Preoperative Exercise Capacity in Symptomatic Patients with Aortic Regurgitation as a Predictor of Postoperative Left Ventricular Function and Long-term Prognosis

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SUMMARY

Forty-five symptomatic patients with aortic regurgitation underwent graded treadmill exercise testing before operation. Twenty-seven patients (group A) could not complete stage I of the National Institutes of Health exercise protocol because of limiting symptoms (exercise duration ≤ 22.5 minutes); 18 patients (group B) completed this stage without limiting symptoms (exercise duration > 22.5 minutes). Patients in group A had higher resting pulmonary capillary wedge pressures (mean 19 vs 13 mm Hg, p < 0.05) and left ventricular (LV) end-diastolic pressures (mean 24 vs 16 mm Hg, p < 0.05) than those in group B, but did not differ with respect to LV systolic dimension or fractional shortening by echocardiography or LV ejection fraction at rest or during exercise by radionuclide cineangiography.

Among 32 patients with subnormal preoperative LV fractional shortening on echo, nine of 17 in group A and 0 of 15 in group B had died (p < 0.01); seven of the nine deaths were from late congestive heart failure. Group A patients also had less decrease postoperatively in LV diastolic size by echocardiography (mean decrease 8 vs 23 mm, p < 0.001) and less increase postoperatively in LV ejection fraction during exercise by radionuclide cineangiography (mean increase 11% vs 23%, p < 0.05) than group B patients. No group A patient and 60% of group B patients had normal exercise ejection fractions postoperatively (p < 0.01). The differences in postoperative mortality and function were not predicted by the differences in preoperative hemodynamics between the two groups. Thus, exercise capacity is imprecise in assessing preoperative LV function in symptomatic patients with aortic regurgitation, but is useful in predicting long-term survival after operation and reversibility of LV dilatation and systolic dysfunction.

THE MAJORITY of symptomatic patients who undergo surgery for aortic regurgitation have symptomatic improvement after valve replacement. Others, however, develop progressive congestive heart failure, the most common cause of late postoperative death. In such patients, irreversible myocardial changes presumably occur before or concomitant with the development of symptoms that lead to operation.1-4

To define more precisely a strategy for determining the optimal timing of operation in patients with aortic regurgitation, we used echocardiography to assess left ventricular systolic function in symptomatic patients before operation. This provided a sensitive means of predicting which patients would undergo operation from irreversible left ventricular failure.5 Despite the enhanced ability to predict long-term prognosis after operation, however, such analyses still identified within the “high-risk” group a substantial number of patients with impaired preoperative systolic function who did well after operation. Thus, while sensitivity in predicting late congestive failure deaths was high, specificity was low.

Exercise testing until exhaustion or the development of symptoms is often used as an index of cardiac function and, as such, in the management of patients with a variety of cardiac disorders. One assumption implicit in using the results of exercise testing in this way is that the response of the heart to stress provides more information concerning left ventricular functional reserve than can be obtained from hemodynamic and echocardiographic studies obtained with the patient at rest.6-12

To ascertain whether graded exercise testing would further aid in the clinical decision analysis of patients with aortic regurgitation, treadmill exercise tests were performed in symptomatic subjects before operation. These subjects were then followed after operation to determine whether preoperative exercise performance could predict long-term postoperative survival. The data were also analyzed to determine whether preoperative exercise performance provided insight into preoperative left ventricular function (determined by echocardiography and radionuclide cineangiography) as well as into reversibility of left ventricular dysfunction.

Methods

Patient Selection

All patients who underwent aortic valve replacement for chronic aortic regurgitation at the National Institutes of Health (NIH) between January 1972 and December 1978 were evaluated consecutively in a prospective manner. The indication for operation in each patient was a history of moderate-to-severe...
dyspnea on exertion, orthopnea, or paroxysmal nocturnal dyspnea, an episode of pulmonary edema, or a history of angina pectoris or syncope. All patients had severe aortic regurgitation as assessed by aortic root cineangiography (early opacification of the cardiac apex that did not clear during the subsequent cardiac cycle). Patients were excluded from evaluation if they had evidence of acute aortic regurgitation, a systolic aortic value gradient greater than 20 mm Hg, or either mitral valvular disease or aortic root disease that required operative repair at the time of aortic valve replacement.

