PATHOPHYSIOLOGY AND NATURAL HISTORY
AORTIC DISEASE

The natural history of asymptomatic patients with aortic regurgitation and normal left ventricular function

ROBERT O. BONOW, M.D., DOUGLAS R. ROISING, M.D., CHARLES L. McINTOSH, M.D., PH.D., MICHAEL JONES, M.D., BARRY J. MARON, M.D., K. K. GORDON LAN, PH.D., EDWARD LAKATOS, PH.D., STEPHEN L. BACHARACH, PH.D., MICHAEL V. GREEN, M.S., and STEPHEN E. EPSTEIN, M.D.

ABSTRACT In asymptomatic patients with severe aortic regurgitation and normal left ventricular function, aortic valve replacement has been recommended to preserve left ventricular function. In such patients, however, the natural history without operation is unknown. We therefore performed serial studies in 77 asymptomatic patients with normal left ventricular ejection fraction at rest as determined by radionuclide angiography and normal left ventricular fractional shortening as determined by echocardiography; 63 patients had $3^+ to 4^+$ aortic regurgitation visualized by aortic root cineangiography, and the other 14 patients had pulse pressures $>70$ mm Hg. During mean follow-up of 49 months (range 6 to 114) no patient died and 12 patients underwent aortic valve replacement because of the onset of symptoms (11 patients) or the onset of left ventricular dysfunction without symptoms (one patient). By life table analysis, the percent of patients who did not require operation was $90 \pm 3\%$ ($\pm$ SE) at 3 years, $81 \pm 6\%$ at 5 years, and $75 \pm 7\%$ at 7 years. In the 12 who did have surgery there were no operative or late deaths (postoperative follow-up 8 to 75 months, mean 38), left ventricular ejection fraction increased (45 to 55 [$\pm$ SD] preoperatively, 58 to 11 postoperatively; $p < .001$), and left ventricular diastolic dimension determined echocardiographically decreased (74 to 4 mm preoperatively, 52 to 5 mm postoperatively; $p < .001$). Thus, in asymptomatic patients with normal left ventricular function, death is rare, and less than 4% per year require aortic valve replacement because symptoms or left ventricular dysfunction develop. When aortic valve replacement is delayed until symptoms or left ventricular dysfunction develop, postoperative survival is excellent, and left ventricular size and function improve postoperatively. Hence, "prophylactic" aortic valve replacement to preserve left ventricular function should not be performed in asymptomatic patients with severe aortic regurgitation and normal left ventricular function.


LEFT VENTRICULAR systolic function is an important determinant of long-term prognosis in patients with chronic aortic regurgitation. Numerous studies indicate that symptomatic patients with impaired preoperative left ventricular function are at risk for irreversible myocardial dysfunction and death from congestive heart failure after aortic valve replacement.1-7 Hence, many investigators recommend that asymptomatic or mildly symptomatic patients with left ventricular dysfunction should undergo operation before the development of severe symptoms.4,8-13 The fear of a patient developing irreversible left ventricular failure has also led to the recommendation that operation be performed in all patients with significant aortic regurgitation, even if left ventricular function is normal.3, 14-16 However, the natural history of asymptomatic patients with aortic regurgitation and normal left ventricular function is unknown.

We therefore performed serial studies in 77 patients with asymptomatic aortic regurgitation and normal left ventricular systolic function to determine the time course of development of either symptoms or left ventricular dysfunction and to identify echocardiographic and radionuclide angiographic variables predictive of these events. We also studied the postoperative survival and functional results when operation is delayed until the onset of symptoms or of left ventricular dysfunction.

Vol. 68, No. 3, September 1983
Methods

Patient selection. We studied 77 consecutive asymptomatic patients with severe aortic regurgitation between January 1973 and February 1982, who fulfilled both M mode echocardiographic and radionuclide angiographic criteria of normal resting left ventricular systolic function for our laboratory. At entry into the study, all but one of the patients had normal left ventricular fractional shortening (29% to 44%) as determined echocardiographically. In one patient, the fractional shortening was above normal (50%). Twenty-five patients entered the study between January 1973 and August 1976, before radionuclide angiography was available for evaluation of left ventricular function at our institution. After August 1976, these patients underwent radionuclide angiographic evaluations and all had normal left ventricular ejection fraction at rest (≥ 45%). In two of these patients the initial radionuclide study demonstrating normal resting ejection fraction was performed after the development of symptoms (after asymptomatic follow-up periods of 30 and 49 months); 23 patients remained asymptomatic at the time of the initial radionuclide study. The other 52 patients entered the study between August 1976 and February 1982; radionuclide angiography was performed at the initial evaluation and demonstrated normal resting left ventricular ejection fraction. Data analysis was performed in August 1982, resulting in potential follow-up periods ranging from 6 to 114 months. At entry into the study, the patients ranged in age from 16 to 67 years (mean 37).

