Clinical Investigation

Long-term Serial Changes in Left Ventricular Function and Reversal of Ventricular Dilatation After Valve Replacement for Chronic Aortic Regurgitation

Robert O. Bonow, MD, Joseph T. Dodd, MD, Barry J. Maron, MD,
Patrick T. O’Gara, MD, Gale G. White, RN, Charles L. McIntosh, MD, PhD,
Richard E. Clark, MD, and Stephen E. Epstein, MD

In most patients with aortic regurgitation, valve replacement results in reduction in left ventricular dilatation and an increase in ejection fraction. To determine the relation between serial changes in ventricular dilatation and changes in ejection fraction, we studied 61 patients with chronic severe aortic regurgitation by echocardiography and radionuclide angiography before, 6–8 months after, and 3–7 years after aortic valve replacement. Between preoperative and early postoperative studies, left ventricular end-diastolic dimension decreased (from 75±6 to 56±9 mm, p<0.001), peak systolic wall stress decreased (from 247±50 to 163±42 dynes×10⁸/cm²), and ejection fraction increased (from 43±9% to 51±16%, p<0.001). Between early and late postoperative studies, diastolic dimension and peak systolic wall stress did not change, but ejection fraction increased further (to 56±19%, p<0.001). The increase in ejection fraction correlated with magnitude of reduction in diastolic dimension between preoperative and early postoperative studies (r=0.63), between early and late postoperative studies (r=0.54), and between preoperative and late postoperative studies (r=0.69). Late increases in ejection fraction usually represented the continuation of an initial increase occurring early after operation. Thus, short-term and long-term improvement in left ventricular systolic function after operation is related significantly to the early reduction in left ventricular dilatation arising from correction of left ventricular volume overload. Moreover, late improvement in ejection fraction occurs commonly in patients with an early increase in ejection fraction after valve replacement but is unlikely to occur in patients with no change in ejection fraction during the first 6 months after operation. (Circulation 1988;78:1108–1120)

In the majority of patients with chronic severe aortic regurgitation, aortic valve replacement results in a substantial reversal of left ventricular dilatation within the first few months of operation.¹⁻¹⁶ In such patients, this beneficial reduction in left ventricular volume overload after operation is associated with a significant increase in left ventricular systolic performance.⁴,⁹,¹³,¹⁶⁻²⁰ In a subset of patients with preoperative left ventricular dysfunction, however, valve replacement leads to less reduction in left ventricular diastolic volume and no demonstrable improvement in systolic function despite correction of valvular regurgitation,⁷,⁹,¹³,¹⁶,²⁰ presumptive evidence for irreversible myocardial dysfunction preceding operation. This change or lack of change in left ventricular volume and function occurring within the 1st year of aortic valve replacement is an important predictor of long-term postoperative prognosis.¹⁶ However, serial long-term studies of the effect of aortic valve replacement on left ventricular systolic function have not been reported, and the relation between the magnitude of reversal of left ventricular dilatation and the increase in left ventricular systolic performance, either short-term or long-term after operation, has not been studied intensively. To address these issues, we studied a series of patients undergoing aortic valve replacement for chronic aortic regurgitation with preoperative and

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From the Cardiology Branch and Cardiac Surgery Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.
Address for correspondence: Robert O. Bonow, MD, Building 10, Room 7B15, National Institutes of Health, Bethesda, MD 20892.
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serial long-term postoperative echocardiographic and radionuclide angiographic evaluations.

**Patients and Methods**

**Patient Selection**

We investigated the long-term effects of aortic valve replacement on left ventricular function in 61 patients with chronic severe aortic regurgitation undergoing operation between August 1976 and December 1983. This study was initiated prospectively in 1976 because this was the year that radionuclide angiography became available for clinical investigation at the National Heart, Lung, and Blood Institute. There were 51 men and 10 women in the study, ranging in age from 19 to 72 years (mean, 43 years). Fifty-one patients underwent operation because of moderate to severe cardiac symptoms (New York Heart Association functional Class III or IV). The other 10 patients were either asymptomatic or mildly symptomatic (functional Class I or II); aortic valve replacement was recommended in this subset because of consistent and reproducible evidence of depressed left ventricular contractile function at rest by both echocardiography and radionuclide angiography. Patients were studied before operation by echocardiography, radionuclide angiography, graded treadmill exercise testing, and cardiac catheterization. These studies were complete in all patients except for one in whom preoperative echocardiographic studies were of suboptimal quality. Patients returned 6–8 months after operation for repeat echocardiograms, radionuclide angiograms, and cardiac catheterization; studies were complete except for four patients who did not undergo repeat catheterization. Echocardiography and radionuclide angiography were then repeated during the long-term follow-up course, ranging from 3 to 7 years (mean, 5 years) after operation, except for one patient who underwent late studies at 9 years. To evaluate the time course of decrease in left ventricular dilatation, a subset of 31 patients also underwent echocardiography at 10–14 days, as well as at 6–8 months and 3–7 years, after operation.

All preoperative studies were performed while patients were taking no cardiac medications. Although attempts were made to also perform postoperative studies free from cardiac drugs, this was not always possible. The late studies were performed during drug therapy in 23 patients; 15 patients received digoxin, six patients received a combination of digoxin and an arterial vasodilator, one patient received hydralazine alone, and one patient received propranolol alone.