Seventeen of the 71 patients (24%) who fulfilled the selection criteria were found to have coexistent coronary artery disease, defined as greater than 50% stenosis of the diameter of at least one major coronary artery. These patients were excluded from graded exercise testing because exercise capacity might be limited by myocardial ischemia caused by inadequate coronary reserve, making it impossible to determine maximal functional capacity of the myocardium per se.

Six other patients were not exercised; two had histories of syncope, three were considered clinically unstable, and another had severe ankylosing spondylitis. Exercise data were unavailable on another three patients. Thus, 45 patients (ages 20–68 years, mean 44 years) made up the study population. There were 38 men and seven women. Thirty-four of the 45 patients underwent coronary arteriography and either had normal studies or less than 50% stenoses. The other 11 patients were all younger than 35 years of age (nine were less than 30 years of age) and none complained of chest pain. We refrain from performing coronary arteriography in such patients with aortic valve disease. Three of these 11 patients died from congestive heart failure after operation and had normal coronary arteries at necropsy. The other eight patients are in New York Heart Association functional class I after operation.

None of the 45 patients had other medical conditions, such as anemia or chronic pulmonary disease, that might limit exercise capacity. Thirty-one of the 45 patients were previously reported in the results of aortic valve replacement.

All patients had unequivocal clinical evidence of severe aortic regurgitation with blowing diastolic murmurs and cardiomegaly on chest x-ray. The average systemic pulse pressure was 95 mm Hg and was less than 60 mm Hg in only one patient. Systemic diastolic pressure averaged 51 mm Hg and exceeded 70 mm Hg in only two patients. Modified Romhilt-Estes point scores, computed as previously described, averaged 6.7 and were less than 5.0 in only seven patients.

**Preoperative Studies**

All patients were evaluated preoperatively by history, physical examination, 12-lead electrocardiography, M-mode echocardiography, left- and right-heart catheterization and graded treadmill exercise testing. In addition, 24 patients underwent radionuclide cineangiography at rest and during exercise. This includes all patients who underwent aortic valve replacement for aortic regurgitation at our institution between April 1976 and December 1978. All studies were performed during a 5-day inpatient evaluation, and the maximum time between any two studies was 4 days, except for 11 patients who underwent catheterization at other institutions before their referral to the NIH. In these patients, the maximum time between catheterization and the noninvasive studies was 6 weeks.

**Left Ventricular Contrast Cineangiography**

Single-plane left ventricular cineangiograms were obtained at catheterization in all patients. End-diastolic and end-systolic volumes were calculated as previously described. In 18 patients, however, poor dye opacification, premature ventricular complexes or technical factors prevented optimal determination of ventricular volumes and ejection fraction. Hence, we could not compare echocardiographic vs cineangiographic measurements in all patients. However, a reasonable correlation was found between cineangiographic left ventricular volumes and echocardiographic left ventricular internal dimensions in the 27 patients with adequate cineangiographic studies, for diastole (r = 0.75), systole (r = 0.71), or diastole and systole combined (r = 0.89). A similar correlation was found between angiographic left ventricular ejection fraction and echocardiographic fractional shortening (r = 0.74).

**Echocardiography**

Echocardiograms were obtained using a 12.5-mm diameter, 2.25-MHz unfocused ultrasound transducer and either an Ekoline 20A or a Hoffrel 201 ultrasound transceiver interfaced with a Honeywell 1856 strip-chart recorder. Echocardiographic measurement of the left ventricular dimensions at end-diastole and end-systole and the thickness of the ventricular septum and the left ventricular free wall were obtained with the ultrasound beam passing through the left ventricle caudal to the tips of the mitral leaflets. Left ventricular fractional shortening was calculated as the ratio of the difference between left ventricular diastolic dimension and systolic dimension to the left ventricular diastolic dimension. In addition, left ventricular ejection fraction and left ventricular mass were calculated.