Cardiac catheterization was performed in 63 of the 77 patients and confirmed isolated severe aortic regurgitation in 59 patients, with 3° to 4° out of a maximum of 4° valvular regurgitation visualized by aortic root cineangiography. Three patients had associated ventricular septal defects with left-to-right shunt ratios less than 1.5:1. One patient had associated mitral regurgitation and subsequently developed symptoms; he was found at operation to have only minimal mitral regurgitation that did not require concomitant mitral valve replacement, and he is now asymptomatic 24 months after isolated aortic valve replacement. Coronary arteriography was not performed in the asymptomatic patients with normal left ventricular function but was performed preoperatively in all patients over 35 years of age who subsequently developed symptoms or left ventricular dysfunction, or in patients under 35 who subsequently developed angina pectoris. One patient had greater than 50% but less than 75% reduction in luminal diameter of the right coronary artery. No other patient had associated coronary artery disease preoperatively. The 14 asymptomatic patients not catheterized had physical findings compatible with severe isolated aortic regurgitation and systemic pulse pressures of 70 mm Hg or greater.

Throughout the course of the study, aortic valve replacement was performed only in patients who developed (1) symptoms of angina, syncope or near syncope, overt evidence of left ventricular failure (paroxysmal nocturnal dyspnea or orthopnea), or dyspnea (if dyspnea was severe enough to interfere greatly with the patient’s quality of life) or (2) evidence of left ventricular dysfunction while asymptomatic, with consistent reductions in fractional shortening and ejection fraction below normal. All but one of the patients undergoing operation had preoperative cardiac catheterization; the exception was a 20-year-old woman who developed symptoms and underwent aortic valve replacement at another institution.

Initial echocardiographic and radionuclide angiographic studies were performed while patients were off all cardiac medications, except one patient, whose initial data were obtained while she was taking digoxin and propranolol. On echocardiographic examination, the degree of left ventricular dilatation in this patient was mild (end-diastolic dimension 57 mm, end-systolic dimension 33 mm). This patient has been followed up for only 8 months, and serial data are not yet available. During the course of the study, we recommended that patients receive no cardiac medications except for antiarrhythmic drugs in those patients demonstrating ventricular tachycardia during routine 24 hr electrocardiogram (ECG) monitoring. After initiation of the study, however, five patients were placed on digoxin by their referring physicians and two patients were placed on hydralazine. In these seven patients, follow-up data over 7 to 61 months were obtained before these drugs were instituted; late studies over 19 to 82 months were repeated while the patients were on either digoxin or hydralazine. In patients undergoing operation, both the preoperative and postoperative studies were performed while patients were off cardiac medications.

Echocardiography. M mode echocardiograms were obtained with a 1.25 cm diameter, 2.25 MHz unfocused ultrasound transducer and an Ekoline 20A or a Hoffrel 210 ultrasonic transceiver interfaced with a Honeywell 1856 strip chart recorder. Echocardiographic measurement of the left ventricular transverse dimensions were obtained with the ultrasound beam passing through the left ventricle just caudal to the tips of the mitral leaflets.\(^5\)\(^7\) The end-diastolic dimension was measured at the R wave of a simultaneously recorded ECG. The end-systolic dimension was measured at the nadir of septal posterior systolic motion. Left ventricular fractional shortening was calculated as the ratio of the difference between the left ventricular diastolic dimension and systolic dimension to the left ventricular diastolic dimension.\(^18\)