Preoperative cardiac catheterization confirmed the diagnosis of isolated severe aortic regurgitation in 57 patients. Four patients had associated small ventricular septal defects with left-to-right shunt ratios less than 1.5:1, which were closed at the time of aortic valve replacement. Coronary arteriography was performed in all patients over 35 years of age, as well as all patients under 35 years old with angina pectoris; no patient had associated coronary artery disease (more than 50% reduction in luminal diameter) of any coronary artery. In addition, no patient had associated mitral valve disease or disease of the ascending aorta requiring repair at the time of aortic valve replacement.

The 61 patients were chosen for evaluation from 83 consecutive and prospectively studied patients undergoing operation for isolated chronic severe aortic regurgitation at our institution during the timeframe of this study. Twenty-two patients were not included in the present study because 1) one patient did not undergo preoperative radionuclide angiography, 2) five patients died before the 6–8-month postoperative evaluation could be performed, 3) two surviving patients did not return for the 6–8-month reevaluation, 4) five patients died between 6–8 months and 3 years, 5) four patients developed prosthetic valve complications before the late evaluation (three patients required repeat aortic valve replacement), and 6) five surviving patients refused or did not return for late studies. Thus, although inferences can be drawn between late changes in left ventricular function after operation and long-term survival, a life-table survival analysis on the basis of late postoperative left ventricular function was not performed because of incomplete data (arising predominantly because 14 patients died or experienced prosthetic valve dysfunction before long-term studies could be performed). However, definitive survival analyses based on the preoperative and early postoperative data in the first 80 of the 83 patients have been reported previously.16

**Echocardiography**

M-mode echocardiograms were obtained as previously described.16 Measurements of left ventricular transverse dimensions were obtained with the ultrasound beam directed through the left ventricle just caudal to the tips of the mitral leaflets.6,21 The end-diastolic left ventricular dimension was measured at the R wave of the electrocardiogram. The upper limit of normal for end-diastolic dimension in our laboratory is 55 mm. Interventricular septal thickness was measured just below the tips of the mitral leaflets, and left ventricular posterior wall thickness was measured at the level of the mitral leaflets. Because abnormal septal motion occurs frequently after operation,6,21,22 left ventricular end-systolic dimension and fractional shortening were not measured at either the early or late postoperative study. Thus, comparative serial echocardiographic measurements were confined to the left ventricular end-diastolic dimension and wall thickness. From these primary measurements, we computed the ventricular radius:wall thickness ratio, an index of the volume:mass ratio and a measure of the degree to which left ventricular muscle mass is appropriate for a given chamber volume,3,10,23,24 by dividing half the end-diastolic dimension by the
posterior wall thickness. In addition, we also estimated the peak systolic left ventricular meridional wall stress from the systolic blood pressure (by cuff sphygmomanometry, measured before radionuclide angiography) and echocardiographic end-diastolic dimension (D) and posterior wall thickness (h) with the formula of Grossman et al.23; peak systolic wall stress = (systolic blood pressure × D)/[4h(1 + h/D)]. We did not attempt to compute end-systolic stress because of the inability to measure end-systolic ventricular pressure, the imprecision in determining the instant of end systole by echocardiography, and difficulties in measuring end-systolic dimension after operation. Finally, the muscle cross-sectional area, an index of left ventricular myocardial mass,3,4,11 was also computed: cross-sectional area = π[D/2 + h]2 − π[D/2]2.

Gated Blood Pool Cardiac Scintigraphy

Radionuclide angiography was performed with patients in the supine position at rest and during maximum symptom-limited bicycle exercise with a previously defined protocol.16,18 Preoperative exercise data were obtained in all but one patient who was severely symptomatic at rest and could not tolerate supine exercise.

Left ventricular ejection fraction was computed from the scintigraphic data as previously described.16,18 In addition, we also computed the regurgitant volume:end-diastolic volume ratio25 from the resting studies. This was accomplished by first computing the ratio of left ventricular stroke volume to right ventricular stroke volume,26 based on ventricular regions of interest constructed from a functional stroke volume image (computer subtraction of the end-diastolic image from the end-systolic image) and amplitude image (created by approximating each single-pixel time-activity curve with the first harmonic of its temporal Fourier expansion27). The regurgitant fraction was then calculated as regurgitant fraction = (stroke volume ratio − 1)/(stroke volume ratio). The regurgitant volume end-diastolic volume ratio was then computed by multiplying the regurgitant fraction by the ejection fraction. Technical limitations prevented calculation of this ratio in 12 of the 61 patients.

Graded Treadmill Exercise Testing

Preoperative exercise capacity was assessed with the National Institutes of Health treadmill protocol.16,28 In the first stage of this protocol, the treadmill is driven at a constant speed of 2.2 mph at inclination of 0%. Every 2.5 minutes the inclination is increased by 2.5% until a maximum of 22.5 minutes elapse, resulting in a maximal workload of 2.2 mph at 20% incline or approximately 8 MET. The inability to obtain and complete this level of exercise was defined as poor preoperative exercise tolerance.16,28 Such impaired exercise tolerance was evident in 19 (31%) of 61 patients, including 11 (28%) of 39 patients in whom the preoperative ejection fraction at rest was subnormal.

Aortic Valve Replacement

At operation, 28 patients received Starr-Edwards prostheses (1260 series in 21, 2320 series in two, and 2400 series in five), 30 received Hancock porcine bioprostheses Model 242, and three received Bjork-Shiley prostheses. Cardiopulmonary bypass was performed with a disk or bubble oxygenator with a flow rate of 2.2 l/min/m². Cardiopulmonary bypass times ranged from 55 to 158 minutes (mean, 84 ± 20 minutes), and aortic cross-clamp times ranged from 33 to 97 minutes (mean, 54 ± 15 minutes). In addition to systemic hypothermia to 25° to 30° C in all patients, myocardial preservation techniques included topical 4° iced saline with coronary perfusion in 27 patients and hyperkalemic cold cardioplegia and topical hypothermia in 34.