**Graded Treadmill Exercise Testing**

Exercise testing was performed in the postabsorptive state. Digitalis and diuretic therapy were discontinued at least 3 days before testing. Heart rate and rhythm were monitored continually during testing with a two-lead ECG with a CM5 electrode and a modified posteroinfxerior electrode. Patients exercised on a motor-driven treadmill using the NIH exercise protocol (table 1). In stage 1 of this protocol, the treadmill is driven at a constant speed of 2.2 mph at an
TABLE 1. National Institutes of Health Exercise Protocol

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Speed (mph) Grade</th>
<th>Speed (mph) Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.2 0%</td>
<td>1.9 10%</td>
</tr>
<tr>
<td>2.5</td>
<td>2.2 2.5%</td>
<td>2.3 12%</td>
</tr>
<tr>
<td>5.0</td>
<td>2.2 5.0%</td>
<td>2.7 14%</td>
</tr>
<tr>
<td>7.5</td>
<td>2.2 7.5%</td>
<td>3.1 16%</td>
</tr>
<tr>
<td>10.0</td>
<td>2.2 10.0%</td>
<td>3.5 18%</td>
</tr>
<tr>
<td>12.5</td>
<td>2.2 12.5%</td>
<td>3.9 20%</td>
</tr>
<tr>
<td>15.0</td>
<td>2.2 15.0%</td>
<td>4.7 20%</td>
</tr>
<tr>
<td>17.5</td>
<td>2.2 17.5%</td>
<td>5.5 20%</td>
</tr>
<tr>
<td>20.0</td>
<td>2.2 20.0%</td>
<td>6.3 20%</td>
</tr>
<tr>
<td>22.5 End of stage I</td>
<td>7.1 20%</td>
<td></td>
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</tbody>
</table>

Initial inclination of 0%. Every 2.5 minutes the inclination is increased 2.5% until a maximum of 22.5 minutes elapse. Exercise is continued to marked fatigue or until the patient complains of angina, limiting dyspnea or lightheadedness. Twenty-seven patients developed limiting symptoms during stage I. Patients who completed the entire 22.5 minutes of stage I without limiting symptoms were then tested within 4-48 hours on stage II of the exercise protocol (table 1). In stage II, the treadmill is initially driven at 1.9 mph at an inclination of 10%. Every 2.5 minutes the treadmill speed and inclination are increased by 0.4 mph and 2%, respectively. After 15 minutes, the inclination is held constant at 20% and the speed is increased 0.8 mph every 2.5 minutes. The indications for cessation of testing are the same as for stage I of the exercise protocol. Each patient who completed stage I without symptoms completed at least 8 minutes of stage II before developing limiting fatigue, dyspnea or angina. Five patients had been followed in our clinic for several years before the onset of symptoms, and previous exercise testing had documented good exercise tolerance. These five patients were tested directly on stage II of the exercise protocol without prior testing on stage I; all five completed more than 8 minutes (9.5–17.1 minutes) of exercise in stage II before limiting symptoms, and were assumed capable of completing stage I without symptoms.

Forty-four patients discontinued exercise testing because of fatigue or dyspnea. Only one patient developed angina during exercise; this patient had normal coronary arteriograms. Isolated ventricular ectopic beats were often observed during exercise, but no patients showed high-grade ventricular arrhythmias that required discontinuation of testing.

In 35 patients, oxygen consumption was measured at the end of symptom-limited exercise using a continuous flow system and paramagnetic oxygen analyzer. Twelve of these patients completed stage I without symptoms and developed limiting symptoms only during stage II; each obtained higher levels of oxygen consumption during stage II than during stage I.

Blood Pool Cardiac Scintigraphy

Technetium-99m radionuclide cineangiography was performed in the supine position at rest and during bicycle exercise using a conventional Anger camera equipped with a high-sensitivity, parallel-hole collimator oriented in a modified left anterior oblique position. Visually interpretable and statistically reliable movies of the blood pool were obtained using the ECG-gated equilibrium procedure previously described. Ejection fractions were determined at rest and during exercise by analysis of count-based left ventricular time-activity curves after background correction. During exercise studies, performed within 30 minutes of the rest studies, supine bicycle exercise was begun at a work load of 25 W; the load was increased at 25-W increments every 2 minutes until the development of angina or limiting dyspnea or fatigue. Heart rate and blood pressure (by sphygmomanometry) were monitored during exercise. Imaging was begun shortly after the onset of exercise, but only the portion of the image series that occurred during maximal exercise, encompassing the final 2 minutes of exercise, was selected for analysis.

Aortic Valve Replacement

At operation, 18 patients received 2320 series Starr-Edwards prostheses, 17 received glutaraldehyde-fixed porcine heterograft prostheses, eight received 2400 series Starr-Edwards prostheses, and two received Björk-Shiley prostheses. In addition to total body hypothermia to 30–31°C in all patients, myocardial preservation techniques included direct coronary artery perfusion with blood cooled to 30°C in 11 patients, topical iced saline lavage (4°C) in three patients, and coronary perfusion plus iced saline lavage in 31 patients.