Gated blood pool cardiac scintigraphy. Radionuclide cineangiography was performed with patients in the supine position at rest and during maximum symptom-limited exercise.\(^19\) From August 1976 to October 1979, studies were performed with 10 to 15 mCi of technetium-99m-labeled human serum albumin. After July 1978, we used in vivo labeling of red blood cells with 15 to 20 mCi technetium-99m. Imaging was accomplished with a conventional Anger camera equipped with a high-sensitivity, parallel-hole collimator oriented in a modified left anterior or oblique position to isolate the left ventricle. The cardiac image sequence spanning the average cardiac cycle was constructed by computer-based ECG gating and high temporal resolution (10 to 20 msec/frame) left ventricular time-activity curves were generated from the cardiac image sequence after background correction. Left ventricular ejection fraction was computed automatically from the time-activity curve.\(^19\)

Exercise studies were performed with a bicycle ergometer and restraining harness to minimize patient motion under the camera. Exercise loads were increased by 25 W increments every 2 min until the development of angina or limiting fatigue or dyspnea. Heart rate and blood pressure (by cuff sphygmomanometry) were monitored during exercise. Imaging was begun shortly after the onset of exercise, but only that portion of the data series that occurred during maximal exercise, encompassing approximately the last 2 min of exercise, was selected for analysis.

Treadmill exercise testing. In patients undergoing aortic valve replacement, preoperative exercise capacity was evaluated by the NIH treadmill protocol. In the first stage of this protocol, the treadmill is driven at a constant speed of 2.2 mph at an initial inclination of 0%. Every 2.5 min the inclination is increased by 2.5% until a maximum of 22.5 min elapses. The maximum workload of this stage is 2.2 mph at 20% incline, or approximately 8 mets. Previous studies demonstrate that symptomatic patients with aortic regurgitation who complete this stage of our exercise protocol without symptoms have improved survival and greater reversal of left ventricular dysfunction after operation than patients who are unable to complete this stage because of limiting symptoms.\(^20\)

Aortic valve replacement. Of the 12 patients in this study

Downloaded from http://circ.ahajournals.org/ by guest on April 13, 2017
who underwent aortic valve replacement, six patients received Starr-Edwards prostheses (1260 series in four and 2400 series in two), five received Hancock porcine bioprosthesis Model 242, and one received a Bjork-Shiley prosthesis. Cardiopulmonary bypass was performed with a disc or bubble oxygenator at a flow rate of 2.2 l/min.m². In addition to systemic hypothermia to 30° to 31° C in all 11 patients undergoing operation at our institution, myocardial preservation techniques included topical 4° C iced saline with coronary perfusion in six patients and hyperkalemic cardioplegia in five.

Postoperative studies. Patients who underwent aortic valve replacement returned 6 to 8 months after operation for repeat cardiac catheterization, echocardiography, and radionuclide angiography. Left heart catheterization was performed with either the transseptal or the left ventricular puncture technique. The patient whose operation was performed at another institution without preoperative catheterization returned for repeat echocardiography and radionuclide angiography but did not undergo postoperative cardiac catheterization. Echocardiographic left ventricular systolic dimension and fractional shortening were not analyzed because of abnormal septal motion in many patients after operation.13,21

Statistical methods. The association between the initial echocardiographic and radionuclide angiographic variables and subsequent clinical course was tested by the Cox method of life table analysis,22 with the onset of symptoms and the onset of asymptomatic left ventricular dysfunction used as end points. Life tables curves were plotted by modification of the method of Kaplan and Meier,23 and differences between subgroups were analyzed by the method of Mantel and Haenszel.24 The relationship between echocardiographic left ventricular dimensions and radionuclide ejection fraction was analyzed by linear regression analysis. Changes in left ventricular end-diastolic dimension and radionuclide angiographic ejection fraction from before to after operation were analyzed by the paired t test.

Results

Patient experience. No patient died during the follow-up period. Sixty-five of the 77 patients have remained asymptomatic with normal left ventricular function during a follow-up period ranging from 6 to 114 months (mean 49). Twelve patients underwent aortic valve replacement within 6 to 100 months of entering the study, with mean preoperative follow-up period of 40 months. Eleven patients underwent operation because of cardiac symptoms. Five of these 11 patients developed left ventricular dysfunction either before or coincident with the onset of symptoms, with decreases in both fractional shortening and ejection fraction below normal, and one other symptomatic patient developed subnormal fractional shortening (22%), with a decrease in ejection fraction into the low normal range (48%). In three of these patients, left ventricular dysfunction predated symptoms by 6 to 7 months; in the other three patients, we cannot rule out the possibility that the onset of left ventricular dysfunction predated the onset of symptoms by several weeks or months, since follow-up visits were usually every 6 to 12 months. One patient underwent operation because of the onset of asymptomatic left ventricular dysfunction over the course of 36 months, manifested by a decrease in ejection fraction from 61% to 45%, a decrease in fractional shortening from 31% to 25%, and an increase in end-systolic dimension from 51 to 58 mm. Despite symptoms, left ventricular dysfunction, or both, none of the 12 patients undergoing operation manifested poor preoperative exercise tolerance, with each completing the first stage of our treadmill protocol without limiting symptoms.20

