 (797-2380)</td>
<td>0.87 ± 0.27 (0.54-1.3)</td>
<td>1.11 ± 0.27 (0.75-1.42)</td>
<td>41 ± 8 (28-50)</td>
</tr>
<tr>
<td>Group 4 (n = 16)</td>
<td>78 ± 16 (59-93)</td>
<td>210 ± 24 (165-242)</td>
<td>26.2 ± 8.5 (10.5-39.7)</td>
<td>76 ± 16 (45-104)</td>
<td>0.58 ± 0.18 (0.3-1.0)</td>
<td>1840 ± 370 (1140-2320)</td>
<td>1.00 ± 0.18 (0.70-1.27)</td>
<td>1.28 ± 0.17 (0.85-1.51)</td>
<td>52 ± 10 (33-73)</td>
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</table>

**p value**

<table>
<thead>
<tr>
<th>1 vs C</th>
<th>2 vs C</th>
<th>3 vs C</th>
<th>4 vs C</th>
<th>1 vs 2</th>
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</table>

Values are mean ± SD. Ranges are given in parentheses.

*Normal range of our laboratory.*

Abbreviations: HR = heart rate; LVSP = left ventricular peak systolic pressure; LVEDP = left ventricular end-diastolic pressure; MSPG = mean systolic pressure gradient; AVA = aortic valve area; max dp/dt = maximal rate of rise of left ventricular pressure; Vpm = peak measured velocity of shortening of the contractile elements; ML = muscle length; Vmax = maximal extrapolated velocity of shortening of the contractile elements; C = control.
### Table 3. Angiographic Data

<table>
<thead>
<tr>
<th>Group</th>
<th>M_d (cm)</th>
<th>h_d (cm)</th>
<th>M_d/h_d</th>
<th>EDVI (ml/m³)</th>
<th>LMMI (g/m³)</th>
<th>EDVI/LMMI</th>
<th>MNSER (EDV/sec)</th>
<th>EF (%)</th>
<th>Stress_end (dyn · 10⁴/cm²)</th>
<th>Stress_peak (dyn · 10⁴/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C (n=13)</td>
<td>5.34 ± 0.55</td>
<td>0.78 ± 0.11</td>
<td>6.99 ± 1.09</td>
<td>81 ± 15</td>
<td>81 ± 18</td>
<td>1.02 ± 0.16</td>
<td>2.59 ± 0.36</td>
<td>70 ± 7</td>
<td>34 ± 12</td>
<td>368 ± 53</td>
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<tr>
<td>(4.22-6.33)</td>
<td>(0.59-0.97)</td>
<td>(4.96-9.17)</td>
<td>(53-98)</td>
<td>(57-117)</td>
<td>(0.8-1.31)</td>
<td>(2.08-3.19)</td>
<td>(61-86)</td>
<td>(15-57)</td>
<td>(275-451)</td>
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<tr>
<td>1 (n=19)</td>
<td>5.49 ± 0.53</td>
<td>1.21 ± 0.26</td>
<td>4.73 ± 1.17</td>
<td>91 ± 17</td>
<td>152 ± 49</td>
<td>0.64 ± 0.20</td>
<td>2.34 ± 0.39</td>
<td>71 ± 7</td>
<td>36 ± 13</td>
<td>405 ± 36</td>
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<tr>
<td>(4.31-6.32)</td>
<td>(0.78-1.68)</td>
<td>(3.12-7.44)</td>
<td>(54-113)</td>
<td>(78-272)</td>
<td>(0.38-1.17)</td>
<td>(1.7-3.25)</td>
<td>(62-85)</td>
<td>(22-61)</td>
<td>(340-452)</td>
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<tr>
<td>2 (n=32)</td>
<td>5.84 ± 0.96</td>
<td>1.14 ± 0.19</td>
<td>5.24 ± 1.24</td>
<td>107 ± 35</td>
<td>160 ± 55</td>
<td>0.70 ± 0.17</td>
<td>2.13 ± 0.29</td>
<td>67 ± 7</td>
<td>49 ± 16</td>
<td>530 ± 54</td>
</tr>
<tr>
<td>(4.4-9.61)</td>
<td>(0.75-1.58)</td>
<td>(3.47-9.01)</td>
<td>(60-169)</td>
<td>(78-363)</td>
<td>(0.46-1.14)</td>
<td>(1.5-2.7)</td>
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<td>(26-94)</td>
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<tr>
<td>3 (n=9)</td>
<td>6.00 ± 0.98</td>
<td>1.37 ± 0.18</td>
<td>4.5 ± 1.18</td>
<td>123 ± 53</td>
<td>202 ± 33</td>
<td>0.59 ± 0.18</td>
<td>1.72 ± 0.34</td>
<td>57 ± 11</td>
<td>75 ± 29</td>
<td>389 ± 47</td>
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<tr>
<td>(5.39-7.53)</td>
<td>(1.12-1.71)</td>
<td>(3.22-6.28)</td>
<td>(73-207)</td>
<td>(173-279)</td>
<td>(0.35-0.87)</td>
<td>(1.28-2.10)</td>
<td>(37-70)</td>
<td>(40-113)</td>
<td>(317-438)</td>
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<tr>
<td>4 (n=16)</td>
<td>6.45 ± 0.87</td>
<td>1.21 ± 0.15</td>
<td>5.38 ± 0.85</td>
<td>137 ± 45</td>
<td>194 ± 60</td>
<td>0.71 ± 0.13</td>
<td>1.48 ± 0.50</td>
<td>47 ± 18</td>
<td>81 ± 32</td>
<td>557 ± 72</td>
</tr>
<tr>
<td>(5.04-7.72)</td>
<td>(0.87-1.44)</td>
<td>(4.05-6.86)</td>
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<td>(92-292)</td>
<td>(0.52-0.98)</td>
<td>(0.58-2.26)</td>
<td>(13-70)</td>
<td>(31-135)</td>
<td>(471-717)</td>
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</table>