Postoperative Studies

All patients who survived 6 months after operation underwent repeat echocardiography and cardiac catheterization, performed using either the transeptal or left ventricular puncture technique. Echocardiographic left ventricular systolic dimension and percent fractional shortening were not analyzed because of abnormal septal motion in most patients after operation. Hemodynamic data demonstrated peak systolic gradients across the prosthetic valve of 0–40 mm Hg (mean 9 mm Hg). Prosthetic valve areas were not computed because of the small systolic gradients. Only two patients had prosthetic valve gradients greater than 20 mm Hg; both are doing well 51 and 67 months after operation. In both, 6-month postoperative echocardiograms demonstrated substantial reduction in left ventricular diastolic dimension compared with the preoperative value (54 vs 74 mm and 52 vs 72 mm) despite the prosthetic valve gradient. Prosthetic valve regurgitation was demonstrated in two patients; each had only mild regurgitation on aortic root angiography (faint opacification of the left ventricular outflow tract clearing with the next cardiac cycle) and each had substantial reduction in left ven-
tricular diastolic dimension by echocardiography compared with the preoperative value (55 vs 79 mm and 45 vs 64 mm). Both patients are asymptomatic 36 and 82 months after operation.

Patients in whom radionuclide cineangiography was performed before operation underwent repeat evaluation 6 months postoperatively. Supine exercise was performed according to a protocol identical with that used before operation for each patient. To achieve similar heart rates, however, we often had to continue exercise to higher load levels than could be obtained before operation. Therefore, results used for assessment of postoperative systolic function were those achieved during maximal exercise. The heart rate at maximal exercise after operation was not significantly different compared with the preoperative value.

Statistical Methods

Linear regression analysis was performed to relate treadmill exercise performance to preoperative hemodynamic, echocardiographic, and radionuclide cineangiographic data. Patients unable to complete stage I of treadmill exercise because of limiting symptoms were compared with patients who completed stage I without symptoms by $t$ test. Postoperative changes in left ventricular diastolic size and systolic function were analyzed by $t$ test (using paired and unpaired data), Fisher's exact test and the method of covariance (to assess relative influences of preoperative hemodynamic values and preoperative exercise capacity), as appropriate. Survival curves were plotted by the Kaplan-Meier life-table method and statistical analysis of the survival data by the method of Mantel and Haenszel.

Results

Patient Experience

Three of the 45 patients died at operation. Seven died late (5–42 months) after operation from congestive heart failure; each had chronic progressive symptoms of pulmonary venous hypertension and low cardiac output before death. Two of these seven patients died before the 6-month postoperative evaluation. One other late death was not associated with congestive failure; 46 months after operation this patient died while swimming, and we do not know whether this represents drowning or sudden cardiac death. Thirty-four patients are alive at a mean follow-up of 38 months (range 6–89 months). Postoperative survival did not correlate with age, type of prosthetic valve, method of myocardial preservation at operation, or systolic gradient across the prosthetic valve.

Preoperative Data

Maximum heart rates during treadmill exercise testing (fig. 1) ranged from 90–205 beats/min (mean 157 beats/min). In only one patient did the heart rate not reach 100 beats/min. This patient could exercise only 45 seconds in stage I before the onset of severe dyspnea, which occurred at a heart rate of 90 beats/min and oxygen consumption of 9.7 ml/min/kg. This patient had echocardiographic evidence of a dilated left ventricle with poor systolic function and at catheterization had a resting mean pulmonary artery wedge pressure of 26 mm Hg. She died from congestive heart failure 5 months after technically successful valve replacement. Four other patients had maximum heart rates less than 120 beats/min (fig. 1). None of these patients could complete stage I of the treadmill exercise protocol because of symptoms, and their maximum oxygen consumptions ranged from 12.5–24.5 ml/min/kg. The remaining 40 patients all reached exercise heart rates of 130 beats/min or more.

The 27 patients who could not complete stage I of treadmill exercise because of limiting symptoms ranged in age from 20–65 years (table 2) and did not differ from the 18 patients who completed stage I without symptoms, who ranged in age from 24–61 years. The male to female ratio was also not significantly different between the two groups. Patients unable to complete stage I, in addition to demonstrating greater impairment of exercise capacity as measured by exercise duration, also achieved significantly lower levels of heart rate and oxygen consumption during treadmill exercise than the patients who completed stage I (table 2).