Postoperative Hemodynamic Studies

Postoperative left heart catheterization was performed with either the transseptal or the left ventricular puncture technique. Postoperative hemodynamic data demonstrated peak systolic gradients across the prosthetic valve of less than 10 mm Hg in 40 patients, between 10 and 20 mm Hg in 11 patients, and 20 mm Hg or more in six patients. No patient had a prosthetic valve gradient of more than 40 mm Hg. One patient with preoperative left ventricular dysfunction had persistent severe (4 + out of 4 +) aortic regurgitation 7 months after operation because of a perivalvular leak. He underwent a second operation 8 months after the initial valve replacement and is now asymptomatic 68 months after repair of the perivalvular leak. For comparison with other patients, the 6–8-month data on this patient were derived from studies obtained 6 months after the second operation, with long-term follow-up data obtained 52 months later.

Statistical Methods

Analysis of serial echocardiographic and radionuclide angiographic data from the preoperative, early postoperative, and late postoperative studies was performed with analysis of variance of repeated measures. Comparisons of data among subgroups of patients were performed with analysis of variance. The association between preoperative data and the magnitude of postoperative change in left ventricular dimensions and function was tested by linear regression analysis. The relation between changes in left ventricular dimensions, wall stress or mass, and changes in left ventricular ejection fraction after operation was also tested with linear regression analysis. Data are presented as mean ± SD.

Results

Left ventricular end-diastolic dimension declined significantly 6–8 months after aortic valve replacement compared with preoperative values (Table 1),
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Table 1. Serial Changes in Left Ventricular Function After Aortic Valve Replacement

<table>
<thead>
<tr>
<th></th>
<th>Before operation</th>
<th>6–8 Months after operation</th>
<th>3–7 Years after operation</th>
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</thead>
<tbody>
<tr>
<td>All patients (n=61)</td>
<td></td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>144±24 &lt;0.001</td>
<td>128±18 &lt;0.05</td>
<td>135±20</td>
</tr>
<tr>
<td>Echocardiographic data</td>
<td></td>
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<tr>
<td>LV end-diastolic dimension (mm)</td>
<td>75±6 &lt;0.001</td>
<td>56±9 NS</td>
<td>55±10</td>
</tr>
<tr>
<td>LV wall thickness (mm)</td>
<td>13±2 NS</td>
<td>12±2 NS</td>
<td>12±2</td>
</tr>
<tr>
<td>R:Th ratio</td>
<td>3.0±0.4 &lt;0.001</td>
<td>2.4±0.5 NS</td>
<td>2.3±0.5</td>
</tr>
<tr>
<td>Peak systolic wall stress (kdynes/cm²)</td>
<td>247±50 &lt;0.001</td>
<td>163±42 NS</td>
<td>168±48</td>
</tr>
<tr>
<td>LV muscle cross-sectional area (cm²)</td>
<td>35±6 &lt;0.001</td>
<td>26±7 NS</td>
<td>26±7</td>
</tr>
<tr>
<td>Radionuclide angiographic data</td>
<td></td>
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</tr>
<tr>
<td>LV EF at rest (%)</td>
<td>43±9 &lt;0.001</td>
<td>51±16 &lt;0.001</td>
<td>56±19</td>
</tr>
<tr>
<td>LV EF during exercise (%)*</td>
<td>36±10 &lt;0.001</td>
<td>51±16 &lt;0.005</td>
<td>57±20</td>
</tr>
<tr>
<td>Change in EF from rest to exercise*</td>
<td>−8±7 &lt;0.001</td>
<td>−0.7±8 NS</td>
<td>0.7±7</td>
</tr>
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<td>Patients with normal before-surgery LV EF at rest (n=22)</td>
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<td></td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>141±16 &lt;0.05</td>
<td>132±12 NS</td>
<td>131±17</td>
</tr>
<tr>
<td>Echocardiographic data</td>
<td></td>
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</tr>
<tr>
<td>LV end-diastolic dimension (mm)</td>
<td>75±6 &lt;0.001</td>
<td>53±6 &lt;0.05</td>
<td>51±5</td>
</tr>
<tr>
<td>LV wall thickness (mm)</td>
<td>13±1 NS</td>
<td>13±2 NS</td>
<td>13±2</td>
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<tr>
<td>R:Th ratio</td>
<td>2.8±0.3 &lt;0.001</td>
<td>2.1±0.5 NS</td>
<td>2.0±0.3</td>
</tr>
<tr>
<td>Peak systolic wall stress (kdynes/cm²)</td>
<td>230±55 &lt;0.001</td>
<td>151±30 NS</td>
<td>141±30</td>
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<td>LV muscle cross-sectional area (cm²)</td>
<td>36±4 &lt;0.001</td>
<td>26±5 NS</td>
<td>26±5</td>
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<tr>
<td>Radionuclide angiographic data</td>
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</tr>
<tr>
<td>LV EF at rest (%)</td>
<td>52±8 &lt;0.001</td>
<td>61±11 &lt;0.01</td>
<td>68±11</td>
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<tr>
<td>LV EF during exercise (%)*</td>
<td>45±9 &lt;0.001</td>
<td>61±14 &lt;0.001</td>
<td>73±11</td>
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<tr>
<td>Change in EF from rest to exercise*</td>
<td>−7±8 &lt;0.005</td>
<td>0.5±10 &lt;0.05</td>
<td>5±6</td>
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<tr>
<td>Patients with subnormal before-surgery LV EF at rest (n=39)</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>146±27 &lt;0.001</td>
<td>127±21 &lt;0.01</td>
<td>137±22</td>
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<tr>
<td>Echocardiographic data</td>
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</tr>
<tr>
<td>LV end-diastolic dimension (mm)</td>
<td>75±7 &lt;0.001</td>
<td>57±9 NS</td>
<td>57±11</td>
</tr>
<tr>
<td>LV wall thickness (mm)</td>
<td>12±2 NS</td>
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</tr>
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<td>2.5±0.5 NS</td>
<td>2.4±0.5</td>
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<tr>
<td>Peak systolic wall stress (kdynes/cm²)</td>
<td>253±51 &lt;0.001</td>
<td>170±47 NS</td>
<td>183±49</td>
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<tr>
<td>LV muscle cross-sectional area (cm²)</td>
<td>34±7 &lt;0.001</td>
<td>27±8 NS</td>
<td>26±8</td>
</tr>
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<td>Radionuclide angiographic data</td>
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<tr>
<td>LV EF at rest (%)</td>
<td>39±6 &lt;0.005</td>
<td>46±15 NS</td>
<td>49±19</td>
</tr>
<tr>
<td>LV EF during exercise (%)*</td>
<td>31±8 &lt;0.001</td>
<td>46±15 NS</td>
<td>48±19</td>
</tr>
<tr>
<td>Change in EF from rest to exercise*</td>
<td>−8±6 &lt;0.001</td>
<td>−1±8 NS</td>
<td>−3±6</td>
</tr>
</tbody>
</table>