The clinical course of the 77 patients is indicated in figure 1. By life table analysis, with the onset of symptoms and the onset of asymptomatic left ventricular dysfunction used as end points, the percent of patients remaining asymptomatic with normal left ventricular function was 90 ± 3% at 3 years, 81 ± 6% at 5 years, and 75 ± 7% at 7 years.

Influence of initial left ventricular size and function on clinical course. By a univariate Cox life table analysis, several echocardiographic variables on initial study were significantly associated with subsequent symptoms or left ventricular dysfunction (table 1). These were the left ventricular fractional shortening, the left ventricular end-systolic dimension, and the left ventricular end-diastolic dimension. The left ventricular ejection fraction at rest determined by radionuclide angiography was not a significant predictor, but the ejection fraction during maximum supine exercise and the magnitude of the change in ejection fraction from rest to exercise were both significantly associated with subsequent clinical course (table 1). The initial echocardiographic and radionuclide angiographic data in patients who remained asymptomatic with normal left ventricular function and those who developed symp-
TABLE 1
Variables on initial study associated with subsequent symptoms or left ventricular dysfunction

<table>
<thead>
<tr>
<th>Variable</th>
<th>p value^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiographic data</td>
<td></td>
</tr>
<tr>
<td>LV fractional shortening</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>LV end-systolic dimension</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>LV end-diastolic dimension</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Radionuclide angiographic data</td>
<td></td>
</tr>
<tr>
<td>LV EF at rest</td>
<td>NS</td>
</tr>
<tr>
<td>LV EF during exercise</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>LV EF response to exercise^b</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

EF = ejection fraction; LV = left ventricular.
^aSignificance data are based on univariate Cox life table analysis.
^bLVEF response to exercise = exercise LVEF minus rest LVEF.

...toms, left ventricular dysfunction, or both are shown in figures 2 and 3.

The relationship between the left ventricular end-systolic dimension and subsequent clinical course is illustrated in figure 4. Patients with end-systolic dimensions of 50 mm or greater had a significantly greater likelihood of developing symptoms or left ventricular dysfunction than patients with smaller end-systolic dimensions (p < .01). At 4.5 years, only 31% of patients with initial systolic dimensions of 50 mm or greater remained asymptomatic with normal left ventricular function. Similar trends regarding subsequent clinical course were observed when patients were sub-grouped on the basis of initial left ventricular end-

![FIGURE 2](image2)

FIGURE 2. Initial echocardiographic data for patients who remained asymptomatic with normal left ventricular function ("stable") and those who subsequently underwent aortic valve replacement (AVR). Open symbol, one patient who subsequently developed asymptomatic left ventricular dysfunction; dashed line, lower limit of normal fractional shortening (29%). Significance values indicate the ability of each variable to predict subsequent operation by life table analysis rather than the differences between subgroups.

![FIGURE 3](image3)

FIGURE 3. Initial radionuclide angiographic data. Patient subgroups, p values, and symbols are presented as in Figure 2. Dashed line, lower limit of normal ejection fraction at rest (45%). Data for two patients in the group that underwent operation are not indicated, since initial radionuclide studies were performed after the development of symptoms.

![FIGURE 4](image4)

FIGURE 4. Influence of initial left ventricular end-systolic dimension (LVSD) on subsequent clinical course. The number of patients in each subgroup is indicated. No patient with initial LVSD <40 mm has developed symptoms or left ventricular dysfunction. Symbols are explained in figure 1.
PATHOPHYSIOLOGY AND NATURAL HISTORY—AORTIC DISEASE

FIGURE 5. Influence of initial left ventricular end-diastolic dimension (LVDD) on subsequent clinical course. The number of patients in each subgroup is indicated. Symbols are explained in figure 1.

diastolic dimension (figure 5). At 4.5 years, only 53% of patients with initial diastolic dimension of 70 mm or greater remained asymptomatic with normal left ventricular function, compared with 96% of patients with initial diastolic dimension less than 70 mm (p < .01).