Exercise Capacity vs Resting Hemodynamic Data

The resting cardiac index of patients who could not complete stage I exercise because of symptoms was

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Preoperative exercise performance. Maximum heart rate during treadmill exercise is plotted as a function of exercise duration at the time of limiting symptoms. The dashed line at 22.5 minutes indicates the end of stage I of the National Institutes of Health exercise protocol. The two patients shown at 22.5 minutes developed limiting symptoms toward the end of stage I and were not tested further. CHF = congestive heart failure.
**Table 2. Exercise Heart Rate and Oxygen Consumption During Treadmill Exercise**

<table>
<thead>
<tr>
<th>Exercise duration ≤ 22.5 min (Unable to complete stage I)</th>
<th>Exercise duration &gt; 22.5 min (Completed stage I)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47 ± 15 (n = 27)</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum heart rate (beats/min)</td>
<td>145 ± 25 (n = 27)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maximum oxygen consumption (ml/min/kg)</td>
<td>21 ± 6 (n = 23)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are mean ± sd.

2.5 ± 0.6 l/min/m² (mean ± sd) and did not differ from that of patients who completed stage I, 2.6 ± 0.4 l/min/m² (fig. 2). Patients unable to complete stage I, however, did have significantly higher resting mean pulmonary artery wedge pressures (19 ± 9 vs 13 ± 6 mm Hg, p < 0.05) and left ventricular end-diastolic pressures (24 ± 11 vs 16 ± 9 mm Hg, p < 0.05) than the group with greater exercise capacity (fig. 2). Pulmonary artery systolic and diastolic pressures were also significantly higher (both p < 0.05) in the group unable to complete stage I exercise, but systemic arterial systolic and diastolic pressures and pulse pressure were not significantly different between the two groups.

**Exercise Capacity vs Left Ventricular Angiographic Volumes**

Among the 27 patients with angiographic data adequate for volume analysis, the 16 patients unable to complete stage I exercise because of symptoms had smaller left ventricular end-diastolic volumes (fig. 3) than the group with greater exercise capacity (282 ± 79 vs 350 ± 61 ml, p < 0.05). The two groups did not differ with respect to left ventricular end-systolic volume or left ventricular ejection fraction.

**Exercise Capacity vs Echocardiographic and ECG Data**

The angiographic volume data were paralleled by the echocardiographic measurements. The 27 patients unable to complete stage I exercise because of symptoms had significantly smaller echocardiographic left ventricular end-diastolic dimensions (fig. 4) than the 18 patients with greater exercise capacity (73 ± 8 vs 77 ± 7 mm, p < 0.05). Calculated left ventricular mass, however, was not significantly different between the two groups. The two groups also did not differ with respect to left ventricular end-systolic dimension or left ventricular fractional shortening (fig. 4). Although the four patients with the lowest fractional shortening
Radionuclide left ventricular ejection fractions at rest in the 24 patients in this study ranged from 29–59% (mean 42%) and were significantly lower than values previously reported for normal subjects.12 Twelve patients had normal ejection fractions at rest (at least 45%). Ejection fractions significantly decreased during maximal supine exercise (fig. 6) and were subnormal in all patients (less than 55%), ranging from 14–52%. Despite greater exercise capacity as assessed by upright exercise studies, the 15 patients who completed stage I of treadmill exercise without symptoms had ejection fractions at rest and during exercise that were not significantly different from the nine patients unable to complete stage I of treadmill exercise because of limiting symptoms (fig. 6). Eight patients who could not complete stage I and 10 patients who completed stage I had severely depressed left ventricular ejection fractions during exercise (less than 40%).