Data are mean ± SD.
LV, left ventricular; R:Th, radius:wall thickness ratio; EF, ejection fraction.
*Complete exercise radionuclide angiographic data were obtained in 56 patients.

decreasing from 75±6 to 56±9 mm (p<0.001). There was no subsequent change in end-diastolic dimension during further long-term studies. Data in the 31 patient subgroup undergoing echocardiograms 10–14 days after operation, as well as at 6–8 months and 3–7 years after operation, demonstrated that the reduction in end-diastolic dimension that was apparent several months after operation occurred predominantly within only 2 weeks of operation (Figure 1). End-diastolic dimension decreased 21% from 77±6 to 61±8 mm 2 weeks after operation (p<0.001), with a further reduction of only 5% (relative to preoperative values) to 57±10 mm 6–8 months after operation and with no additional decrease during subsequent long-term studies. Thus, 80% of the overall reduction in end-diastolic dimension observed during long-term postoperative evaluation occurred within 2 weeks of aortic valve replacement.

In keeping with the postoperative reduction in end-diastolic dimension and systolic blood pressure, peak systolic wall stress and muscle cross-sectional area decreased significantly 6–8 months after operation compared with preoperative values (Table 1), with no further change during longer-term follow-up. Changes in left ventricular radius:wall...
thickness ratio reflected the significant decrease in end-diastolic dimension at 6–8 months. The lack of further change in this ratio at 3–7 years confirms the muscle cross-sectional area data indicative of no important change in left ventricular mass 6–8 months after operation.

In contrast, left ventricular ejection fraction under resting conditions, which increased significantly 6–8 months after operation (from 43 ± 9% to 51 ± 16%, \( p<0.001 \)), increased further to 56 ± 19% at the late postoperative evaluation (\( p<0.001 \)). Similarly, the ejection fraction during maximum supine exercise, as well as the magnitude of change in ejection fraction from rest to exercise, increased between the preoperative and 6–8-month postoperative studies. Exercise ejection fraction increased further at the late postoperative reevaluation although the increment from rest to exercise remained fixed (Table 1). The magnitude of the early and late increase in ejection fraction was related to several factors, principally the extent of postoperative reduction in left ventricular end-diastolic dimension.

**Postoperative Change in Ejection Fraction in Relation to Reduction in Left Ventricular End-diastolic Dimension**

The magnitude of increase in left ventricular ejection fraction after operation, in patients with normal as well as those with subnormal preoperative systolic function, correlated significantly with the change in left ventricular end-diastolic dimension (Figure 2), both short-term (\( r=0.63, p<0.001 \)) and long-term (\( r=0.69, p<0.001 \)). Although there was no mean decrease in end-diastolic dimension between 6–8 months and 3–7 years for the total group, end-diastolic dimension significantly decreased (from 55 ± 9 to 52 ± 8 mm, \( p<0.05 \)) in those patients manifesting an increase in ejection fraction after the 6–8 month study. Moreover, for the entire group, changes in ejection fraction from 6–8 months to 3–7 years also correlated with changes in end-diastolic dimension occurring during this period (\( r = 0.54, p<0.001 \)). Although the correlations were less strong, the postoperative increase in ejection fraction was also related to the reduction in peak systolic wall stress (\( r=0.42, p<0.01 \) for both short-term and long-term changes, compared with preoperative values) and in muscle cross-sectional area (\( r=0.37 \) and \( r=0.41 \) for short-term and long-term changes, respectively; \( p<0.01 \)). Changes in ejection fraction and end-diastolic dimension were not related to changes in blood pressure, either at the short-term (\( r=0.13 \) and 0.07, respectively) or long-term (\( r=0.09 \) and 0.16, respectively) reevaluations.

**Preoperative Determinants of Postoperative Reversal of Ventricular Dilatation and Improved Systolic Function**

The preoperative regurgitant volume: end-diastolic volume ratio was only weakly related to the magnitude of decrease in end-diastolic dimension.
sion after operation ($r = 0.39$ and $0.35$ for short-term and long-term changes, respectively; $p < 0.01$). More significant correlations developed when the analysis was applied to patients with normal preoperative ejection fractions ($r = 0.56$ and $0.49$, respectively; $p < 0.001$), but there was no such correlation in patients with systolic dysfunction ($r = 0.25$ and $0.18$).