*p value:

1 vs C NS < 0.01 < 0.01 NS < 0.01 < 0.01 NS NS NS NS NS
2 vs C NS < 0.01 < 0.01 < 0.05 < 0.01 < 0.01 < 0.01 NS < 0.05 < 0.01
3 vs C NS < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 NS < 0.01 NS
4 vs C < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 NS < 0.01 NS
1 vs 2 NS NS NS NS NS NS NS NS < 0.05 < 0.01 NS
1 vs 3 NS < 0.05 NS < 0.05 < 0.02 NS NS NS NS NS NS ≤ 0.02 NS
2 vs 4 < 0.02 NS < 0.01 < 0.05 NS < 0.01 < 0.01 NS < 0.01 NS
3 vs 4 NS NS NS NS NS NS NS NS NS < 0.01 NS

Values are mean ± SD. Ranges are given in parentheses.

Abbreviations: M_d = end-diastolic minor axis of the left ventricle; h_d = end-diastolic left ventricular wall thickness; EDVI = left ventricular end-diastolic volume index; LMMI = left ventricular muscle mass index; MNSER = mean normalized systolic ejection rate; EDV = end-diastolic volume; EF = left ventricular ejection fraction; Stress_end = end-diastolic circumferential wall stress; Stress_peak = peak systolic circumferential wall stress.
TABLE 4. Patient Groups When Circumferential Stress Was Calculated According to the Thick-walled Model of Falsetti et al.17

<table>
<thead>
<tr>
<th></th>
<th>MNSER (EDV/sec)</th>
<th>EF (%)</th>
<th>stressed (10^5 dyn/cm²)</th>
<th>stresspeak (10^5 dyn/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group C (n = 13)</td>
<td>2.59 ± 0.36</td>
<td>70 ± 7</td>
<td>31 ± 12</td>
<td>341 ± 50</td>
</tr>
<tr>
<td></td>
<td>(2.08-3.19)</td>
<td>(61-86)</td>
<td>(14-54)</td>
<td>(250-425)</td>
</tr>
<tr>
<td>Group 1 (n = 22)</td>
<td>2.33 ± 0.37</td>
<td>71 ± 7</td>
<td>34 ± 12</td>
<td>374 ± 41</td>
</tr>
<tr>
<td></td>
<td>(1.70-3.25)</td>
<td>(62-85)</td>
<td>(20-57)</td>
<td>(297-425)</td>
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<tr>
<td>Group 2 (n = 29)</td>
<td>2.12 ± 0.29</td>
<td>67 ± 7</td>
<td>45 ± 15</td>
<td>484 ± 52</td>
</tr>
<tr>
<td></td>
<td>(1.50-2.70)</td>
<td>(56-81)</td>
<td>(23-82)</td>
<td>(426-618)</td>
</tr>
<tr>
<td>Group 3 (n = 11)</td>
<td>1.75 ± 0.35</td>
<td>57 ± 11</td>
<td>67 ± 25</td>
<td>361 ± 52</td>
</tr>
<tr>
<td></td>
<td>(1.28-2.28)</td>
<td>(37-70)</td>
<td>(37-104)</td>
<td>(286-421)</td>
</tr>
<tr>
<td>Group 4 (n = 14)</td>
<td>1.41 ± 0.49</td>
<td>45 ± 19</td>
<td>76 ± 31</td>
<td>516 ± 63</td>
</tr>
<tr>
<td></td>
<td>(0.58-2.01)</td>
<td>(13-70)</td>
<td>(27-128)</td>
<td>(433-646)</td>
</tr>
</tbody>
</table>