**Postoperative Survival**

Preoperative echocardiographic evidence of left ventricular systolic dysfunction, manifested by subnormal left ventricular fractional shortening (less than 29%) or left ventricular end-systolic dimension greater than 55 mm, identified patients at high risk of operative death or death from congestive heart failure during long-term postoperative follow-up (fig. 4), as we have previously demonstrated.6 Prediction of operative or late death was considerably improved, however, when exercise capacity was also considered. Thus, no deaths occurred in any of the 18 patients who could complete stage I of treadmill exercise before operation, despite the fact that many of these patients had evidence of systolic dysfunction by echocardiography (fig. 4). Analysis of the 32 patients with subnormal preoperative left ventricular fractional shortening (fig. 7) indicated that the 15 patients who

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**Figure 4.** Preoperative echocardiographic data. Left ventricular dimension (LVD) at end-diastole and end-systole and left ventricular fractional shortening (%FS) in patients unable to complete stage I (≤22.5 minutes) are compared with patients who completed stage I (>22.5 minutes). The stippled area identifies the normal range of %FS for our laboratory (29–45%). Symbols and abbreviations are explained in figures 1 and 2.

(below 15%) could not complete stage I without limiting symptoms, 10 of 13 patients (77%) with normal fractional shortening were also unable to complete stage I without symptoms. Other echocardiographic variables, including ventricular septal thickness, left ventricular free wall thickness, aortic root dimension, and left atrial dimension, as well as the calculated electrocardiographic Romhilt-Estes point score, did not differ between the two groups.

**Exercise Capacity vs Left Ventricular Ejection Fraction**

Echocardiographic left ventricular fractional shortening was compared with resting radionuclide left ventricular ejection fraction. Figure 5 is a comparison of fractional shortening and resting ejection fraction data for the 24 patients in this study and for an additional 39 patients with aortic regurgitation studied in our laboratory by these techniques. There was good correlation between these two independent measures of left ventricular systolic function for all 63 patients (r = 0.85) and for the 24 patients included in this study (r = 0.82). The relation between ventricular size by echocardiography and resting and exercise ejection fractions by radionuclide cineangiography has been reported separately.27

**Figure 5.** Echocardiographic left ventricular (LV) fractional shortening compared with resting radionuclide LV ejection fraction. Data are shown for the 24 patients in this study (solid circles) and for 39 other patients with aortic regurgitation studied by these two techniques (open circles). The dashed line indicates the lower limits of normal for each variable. The correlation coefficient was 0.82 for the 24 patients and 0.85 for the 63 patients.
FIGURE 6. Preoperative left ventricular ejection fractions at rest and during maximal supine exercise obtained by technetium-99m radionuclide cineangiography. Patients who could not complete stage I of treadmill exercise (<22.5 minutes) did not significantly differ at rest or during exercise (Ex) from patients who completed stage I (>22.5 minutes). The dashed line at 55% indicates the lower limit of normal for ejection fraction during exercise.

completed stage I without symptoms before operation had significantly better survival after operation than the 17 patients unable to complete stage I (100% survival at 3 years vs 53% survival, p < 0.01). Similar analysis of the smaller subgroup of patients with preoperative left ventricular systolic dimension greater than 55 mm (20 patients) also revealed better survival in the nine patients who completed stage I before operation than in the 11 patients unable to complete stage I (100% survival at 3 years vs 38% survival, p = 0.05).

When the survival of all 45 patients was analyzed (life-table method) independent of echocardiographic assessment of left ventricular function, exercise capacity alone was helpful in determining relative postoperative prognosis: 100% survival at 3 years in the 18 patients who could complete stage I without symptoms before operation, and 68% survival in the 27 who could not (p < 0.05).

Postoperative Left Ventricular Function

Left Ventricular Diastolic Size

Among the 32 patients with subnormal preoperative left ventricular fractional shortening, preoperative echocardiographic left ventricular end-diastolic dimension was not significantly different between patients who could complete stage I of treadmill exercise and those who could not (fig. 8). The patients who completed stage I before operation, however, achieved significantly greater reduction in end-diastolic dimension 6 months after operation than patients unable to complete stage I (mean decrease 23 ± 7 vs 8 ± 9 mm, p < 0.001), such that their end-diastolic dimensions were significantly lower (mean 56 ± 8 vs 68 ± 11 mm, p < 0.005). Of the 32 patients, all but five had decreases in left ventricular end-diastolic dimension after operation of 10 mm or greater; these five (whose change in diastolic dimension ranged from a 4 mm decrease to a 5 mm increase) all had limited exercise capacity before operation and could not complete stage I because of symptoms. Eight patients had persistent left ventricular diastolic dilatation of 70 mm or greater at 6-month postoperative study (fig. 8) and five
of the eight died from congestive heart failure. Seven of these eight patients (including the five late deaths) could not complete stage I exercise before operation ($p < 0.05$). Two additional patients (not shown in figure 8), who had subnormal left ventricular fractional shortening and could not complete stage I exercise, died from congestive heart failure before 6-month postoperative study.