The magnitude of increase in ejection fraction at rest after operation was unrelated to the preoperative regurgitant volume:end-diastolic volume ratio ($r = 0.17$ and $0.20$ for short-term and long-term changes, respectively) and also was not related to the preoperative change in ejection fraction occurring from rest to exercise. Similarly, the postoperative ejection fraction was not predicted by preoperative values of resting ejection fraction or echocardiographic ventricular cavity dimensions, fractional shortening, muscle cross-sectional area, or radius:wall thickness ratio. However, the magnitude of regression of dilatation and increase in ejection fraction after operation differed among patients with normal, compared with those with subnormal, preoperative ejection fractions.

**Patients with normal preoperative ejection fraction.** In the 22 patients with normal preoperative left ventricular systolic function at rest, end-diastolic dimension decreased significantly by the early postoperative study, (from $75 \pm 6$ to $53 \pm 6$ mm) (Table 1 and Figure 3) with a further slight but significant decrease to $51 \pm 5$ mm between the early and late postoperative studies. Despite the late reduction in end-diastolic dimension, only three (30%) of 10 patients with persistent ventricular dilatation 6–8 months after operation had return of end-diastolic dimension to normal at the late study. Similarly, peak systolic wall stress and muscle cross-sectional area decreased significantly by 6–8 months after operation but did not change thereafter.

Despite normal preoperative ejection fraction ($52 \pm 8\%$) in these patients, ejection fraction increased to even higher levels reaching $61 \pm 11\%$ ($p < 0.001$) 6–8 months after operation, with a further increase to $68 \pm 11\%$ ($p < 0.01$) during the long-term postoperative course (Table 1 and Figure 3). The ejection fraction during exercise responded in similar fashion, increasing from $45 \pm 9\%$ to $61 \pm 14\%$ ($p < 0.001$) at the 6–8-month postoperative study and to $72 \pm 11\%$ ($p < 0.001$) at the late postoperative reevaluation. Thus, the magnitude of the ejection fraction response during exercise compared with resting values also increased, from $-7 \pm 8\%$ before operation to $0.5 \pm 10\%$ early after operation ($p < 0.005$) and to $5 \pm 6\%$ late after operation ($p < 0.05$).

**Patients with preoperative left ventricular systolic dysfunction.** In the 39 patients with subnormal preoperative ejection fraction at rest, changes in left ventricular end-diastolic dimension after operation followed similar trends as those observed in the total patient cohort (Table 1), with a significant
decrease 6–8 months after operation compared with preoperative values (from 75 ±7 to 57 ± 9 mm, p<0.001) and with no further change during long-term follow-up (57 ± 11 mm). Substantial reduction in end-diastolic dimension after 6–8 months was unusual (Figure 4). Of 18 patients with persistent ventricular dilatation 6–8 months after operation, only two (11%) had a decrease in diastolic dimension to normal (≤55 mm) at the late follow-up study. Peak systolic wall stress and muscle cross-sectional area also did not change significantly between the early and late postoperative studies.

The changes in ejection fraction occurring after operation in these patients demonstrated a variable response (Figure 4). In the majority of patients, ejection fraction increased during the early postoperative course, but there were nonetheless many patients in whom ejection fraction was unchanged or decreased 6–8 months after operation. Moreover, there was no further significant change in ejection between the early and late postoperative studies (from 46 ±15% to 49 ±19%, p = NS). Six patients with persistent left ventricular dysfunction at the late study, including five with severe depression of ejection fraction (ejection fraction <30%), subsequently died from chronic congestive heart failure. These six patients also had persistent left ventricular dilatation at the late postoperative study (Figure 4).

In these patients with preoperative left ventricular dysfunction, late postoperative changes in ejection fraction were influenced importantly by the directional changes in ejection fraction occurring during the first 6–8 months after operation (Figure 5). In the subgroup manifesting an early increase in ejection fraction 6–8 months after operation, ejection fraction increased further during subsequent long-term follow-up in 20 of 24 patients, a mean change from 54 ± 5% to 61 ± 7% (p<0.001); ejection fraction was normal in 21 patients at the late postoperative evaluation. In contrast, patients with no improvement in ejection fraction during the early postoperative course demonstrated no subsequent change during long-term follow-up; ejection fraction subsequently decreased in six of the 14 patients after the early postoperative study and was normal in only one patient at the long-term evaluation. Although long-term follow-up periods varied among patients, the direction and magnitude of these changes in ejection fraction were not related to the duration of follow-up. The late follow-up periods in these two patient subgroups were similar at 58 ± 13 and 60 ± 14 months, respectively.

**Patient subgroup analysis.** Patients with subnormal preoperative left ventricular ejection fraction at
rest were divided into subgroups on the basis of clinical data we have previously observed to provide important information regarding postoperative prognosis. This subgrouping was performed initially on the basis of preoperative exercise tolerance as assessed by treadmill testing. Patients were divided into those with preserved exercise tolerance (completing the first stage of the National Institutes of Health protocol) and those with impaired exercise tolerance (who were unable to complete this stage because of symptoms). Patients with preserved exercise tolerance were then further subdivided into two groups on the basis of the duration of preoperative left ventricular dysfunction, in those patients in whom such information could be determined from serial preoperative studies: 1) six patients with prolonged duration of left ventricular dysfunction (subnormal resting ejection fraction of more than 18 months before operation) and 2) 11 patients with a brief duration of left ventricular dysfunction (normal ejection fraction within 14 months of operation).