*p value
1 vs C NS NS NS NS
2 vs C < 0.01 NS < 0.05 < 0.01
3 vs C < 0.01 < 0.01 < 0.01 NS
4 vs C < 0.01 < 0.01 < 0.01 < 0.01
1 vs 2 NS NS < 0.05 < 0.01
1 vs 3 < 0.01 < 0.01 < 0.01 NS
2 vs 4 < 0.01 < 0.01 < 0.01 NS
3 vs 4 NS < 0.01 NS < 0.01

Values are mean ± sd. Ranges are given in parentheses.
Abbreviations: MNSER = mean normalized systolic ejection rate; EDV = end-diastolic volume; EF = left ventricular ejection fraction; stressed = end-diastolic circumferential wall stress; stresspeak = peak systolic circumferential wall stress.

Discussion

Assessment of left ventricular contractility in patients with pressure overload is difficult because the standard ejection phase measures might be reduced by excessive afterload in the absence of any derangements of myocardial contractility and because the afterload-independent pressure-derived contractile indexes (e.g., Vpm and Vmax) might indicate an erroneously reduced contractility at high end-diastolic pressures consequent to decreased chamber compliance.1 Although we recognize this dilemma with the total pressure contractile indexes, we used them to divide the patients with aortic stenosis into groups with normal and presumably depressed contractility. Because Vpm and Vmax can be falsely depressed but not falsely increased by the influence of an increased left ventricular end-diastolic pressure, the patients with normal indexes (groups 1 and 2) can confidently be classified as having truly normal contractility at rest. Although chamber compliance disorders cannot be excluded as a cause for depressed isovolumic indexes in the patients in groups 3 and 4, in a series of patients with predominantly arteriosclerotic heart disease in whom chamber compliance disturbances might have been present as well, Vpm and total pressure Vmax were not excessively depressed and, in some instances, were normal.11 Thus, we feel the presence of
depressed \( V_{pm} \) and \( V_{max} \) justifies classifying these patients as having impaired contractility. The rightward and downward displacement of the groups 3 and 4 in the ventricular function diagram (fig. 2) opposing max \( dP/dt \) and end-diastolic circumferential wall stress is additional evidence that in these two groups left ventricular contractile function was depressed as compared with groups 1 and 2 and the controls.

With this background of an evaluation of contractile state independent of the pumping action, we then could define the relative contribution of contractility and afterload in determining the ejection performance as estimated by the MNSER. There was an inverse relationship between afterload estimated by the circumferential \( S_{peak} \) and MNSER modulated by the level of myocardial contractility (fig. 3). The conclusion that in aortic stenosis the inotropic state is a determinant of ejection performance is further strengthened by the fact that in groups 3 and 4, preload as estimated from the end-diastolic circumferential wall stress was significantly higher than in groups 1 and 2. If a similar contractile state were present in the four groups, MNSER at a given afterload should have been increased in the patients with augmented preload (groups 3 and 4). In fact, the opposite was the case. Nevertheless, afterload in itself could be shown to be a determinant of ejection performance. At a given inotropic state, an increase in afterload tended to be associated with a decrease of MNSER (fig. 3).

Evidence for the concept that left ventricular ejection performance in aortic stenosis is determined by more than one factor has been presented by others. In 19 patients with severe aortic stenosis, Liedtke and co-workers\(^1\) could not find significant correlations between EF or mean circumferential fiber shortening rate and indexes of afterload, including left ventricular systolic pressure, aortic orifice area and an index of peak systolic tension (calculated as the product of peak systolic pressure and the midystolic radius of the minor left ventricular circumference). Although they recognized that the index of peak systolic tension was not a completely accurate representation of afterload, they concluded that afterload alone could not explain depression of left ventricular ejection performance in severe aortic stenosis and that myocardial hypertrophy and other consequences of long-standing obstruction to outflow played a primary role in depression of left ventricular performance. Similarly, Thompson and co-workers\(^1\) found no correlation between left ventricular peak systolic pressure and EF in 103 operative patients with aortic stenosis and therefore suspected that depressed left ventricular contractility had been present in some patients with depressed ejection performance. In patients with operative aortic stenosis, Schwarz and co-workers\(^1\) described a disproportionate decrease of MNSER compared with the increase in \( S_{peak} \) when left ventricular mass was 250% of the normal level. Thus, in severe hypertrophy there was evidence of depression of inotropic state. In our two groups with depression of contractility (groups 3 and 4), augmentation of left ventricular muscle mass was 249% and 240%, respectively, of the mass in the control subjects. Using cineangiographic frame-by-frame analysis and left ventricular tipmanometer measurements, Peterson\(^1\) determined mean equatorial wall stress and mean velocity of circumferential fiber shortening at midwall (mean \( V_{cf} \)) in 19 patients with aortic stenosis. He observed that at a given wall stress patients who had peak \( dP/dt \) greater than 1438 mm Hg/sec had a higher mean \( V_{cf} \) than those with peak \( dP/dt \) less than 1438 mm Hg/sec. Conversely, in the two groups of patients with different peak \( dP/dt \), either above or below 1438 mm Hg/sec, mean \( V_{cf} \) decreased at increasing mean wall stress. Peterson suggested that both myocardial failure and excess equatorial stress play a role in depression of midwall circumferential velocity of shortening.