Similar but less significant findings resulted when patients were subgrouped on the basis of either the initial left ventricular ejection fraction during exercise or the magnitude of the change in ejection fraction from rest to exercise (figure 6). No patient whose ejection fraction increased during exercise compared with the value at rest on initial study developed symptoms or left ventricular dysfunction during subsequent follow-up. In contrast, in patients whose ejection fraction decreased greater than 5 percentage points compared

with the value at rest, 33% have undergone operation within 4 years and 67% remain asymptomatic with normal resting left ventricular function. The clinical course of patients whose decrease in ejection fraction during exercise was less marked (0 to 5% decrease compared with the resting value) was not different from that of patients with more marked decreases in ejection fraction during exercise (figure 6). Thus the ejection fraction response to exercise was significantly associated with subsequent clinical course when this variable was analyzed as a continuous function by the Cox model (p < .01) but not when patients were placed in discrete subgroups by the Mantel-Haenszel method (p = .074).

Ejection fraction response to exercise vs echocardiographic dimensions. The relationship between the change in ejection fraction with exercise on initial study and resting echocardiographic left ventricular dimensions is shown in table 2. In patients with end-systolic dimensions of 40 mm or less, ejection fraction increased during exercise in 65% of patients and did not change or decreased in 35%. In comparison, ejection fraction decreased during exercise in 62% of patients with systolic dimensions of 41 to 49 mm and in 90% of patients with systolic dimensions of 50 mm or greater. In this latter subgroup, 40% manifested a decrease of 10 ejection fraction units or greater during exercise. Similarly, ejection fraction decreased during exercise in only 29% of patients with left ventricular end-diastolic dimensions less than 60 mm but in 54% of patients with diastolic dimensions of 60 to 69 mm and 82% of patients with diastolic dimensions of 70 mm or greater. The correlation coefficients between the magnitude of the ejection fraction response and both systolic and diastolic dimensions were significant at p < .01 (r = .44 and .42, respectively). Because of this significant correlation between ejection fraction response to exercise and resting left ventricular dimensions obtained echocardiographically, it is uncertain whether the ejection fraction response provides additional prognostic information that is independent of or additive to the echocardiographic data at rest. In this regard, a stepwise Cox regression indicated that the change in ejection fraction during exercise did not significantly improve the ability to predict subsequent clinical course above that of the echocardiographic dimensions alone, increasing the likelihood ratio chi square from 16.6 to only 18.2 (p = NS). This suggests that when adequate echocardiographic data can be obtained, it is not necessary to determine the ejection fraction response to exercise. However, this conclusion, based on a multivariate analysis, must be regard-
TABLE 2
Influence of left ventricular dimensions on ejection fraction response to exercise

<table>
<thead>
<tr>
<th>EF response to exercise</th>
<th>&gt;0% increase</th>
<th>1%–9% decrease</th>
<th>&gt;10% decrease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-systolic dimension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40 mm</td>
<td>15 (65)</td>
<td>6 (26)</td>
<td>2 (9)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>41–49 mm</td>
<td>12 (38)</td>
<td>13 (40)</td>
<td>7 (22)</td>
<td>32 (100)</td>
</tr>
<tr>
<td>≥50 mm</td>
<td>2 (10)</td>
<td>10 (50)</td>
<td>8 (40)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>LV end-diastolic dimension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 mm</td>
<td>10 (71)</td>
<td>3 (22)</td>
<td>1 (7)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>60–69 mm</td>
<td>13 (46)</td>
<td>12 (43)</td>
<td>3 (11)</td>
<td>28 (100)</td>
</tr>
<tr>
<td>≥70 mm</td>
<td>6 (18)</td>
<td>14 (43)</td>
<td>13 (39)</td>
<td>33 (100)</td>
</tr>
</tbody>
</table>

EF = ejection fraction; LV = left ventricular.

*EF response to exercise = EF during exercise minus EF at rest. Data are shown for 75 asymptomatic patients at time of first radionuclide angiogram.

Data expressed as number of patients, with percent of the total number of patients in each subgroup in parentheses.

ed as tentative because of the small sample size and the few end points.