Patients with preoperative left ventricular systolic dysfunction and impaired exercise tolerance and those with preserved exercise tolerance but evidence of a prolonged duration of ventricular dysfunction demonstrated no change in mean ejection fraction either early or late after operation (Figure 6). All six patients who died after the late postoperative studies were in these two subgroups; five had impaired preoperative exercise tolerance, and one had preserved exercise tolerance but prolonged preoperative left ventricular dysfunction. In contrast, patients with preserved exercise tolerance, and a brief duration of left ventricular dysfunction manifested substantial increases in ejection fraction early after operation with a further significant increase during subsequent long-term follow-up. The late ejection fractions in these latter patients were similar to those observed in patients in whom the preoperative resting ejection fraction was normal (Figure 6), and no patient in this subgroup died.

Similar trends were observed regarding postoperative changes in left ventricular end-diastolic dimension in these five patient subgroups (Figure 7). Preoperative end-diastolic dimension did not differ among subgroups, but diastolic dimension decreased to a greater extent after operation in patients with normal preoperative ejection fraction and in those with a brief duration of left ventricular dysfunction compared with patients with either impaired exercise tolerance or a prolonged duration of ventricular dysfunction ($p<0.01$). There were no important changes in mean end-diastolic dimension after the early postoperative study, and such changes achieved...
statistical significance only in patients with normal preoperative ejection fractions. Thus, the important influence of reversal of left ventricular dilatation on improved systolic function was determined principally by reductions in end-diastolic dimension occurring during the first 6–8 months after operation. Patient subgroups with different postoperative functional responses to operation did not differ with respect to preoperative left ventricular end-diastolic dimension, hypertrophy, or peak systolic wall stress (Table 2). Patients with normal preoperative ejection fractions had significantly higher regurgitant volume:end-diastolic volume ratios than those with subnormal ejection fractions, and, among patients with subnormal ejection fractions, this ratio was lowest in patients with impaired exercise tolerance (Table 2). However, the importance of this finding is unclear because the regurgitant volume:end-diastolic volume ratio is related to ejection fraction (because reduced total stroke volume relative to end-diastolic volume would result in lower regurgitant volume), and the correlation between these two variables was significant \( r = 0.65 \).

**Influence of Medical Therapy**

In the 23 patients who underwent late postoperative studies while receiving cardioactive drugs, drug therapy did not appear to affect left ventricular function importantly. Ejection fraction increased compared with the early postoperative study in 12 patients, was unchanged in one patient, and decreased in 10 patients. Similarly, left ventricular end-diastolic dimension decreased further compared with the early postoperative value in nine patients but increased in 14 patients.

These 23 patients were then excluded, and the serial postoperative data were reanalyzed in the remaining 38 patients who were studied free from cardiac drugs. The results were identical to those observed in the total study population. In these 38 patients, ejection fraction at rest increased both early (from 44 ± 9% to 53 ± 14%, \( p < 0.001 \)) and late (to 58 ± 17%, \( p < 0.001 \)). End-diastolic dimension decreased initially (from 76 ± 7 to 55 ± 8 mm, \( p < 0.001 \)) with no further change at the late postoperative study (54 ± 9 mm). Changes relative to preoperative data in end-diastolic dimension correlated with changes in resting ejection fraction for both early \( (r = 0.54, p < 0.001) \) and late \( (r = 0.60, p < 0.001) \) postoperative data. Peak systolic wall stress decreased initially with no subsequent change after the early postoperative study, and changes in wall stress correlated only weakly with early and late changes in ejection fraction (both, \( r = 0.39, p < 0.01 \)). The late changes in ejection fraction were most notable in patients with normal preoperative ejection fractions; ejection fraction increased from 59 ± 11% at the early study to 66 ± 9% at the late study \( (p < 0.005) \). In contrast, there were no late changes in ejection fraction (from 55 ± 9% to 55 ± 11%) in patients with subnormal preoperative ejection fractions.
FIGURE 7. Bar graph of change in echocardiographic left ventricular (LV) end-diastolic dimension in the five patient subgroups. Data are displayed as in Figure 6. In addition to the significant changes shown (*), early and late postoperative diastolic dimensions were significantly less in patients with normal preoperative ejection fractions and those with brief duration of systolic dysfunction compared with patients with preoperative systolic dysfunction and either poor exercise tolerance or prolonged duration of systolic dysfunction (p<0.01).

Discussion

Left ventricular systolic function is an important determinant of long-term prognosis in patients with chronic aortic regurgitation undergoing aortic valve replacement. Patients with impaired preoperative left ventricular function have a greater risk of developing postoperative congestive heart failure and of dying than do patients in whom preoperative left ventricular function is normal. Importantly, numerous recent studies indicate that depressed left ventricular systolic performance may improve and, in some patients, normalize after reversal of the volume overload by valve replacement. These changes, documented within the 1st year of operation, correlate with survival during the subsequent 4–5 years; patients with normal postoperative systolic performance have an excellent prognosis, whereas survival rates are reduced in patients with persistent left ventricular dysfunction. The purpose of the current study was to determine serial long-term changes in left ventricular dilatation, mass, systolic wall stress, and systolic function and to assess the preoperative and early postoperative determinants of subsequent late postoperative ventricular function.