**Left Ventricular Ejection Fraction**

The trends encountered in postoperative left ventricular diastolic size by echocardiography were paralleled by the changes in left ventricular systolic function by radionuclide cineangiography (fig. 9). Resting left ventricular ejection fraction improved in 20 of 22 patients after operation, and was normal (45% or greater) in 18 patients. Patients who completed stage I of treadmill exercise before operation did not have significantly higher postoperative ejection fractions at rest than patients unable to complete stage I. However, while ejection fraction during exercise increased after operation in 22 of 23 patients, the patients who completed stage I of treadmill exercise before operation manifested greater improvement and had higher exercise ejection fractions after operation than patients unable to complete stage I (mean 58 ± 15% vs 42 ± 8%, $p < 0.01$). Moreover, although six of eight patients unable to complete stage I before operation had normal ejection fractions after operation at rest, ejection fraction during exercise remained subnormal in all eight (fig. 9). In contrast, nine of 15
patients (60%) who completed stage I before operation had normal exercise ejection fractions after operation (p < 0.01). Of 10 patients who completed stage I before operation despite severely depressed exercise ejection fractions (less than 40%), five had normal exercise ejection fractions after operation (ranging from 58–74%) and three were near normal (52%, 52% and 54%).

Exercise ejection fraction failed to improve after operation in only one patient (fig. 9). This patient had evidence of intraoperative myocardial damage manifested by new anteroseptal Q waves on postoperative ECG and new septal dyskinesia on postoperative radionuclide study. This patient is also the only patient who completed stage I exercise before operation whose postoperative echocardiographic left ventricular diastolic dimension failed to decrease below 70 mm (fig. 8).

Influence of Preoperative Hemodynamic Values

Patients who could not complete stage I exercise before operation because of symptoms had significantly higher preoperative pulmonary artery wedge and left ventricular end-diastolic pressures than patients who could complete stage I (fig. 2). A multivariate analysis, however, demonstrated that the differences in postoperative diastolic size and systolic function between the two groups were not significantly altered after adjustment for differences in preoperative hemodynamics, and that the preoperative hemodynamic data did not further enhance the accuracy of preoperative exercise capacity in predicting reversibility of left ventricular dysfunction. For example, postoperative echocardiographic left ventricular end-diastolic dimensions, and changes in this dimension from before to after operation, did not significantly differ between patients with pulmonary artery wedge pressures less than 15 mm Hg and those with wedge pressures of 15 mm Hg or greater, whether this analysis was performed on all patients, on patients who could not complete stage I exercise before operation, or on patients who could complete stage I. Moreover, a multivariate analysis of the postoperative survival data relative to preoperative pulmonary artery wedge or left ventricular end-diastolic pressure failed to enhance the significant correlations provided by exercise capacity alone (fig. 7).

Discussion

Patients with aortic regurgitation may remain asymptomatic for many years despite the burden of a large volume load on the left ventricle. The major dilemma in managing these patients is determining the proper timing of operation. Valve replacement in all asymptomatic patients would result in operative deaths or prosthetic valve complications in many patients who would otherwise have been asymptomatic for many years. On the other hand, when symptoms alone are used as the criteria for operation, many patients who survive valve replacement will develop progressive left ventricular decompensation and die many months after operation from congestive heart failure. Such patients have insidiously developed irreversible myocardial dysfunction while asymptomatic or only mildly symptomatic. Thus, more objective and prognostically relevant measures of left ventricular function are required to determine the optimal timing of aortic valve replacement.

In a recent study of 50 patients with aortic regurgitation who underwent valve replacement at the NIH, of which 31 patients in the present series form a part, we found that preoperative echocardiographic indexes of left ventricular systolic dysfunction (left ventricular fractional shortening less than 25% and left ventricular dimension at end systole greater than 55 mm) are highly sensitive in identifying patients at risk of dying after operation because of congestive heart failure. We also recently reported radionuclide cineangiographic studies demonstrating that patients who had severely reduced left ventricular ejection fractions during exercise (less than 40%) before operation usually have persistent left ventricular dysfunction after operation, and only rarely does ejection fraction return to normal at rest or during exercise.