Change in left ventricular function. Changes in left ventricular dimensions and function during the course of the study are shown in figures 7 and 8. Follow-up echocardiographic data were available in 72 patients and follow-up radionuclide angiographic data were available in 67 patients. Left ventricular end-diastolic dimension did not change significantly for the group between initial and late studies, although increases in end-diastolic dimension greater than 5 mm were observed in 11 patients (figure 7). The minimum diastolic dimension in patients undergoing operation was 67 mm. Left ventricular end-systolic dimension increased significantly during follow-up for both patients who remained asymptomatic with normal left ventricular function and those who underwent operation. Five of 12 patients whose end-systolic dimension increased greater than 5 mm developed symptoms, left ventricular dysfunction, or both and underwent operation, including five of nine patients in whom this increase resulted in an end-systolic dimension of 48 mm or greater. The minimum preoperative end-systolic dimension was 48 mm. Left ventricular fractional shortening did not change during serial studies in the clinically stable group, although seven patients manifested a decrease greater than 5%. Fractional shortening significantly decreased in the group undergoing operation and decreased greater than 5% in six patients. Preoperative fractional shortening was at the lower limit of normal in three patients and below normal in seven patients (figure 7). Left ventricular ejection fraction determined by radionuclide angiography (figure 8) decreased during serial studies in both patients who remained asymptomatic with normal left ventricular function and patients who underwent operation. Eight of 17 patients manifesting a decrease in ejection fraction greater than 5% during follow-up developed symptoms, left ventricular dysfunction, or both, including eight of 12 patients in whom this change resulted in an ejection fraction of 50% or less. Preoperative ejection fraction was at the lower limit of normal in two patients and below normal in five patients. The magnitude of the change in ejection fraction from rest

![FIGURE 7. Change in echocardiographic data during follow-up studies. Patient subgroups and symbols are presented as described in figure 2. LV = left ventricular. Slashed circles, mean values.](http://circ.ahajournals.org/doi/fig/10.1161/01.CIR.81.6.514)
to exercise showed greater variability during serial studies and did not differ between initial and late studies in either group.

The seven patients who received digoxin or hydralazine during the study have remained asymptomatic with normal left ventricular ejection fraction and fractional shortening. The influence, if any, of these drugs on clinical course cannot be determined because of the small numbers of patients and the brief follow-up period of drug therapy. However, these drugs did not appreciably alter left ventricular dimensions or ejection fraction compared with the premedication studies beyond the variation in these measurements observed in patients who did not receive cardiac medications.

Results of aortic valve replacement. None of the 12 patients who underwent aortic valve replacement died at operation or during the long-term postoperative course, which ranged from 8 to 75 months (mean 38). Eleven patients returned for postoperative reevaluation 6 to 8 months (median 6) after operation, and one patient returned at 18 months. Echocardiographic left ventricular end-diastolic dimension decreased in all patients (figure 9), from $74 \pm 4$ mm (mean $\pm$ SD) before to $52 \pm 5$ mm after operation ($p < 0.001$) and was below $55$ mm, the upper limit of normal, in all but three patients. Ten patients manifested end-diastolic dimensions greater than $70$ mm before operation; the largest diastolic dimension after operation was $62$ mm. The reductions in diastolic dimension after operation were associated with improvement in left ventricular ejection fraction (figure 10), which increased from $45 \pm 5\%$ before to $58 \pm 11\%$ after operation ($p < .001$) and was within the normal range in all patients. Left ventricular ejection fraction during maximum exercise also increased after operation (from $36 \pm 7\%$ to $56 \pm 15\%; p < .001$), as did the change in ejection fraction.

**FIGURE 8.** Change in radionuclide angiographic data during follow-up studies. Patient subgroups and symbols are presented as described in figures 2 and 3. EF = ejection fraction; AVR = aortic valve replacement. Slashed circles, mean values.

**FIGURE 9.** Change in left ventricular end-diastolic dimension from before (preop) to 6 months after (postop) aortic valve replacement. No patient manifested a diastolic dimension greater than $70$ mm (dashed line) after operation. Open symbols, patient without preoperative symptoms; slashed circles, mean values.
FIGURE 10. Change in left ventricular ejection fraction before (preop) and 6 months after (postop) operation. Dashed line, lower limit of normal; slashed circles, mean values.

from rest to exercise (from $-10 \pm 5\%$ to $-1 \pm 8\%$; $p < .005$).