Our data demonstrate a substantial decrease in left ventricular end-diastolic dimension within 6–8 months of operation (Table 1 and Figures 3 and 4). In the majority of patients, the greatest reduction in end-diastolic dimension developed within only 14 days of operation; 80% of the overall decrease in diastolic dimension observed during the long-term postoperative course occurred within 2 weeks of valve replacement (Figure 1). These findings are strikingly similar to the echocardiographic data reported by Schuler et al and Carroll et al in smaller groups of patients, in which 82% and 78%, respectively, of the overall reduction in end-diastolic dimension after 1 year of valve replacement occurred within the first few weeks after operation.

In our patients, most exhibited no further change in end-diastolic dimension after 6–8 months. Patients with normal preoperative ejection fractions manifested a statistically significant decrease in diastolic dimension after 6–8 months, but the mean decrease in diastolic dimension was only 2 mm (Table 1 and Figure 3). In patients with depressed preoperative left ventricular systolic function, there was no mean change in diastolic dimension after the 6-month study, and important reductions in diastolic dimension during long-term follow-up were uncommon. Only five (17%) of 28 patients with persistent left ventricular dilatation at 6–8 months showed a further reduction in diastolic dimension to normal with longer follow-up (Figures 3 and 4). These findings are consistent with the angiographic data of Toussaint et al and the echocardiographic data of Fioretti et al, who also demonstrated that only a minority of patients with persistent left ventricular dilatation 6–12 months after operation manifest a subsequent reduction in ventricular cavity size to normal. Thus, all of the available information indicates that patients with persistent ventricular dila-
tation in the 1st year after operation have a high likelihood of continuing ventricular dilatation during the long-term postoperative course. This has important prognostic implications, because numerous studies indicate that persistent ventricular dilatation identifies patients at risk of subsequent death from congestive heart failure, as was the case in this study (Figure 4). Because the greatest reduction in end-diastolic dimension occurs within 2 weeks after operation, data relevant to long-term prognosis may be obtained in many patients by echocardiography before hospital discharge.

Levine and Gaasch postulated that the magnitude of reduction in end-diastolic dimension after aortic valve replacement might be predicted on the basis of the preoperative ratio of regurgitant volume to end-diastolic volume. In our patients, this ratio did not correlate well with the postoperative decrease in end-diastolic dimension. However, in the subgroup with normal preoperative ejection fractions, this ratio was significantly related to the postoperative reduction in end-diastolic dimension. The lack of correlation among patients with subnormal preoperative ejection fraction suggests that irreversible myocardial dysfunction, independently of the regurgitant volume, contributes in many such patients to preoperative left ventricular dilatation. Hence, persistent ventricular dilatation occurs commonly in patients with preoperative systolic dysfunction (Figure 4), even in patients with a high regurgitant volume: end-diastolic volume ratio.

Changes in peak systolic wall stress and myocardial cross-sectional area paralleled those observed in left ventricular end-diastolic dimension. These indexes of left ventricular wall stress and hypertrophy decreased substantially within 6–8 months after operation with no further change during long-term follow-up.

In contrast to the lack of late changes in left ventricular dilatation, wall stress, and mass, left ventricular ejection fraction increased significantly during both short-term and long-term follow-up studies. Late improvement in ejection fraction during long-term follow-up usually represented the continuation of an initial increase occurring early after operation (Figure 5). These increases in ejection fraction, both short-term and long-term, were significantly related to the magnitude of decrease in end-diastolic dimension (Figure 2). Although improved systolic function was also related to reduction in peak systolic wall stress and to regression of hypertrophy, the changes in ejection fraction correlated less strongly with changes in left ventricular wall stress and mass than they did with changes in end-diastolic dimension. Our methods did not allow computation of end-systolic stress, a more pure measure of the afterload affecting left ventricular emptying than peak systolic wall stress. Nor could we measure circumferential wall stress (because of the lack of long-axis diameters from the M-mode measurements). It is possible that changes in these measures of systolic wall stress, reflecting reduced afterload after operation, might have shown a closer correlation to the postoperative changes in ejection.

### TABLE 2. Preoperative Data in Patient Subgroups

<table>
<thead>
<tr>
<th>Patients with normal LV EF at rest (n = 22)</th>
<th>All patients (n = 39)</th>
<th>Patients with subnormal LV EF at rest</th>
<th>Good exercise tolerance</th>
<th>Patients with poor exercise tolerance (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>46 ± 13</td>
<td>43 ± 13</td>
<td>43 ± 13</td>
<td>38 ± 9</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>141 ± 6</td>
<td>146 ± 27</td>
<td>157 ± 29</td>
<td>140 ± 22</td>
</tr>
<tr>
<td>Echocardiographic data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic dimension (mm)</td>
<td>75 ± 6</td>
<td>75 ± 7</td>
<td>75 ± 4</td>
<td>75 ± 6</td>
</tr>
<tr>
<td>LV end-systolic dimension (mm)</td>
<td>51 ± 5</td>
<td>56 ± 6</td>
<td>55 ± 3</td>
<td>56 ± 5</td>
</tr>
<tr>
<td>LV wall thickness (mm)</td>
<td>13 ± 1</td>
<td>12 ± 2</td>
<td>12 ± 1</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>R:Th ratio</td>
<td>2.8 ± 0.3</td>
<td>3.1 ± 0.4</td>
<td>3.1 ± 0.3</td>
<td>3.1 ± 0.4</td>
</tr>
<tr>
<td>Peak systolic wall stress (kdynes/cm²)</td>
<td>230 ± 55</td>
<td>252 ± 51</td>
<td>277 ± 47</td>
<td>247 ± 35</td>
</tr>
<tr>
<td>Cross-sectional area (cm²)</td>
<td>36 ± 4</td>
<td>34 ± 7</td>
<td>34 ± 5</td>
<td>34 ± 3</td>
</tr>
</tbody>
</table>