However, although all patients (with the exception of the occasional patient sustaining intraoperative myocardial damage) who die after operation from congestive heart failure could be identified by detection of preoperative systolic dysfunction, many patients with impaired function did well after operation. Moreover, other institutions have reported that return of normal left ventricular systolic function frequently occurs after valve replacement. We therefore sought to document whether maximum exercise testing in symptomatic patients with aortic regurgitation provided additional insights and predictive information regarding preoperative left ventricular dysfunction, reversibility of preoperative left ventricular dysfunction, and long-term survival after operation.

The results of the present study demonstrate that preoperative treadmill exercise testing alone does not identify patients who have severe left ventricular dysfunction. Exercise capacity did not correlate with indexes of resting left ventricular systolic function derived from echocardiographic studies, or with left ventricular ejection fractions at rest or during exercise derived from radionuclide cineangiographic studies. In fact, some patients with the greatest impairment of left ventricular systolic function exercised much longer, and to higher levels of heart rate and oxygen consumption, than other patients with apparently normal systolic function. Moreover, patients who completed stage I of the NIH exercise protocol, surprisingly, showed greater left ventricular dilatation by contrast angiography and by echocardiography than those who could not complete stage I because of symptoms (figs. 3 and 4). These findings document the clinical impression that certain patients with aortic regurgitation develop severe ventricular dysfunction while virtually free of symptoms and with apparently normal exercise capacity.
Since objective determination of preoperative exercise capacity is not useful in assessing left ventricular function in symptomatic patients with aortic regurgitation, it would appear to be a poor method, in itself, with which to prospectively screen or select patients for operation. Despite the lack of correlation with echocardiographic or radionuclide indexes of left ventricular function, however, preoperative exercise capacity appears capable of enhancing our ability to predict long-term postoperative survival beyond that provided by documentation of preoperative left ventricular systolic dysfunction.\textsuperscript{6, 8} and to predict reversibility of left ventricular dysfunction.

Regarding long-term survival, none of the patients with subnormal preoperative fractional shortening or end-systolic dimension greater than 55 mm who could complete stage I of the NIH exercise protocol without symptoms died at or after operation (fig. 7). In contrast, over 50% of the patients with subnormal preoperative fractional shortening or end-systolic dimension greater than 55 mm who could not complete stage I exercise because of limiting symptoms died at operation or during long-term postoperative follow-up (figs. 4 and 7). Likewise, while all patients who completed stage I of the exercise protocol improved significantly after operation in left ventricular diastolic size, with reduction to less than 70 mm in all but one patient (fig. 8), seven of 13 patients (54%) who could not complete stage I of the exercise protocol had postoperative diastolic dimensions of 70 mm or greater. The improvement in left ventricular end-diastolic dimension is important because postoperative echocardiographic evidence of persistent left ventricular dilatation (70 mm or greater) after technically successful valve replacement strongly correlates with subsequent late death from congestive heart failure.\textsuperscript{8}

Regarding reversibility of left ventricular dysfunction, we found that although all patients who could complete stage I of the exercise protocol had subnormal left ventricular ejection fractions during exercise before operation, nine of 15 (60%) had return of exercise ejection fraction to the normal range, including five of 10 patients (50%) with preoperative exercise ejection fractions of less than 40%. In contrast, none of the eight patients who could not complete stage I of exercise had normal exercise ejection fractions after operation (fig. 9).

Thus, in symptomatic patients with aortic regurgitation and left ventricular dysfunction, good preoperative exercise capacity appears to indicate that irreversible myocardial dysfunction has not developed; the converse is true for patients with left ventricular systolic dysfunction who have poor preoperative exercise capacity. These results suggest that subtle factors that influence exercise capacity, but which are not reflected in usual indexes of left ventricular systolic function at rest or exercise, are important determinants of reversibility of myocardial abnormalities.

Our data support the concept that patients with aortic regurgitation should undergo operation once left ventricular systolic dysfunction is detected under resting conditions,\textsuperscript{8, 9} even though appreciable deterioration in symptoms and exercise capacity is not yet evident; once the latter occurs, irreversible myocardial damage is likely. These findings also demonstrate that the incidence of reversibility of left ventricular dysfunction after operation for aortic regurgitation at any institution depends to a large extent on the degree of symptomatic limitation of the patients at the time of operation.

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