Gunther and Grossman,\(^1\) however, disagree with the view that myocardial contractility can be at the origin of depressed ejection performance in aortic stenosis. These investigators found close inverse correlations between mean midwall circumferential wall stress and both EF and mean midwall velocity of circumferential fiber shortening. Thus, in contrast to our study, a unique relationship between ejection performance and afterload was described. Gunther and Grossman\(^1\) used mean wall stress as a measure of afterload whereas we used peak wall stress, which does not require tedious frame-by-frame analysis but might be less accurate. We compared circumferential \( S_{peak} \) with mean systolic wall stress obtained from instantaneous pressure and dimensional measurements at 20-msec intervals throughout systole in 23 patients with aortic valve disease, and obtained an excellent correlation (\( r = 0.94 \), mean values 468 and 308 \( \times 10^6 \) dyn/cm\(^2\), see 67 \( \times 10^6 \) dyn/cm\(^2\)). Thus, it seems unlikely that the use of \( S_{peak} \) instead of mean wall stress would have led to different conclusions.

Similarly, use of MNSER instead of EF as a measure of ejection performance does not appear to have affected our conclusions. Both MNSER and EF differed significantly in groups 1 and 3 and in groups 2 and 4. The main reason for the discrepancy between our study and that of Gunther and Grossman\(^1\) probably lies in the larger number of patients with aortic stenosis that we studied (76 vs 14). It appears likely that the large number of patients has provided a more complete spectrum of the relationships between ejection performance and afterload than Gunther and Grossman's study, in which the unique relationship between EF and mean systolic wall stress was probably somewhat fortuitous.

According to Gunther and Grossman,\(^1\) inadequate wall thickness and inappropriate left ventricular geometry with eccentric rather than concentric hypertrophy appear to play an important role in the manifestation of poor cardiac performance in aortic stenosis. In their patients with depressed ejection fraction, the ratio of left ventricular wall thickness to
cavity radius was significantly smaller than in those with aortic stenosis having a normal or nearly normal EF and was in the same range as in the control subjects. In the present study, we found no significantly different ratio of left ventricular diameter to wall thickness at end-diastole in patients with aortic stenosis.

However, it would be incorrect to conclude from the similar $M_{ed}/h_{ed}$ ratio that left ventricular hypertrophy was similarly adequate in the four groups. When this ratio was normalized for pressure, it was obvious that hypertrophy was inadequate in groups 2 and 4 because it had not progressed enough to maintain a normal systolic wall stress. Although MNSER tended to be smaller in inadequate hypertrophy than in adequate hypertrophy, systolic wall stress (afterload) was clearly not the sole determinant of left ventricular ejection performance. The quality of the myocardium (i.e., the contractile state) was shown to be a major factor for the left ventricular ejection performance regardless of whether systolic wall stress was normal or elevated. At a given systolic wall stress, however, the patients with depressed contractile state (groups 3 and 4) had a significantly higher angiographic muscle mass than those in whom the isovolumic contractile indexes were normal (groups 1 and 2). This finding is consistent with the concept that advanced myocardial hypertrophy is associated with depressed contractile quality. Patients with aortic valve disease who had residual left ventricular dysfunction after aortic valve replacement showed a significantly higher preoperative muscle mass than those with a normal or nearly normal postoperative left ventricular function.

In conclusion, we present evidence that in chronic pressure overload from aortic stenosis, ejection performance is not solely determined by the extent of afterload, but is also influenced by the actual inotropic state. Thus, there is no unique inverse relationship between systolic stress and ejection performance; rather, this relationship is shifted to a lower level when contractility is depressed. The practical implications are that in patients with severe depression of angiographic ejection performance, left ventricular contractility is almost invariably decreased, whereas moderate depression of ejection performance can be caused by excessive afterload alone.

References

Determinants of ejection performance in aortic stenosis.

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