Discussion

Ejection phase indices of left ventricular systolic function are important predictors of long-term survival and functional results after aortic valve replacement for aortic regurgitation. Symptomatic patients with impaired left ventricular function, manifested by subnormal angiographic ejection fraction or echocardiographic fractional shortening, are at risk for irreversible left ventricular dysfunction and death from congestive heart failure after technically successful valve replacement.\(^{1-7}\) Within the subgroup of patients with left ventricular dysfunction, however, those with less marked symptomatic limitation, as measured by functional class\(^6\) or by exercise capacity,\(^8\) have an excellent prognosis after operation and a greater likelihood that left ventricular function will improve than in patients with severe symptoms. These findings have led to the recommendation that aortic valve replacement be performed in patients with left ventricular dysfunction before the onset of significant symptoms.\(^8\)-\(^{13}\), \(^20\)

The management of the asymptomatic patient with normal left ventricular function is less certain. Previous natural history studies\(^{16, 25-28}\) detailed the clinical course of asymptomatic patients and identified the risk of irreversible left ventricular failure but did not subgroup patients on the basis of left ventricular size or function. Hence, the natural history of asymptomatic patients with aortic regurgitation and normal left ventricular contractile function is unknown. Nonetheless, the concern that a patient might develop irreversible left ventricular dysfunction has resulted in the recommendation that valve replacement be performed in all patients with significant aortic regurgitation,\(^1\), \(^14\)-\(^16\) even if left ventricular contractile function is normal.

Our data indicate that asymptomatic patients with normal left ventricular function have an excellent prognosis with conservative, nonoperative management. No patient in our series died, and 75% remained asymptomatic with normal left ventricular function after 7 years of follow-up (figure 1). Thus less than 4% per year required aortic valve replacement because symptoms or left ventricular dysfunction developed.

Our data also demonstrate a significant association in asymptomatic patients with normal resting left ventricular function between subsequent clinical course and indices of left ventricular function, including left ventricular systolic and diastolic dimensions and fractional shortening determined echocardiographically and the ejection fraction response to exercise determined by radionuclide angiography. Thus echocardiography and radionuclide angiography appear to be valuable techniques in the serial follow-up of the asymptomatic patient.\(^10\), \(^13\) However, although these noninvasive data identify patients who are more likely to require operation within a few years, they do not necessarily indicate that such patients, once identified, should undergo early operation before symptoms or left ventricular dysfunction develop. If postoperative results are excellent when valve replacement is delayed until either symptoms or left ventricular dysfunction develop, then an early prophylactic operation would not be justified.

In this regard, of the 12 initially asymptomatic patients with normal left ventricular function in our series who underwent valve replacement after the onset of symptoms, left ventricular dysfunction, or both, none
died at operation or during the long-term postoperative course. Moreover, left ventricular dilatation was re-versed in all patients when they were reevaluated 6 months after operation (figure 9). The reduction in echocardiographic diastolic dimension is important prognostically, since previous studies indicate that patients with persistent left ventricular dilatation after operation, with postoperative diastolic dimensions of 70 mm or greater, are at risk of death from congestive heart failure. 20, 29, 30 Left ventricular ejection fraction also improved after operation and was within the normal range in all patients (figure 10).

Thus when aortic valve replacement is delayed in asymptomatic patients with normal left ventricular function until symptoms or left ventricular dysfunction develop, postoperative survival is excellent and left ventricular dimensions and function improve after operation. This is compatible with our previous experience with symptomatic patients who exhibited left ventricular dysfunction but preserved exercise tolerance. 20 Hence, the current data suggest that prophylactic aortic valve replacement to preserve left ventricular function until symptoms or left ventricular dysfunction is not required in asymptomatic patients with severe aortic regurgitation and normal resting left ventricular function.

We acknowledge the excellent technical assistance of A. Michael Harding and Bonnie Wesley in performance of the echocardiographic studies, and Terri Frederick, Gale White, Sharon Findley, Susan Farkas, and Bonnie Mack in performance of the radionuclide angiographic studies.

References


Vol. 68, No. 3, September 1983
The natural history of asymptomatic patients with aortic regurgitation and normal left ventricular function.

R O Bonow, D R Rosing, C L McIntosh, M Jones, B J Maron, K K Lan, E Lakatos, S L Bacharach, M V Green and S E Epstein

_Circulation_. 1983;68:509-517
doi: 10.1161/01.CIR.68.3.509

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/68/3/509.citation