Radionuclide angiographic data

<table>
<thead>
<tr>
<th>LV EF at rest (%)</th>
<th>52 ± 8</th>
<th>39 ± 6</th>
<th>40 ± 5</th>
<th>41 ± 3</th>
<th>42 ± 3</th>
<th>33 ± 8‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EF during exercise (%)</td>
<td>45 ± 9</td>
<td>31 ± 8</td>
<td>30 ± 10</td>
<td>32 ± 4</td>
<td>36 ± 8</td>
<td>28 ± 6</td>
</tr>
<tr>
<td>Change in EF from rest to exercise</td>
<td>-7 ± 8</td>
<td>-8 ± 6</td>
<td>-10 ± 10</td>
<td>-8 ± 3</td>
<td>-6 ± 7</td>
<td>-6 ± 5</td>
</tr>
<tr>
<td>RV:EDV ratio at rest</td>
<td>0.34 ± 0.09</td>
<td>&lt;0.005</td>
<td>0.26 ± 0.08</td>
<td>0.31 ± 0.07</td>
<td>0.24 ± 0.08</td>
<td>0.28 ± 0.04</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

*Comparison between patients with normal ejection fraction and all patients with subnormal ejection fraction (unpaired t test).

+Comparison not made since patient subgroups defined on basis of ejection fraction.

‡Significance different compared to other subgroups with subnormal ejection fraction at rest (analysis of variance).
fraction. Nonetheless, our data clearly indicate that afterload was increased before operation, consistent with previous reports, as end-diastolic dimension and systolic blood pressure were elevated, resulting in increased peak systolic wall stress. Postoperative reduction in these determinants of afterload was associated with improvement in left ventricular ejection performance.

These data indicate that in many patients with left ventricular dysfunction, systolic performance is reversibly depressed on the basis of afterload excess arising from the severe volume overload, and, in these patients, systolic function responds favorably to surgical removal of valvular regurgitation and to reversal of ventricular dilatation. Of note, this effect is evident also in patients with “normal” preoperative systolic function, in that ejection fraction increases significantly after operation (Figure 3), suggesting that ventricular performance in these patients, although within normal limits, may also be subject to afterload excess before operation. Ejection fraction continued to increase late after operation in many patients. In this particular subgroup, characterized by late increases in ejection fraction, there were also further significant decreases in end-diastolic dimension. Moreover, for the entire group, the subsequent late changes in ejection fraction after the early postoperative study also correlated with simultaneous further changes in end-diastolic dimension. However, the correlation between changes in ejection fraction and changes in diastolic dimension occurring between 6–8 months and 3–7 years after operation, although significant, was relatively weak ($r = 0.54$). Thus, it appears that additional factors, other than decreases in left ventricular diastolic volume and, therefore, wall stress, may contribute to the late increase in ejection fraction. It is also possible that further reduction in cavity size along the long axis of the left ventricle (resulting in reduced circumferential wall stress), which would not have been sampled by our echocardiographic technique, could account for the late increase in ejection fraction.

Patients manifesting the greatest reduction in end-diastolic dimension after operation, hence those with the greatest likelihood of early and late increases in ejection fraction, were either those with normal preoperative ejection fraction or those with depressed ejection fraction but preserved exercise tolerance and only a brief duration of left ventricular dysfunction (Figures 6 and 7). We have previously demonstrated that such patients have an excellent postoperative prognosis, and of all the deaths that occurred in our total consecutive series of 83 patients during the time frame of this study, only one was in this subgroup of patients.

In contrast, among patients with preoperative left ventricular dysfunction and reduced exercise tolerance or those with good exercise tolerance but a prolonged duration of preoperative systolic dysfunction, the magnitude of decrease in end-diastolic dimension was less pronounced, and there was no significant change in ejection fraction after operation either short-term or long-term (Figures 6 and 7). These data indicate that depressed systolic performance in these latter patients is not related purely to volume overload but also to a considerable extent to irreversible myocardial dysfunction that will not improve despite technically successful reversal of the regurgitant volume by valve replacement. Our previous analysis indicates that patients with these preoperative characteristics have reduced postoperative survival. Indeed, all six deaths occurring in the current series after the late postoperative studies occurred in these patients. In addition, of the 10 deaths occurring before late postoperative studies (and thus not included in the current study), five were in this subgroup of patients and four occurred in the subgroup with left ventricular dysfunction of unknown duration. Thus, among the 83 consecutive patients undergoing aortic valve replacement during the timeframe of this study, 15 of the 16 postoperative deaths occurred in patients with preoperative left ventricular dysfunction and impaired exercise tolerance or with preoperative systolic dysfunction, the duration of which was prolonged or unknown. The current data indicate that such patients have a higher risk of irreversible left ventricular dysfunction and death after operation than do patients with preserved exercise tolerance and only a brief duration of preoperative systolic dysfunction and are further evidence that patients with impaired left ventricular systolic performance benefit from early operation.

References

8. Boucher CA, Bingham JB, Osbakken MD, Okada RD, Strauss HW, Block PC, Levine FH, Phillips HR, Pohost GM: Early changes in left ventricular size and function after
correction of left ventricular volume overload. Am J Cardiol 1981;47:991–1004
22. Burgraff GW, Craig E: Echocardiographic studies of left ventricular wall motion and dimension after valvular heart operation. Am J Cardiol 1975;35:473–480

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R O Bonow, J T Dodd, B J Maron, P T O'Gara, G G White, C L McIntosh, R E Clark and S E Epstein

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