Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function.

R O Bonow, E Lakatos, B J Maron and S E Epstein

*Circulation*. 1991;84:1625-1635
doi: 10.1161/01.CIR.84.4.1625

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 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/84/4/1625

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/
Serial Long-term Assessment of the Natural History of Asymptomatic Patients With Chronic Aortic Regurgitation and Normal Left Ventricular Systolic Function

Robert O. Bonow, MD; Edward Lakatos, PhD; Barry J. Maron, MD; and Stephen E. Epstein, MD

Background. Many asymptomatic patients with aortic regurgitation and normal left ventricular systolic function remain clinically stable for many years, but others ultimately develop symptoms or left ventricular dysfunction and require operation. To identify indexes of left ventricular function predictive of symptomatic and functional deterioration during the long-term course of asymptomatic patients, we studied 104 asymptomatic patients with chronic severe aortic regurgitation and normal left ventricular ejection fraction at rest.

Methods and Results. Serial echocardiographic (average, 7.8 per patient) and radionuclide angiographic (average, 5.0 per patient) studies were obtained over a mean follow-up period of 8 years (range, 2–16 years). By Kaplan-Meier life table analysis, 58±9% of patients remained asymptomatic with normal ejection fraction at 11 years, an average attrition rate of less than 5% per year; two patients died suddenly, four developed asymptomatic left ventricular dysfunction, and 19 underwent operation because symptoms developed. By univariate Cox regression analysis, many variables on initial study were associated with death, ventricular dysfunction, or symptoms, including age, left ventricular end-systolic dimension and end-diastolic dimension, fractional shortening, and both rest and exercise ejection fraction (all p<0.001). The average rates of change of rest ejection fraction, fractional shortening, and end-systolic dimension were also associated with death or symptoms by univariate Cox analysis (all p<0.01). However, when all variables were included in a multivariate Cox analysis, only age (p<0.05), initial end-systolic dimension (p<0.001), and rate of change in end-systolic dimension and rest ejection fraction during serial studies (both p<0.05) predicted outcome.

Conclusions. Thus, in addition to indexes of left ventricular function determined on initial evaluation, serial long-term changes in systolic function identify patients likely to develop symptoms and require operation. Patients have a higher risk of symptomatic deterioration if there is progressive change in end-systolic dimension or resting ejection fraction during the course of serial studies. (Circulation 1991;84:1625–1635)

Left ventricular systolic function and the severity of left ventricular dilatation have important prognostic implications in patients with chronic severe aortic regurgitation. In addition to ejection phase indexes of left ventricular performance, measures of left ventricular end-systolic volume or end-systolic dimension identify symptomatic patients undergoing aortic valve replacement who are at risk of persistent ventricular dilatation, systolic dysfunction, and death during the long-term postoperative course.1-13 These same indexes, when applied in the initial evaluation of asymptomatic patients, provide valuable insights regarding the likelihood that symptoms or left ventricular dysfunction, or both, will develop over the course of the next 4–5 years.14 Therefore, data obtained on initial evaluation may be used to predict the need for valve replacement in the near future. However, during the long-term natural history of asymptomatic aortic regurgitation, it is likely that the rate and magnitude of changes in left ventricular size and function, as well as those measurements made initially, determine the subsequent clinical outcome. The impact of changes in left ventricular dimensions and systolic dysfunction, and death during the long-term postoperative course.1-13

From the Cardiology Branch, National Heart, Lung, and Blood Institute, Bethesda, Md.
Address for correspondence: Robert O. Bonow, MD, Building 10, Room 7B-15, National Institutes of Health, Bethesda, MD 20892.
Received August 1, 1990; revision accepted June 4, 1991.
function on the clinical course of untreated asymptomatic patients has not been investigated. In this report, we extend our previous observations on the natural history of chronic aortic regurgitation\textsuperscript{14} to include a larger number of patients with longer follow-up periods in order to examine the relation between serial long-term changes in left ventricular function and clinical outcome in asymptomatic patients with this disease.

**Methods**

**Patient Selection**

We studied 104 consecutive asymptomatic patients with severe chronic aortic regurgitation between January 1973 and March 1988 who fulfilled echocardiographic and radionuclide angiographic criteria of normal resting left ventricular systolic function for our laboratory. There were 89 men and 15 women ranging in age from 17 to 67 years (mean, 36 years). On entry into the study, all patients had echocardiographic fractional shortening of 29% or greater. Radionuclide angiography became available in our institution for clinical investigation in 1976; all patients entering the study after August 1976 had normal ejection fractions under resting conditions (45% or greater\textsuperscript{15}) on initial evaluation. Twenty-five patients entered the study before August 1976 but subsequently had radionuclide angiograms in 1976 or thereafter demonstrating normal resting ejection fractions. In two of these latter patients, the first radionuclide angiogram demonstrating normal left ventricular ejection fraction was performed after the development of symptoms warranting valve replacement surgery (after asymptomatic follow-up periods of 30 and 49 months), and this radionuclide angiogram was used as a preoperative study.

Cardiac catheterization was performed in 85 of the 104 patients and confirmed isolated severe aortic regurgitation in 81 patients, with 3+ to 4+ out of a maximum of 4+ valvular regurgitation visualized by aortic root cineangiography. Three patients had small ventricular septal defects with left-to-right shunt ratios of less than 1.5:1. One patient had associated mitral regurgitation; this patient subsequently developed symptoms and was found at operation to have only minimal mitral regurgitation that did not require concomitant mitral valve replacement. Coronary arteriography was not performed in the asymptomatic patients with normal left ventricular function but was performed preoperatively in patients who subsequently underwent operation if they were more than 35 years of age or if they complained of angina pectoris. Two patients had coronary artery disease at preoperative coronary arteriography; one patient had greater than 50% but less than 75% stenosis of the right coronary artery, and another had greater than 75% stenosis of the left anterior descending coronary artery. Neither of these two patients, nor any other patient in this series, had evidence of myocardial infarction before or during the study. The 19 patients not catheterized all had physical findings compatible with severe isolated aortic regurgitation and systemic pulse pressures of 70 mm Hg or greater. No patient had evidence of primary aortic root disease.

**Echocardiography**

Echocardiographic studies were performed as previously described.\textsuperscript{5,14} 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.\textsuperscript{5,16} The end-diastolic left ventricular dimension was measured at the R wave of the electrocardiogram, and the end-systolic dimension was measured at the peak of systolic posterior wall motion. Left ventricular fractional shortening was calculated as the ratio of the difference between the left ventricular diastolic and systolic dimensions to the end-diastolic dimension. 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.

**Gated Blood Pool Cardiac Scintigraphy**

Gated equilibrium radionuclide angiography was performed with patients in the supine position at rest and during maximum symptom-limited supine bicycle exercise. Left ventricular ejection fraction was computed from the scintigraphic data as previously described.\textsuperscript{11,13,15}

Exercise studies were performed with a bicycle ergometer and a restraining harness to minimize patient motion under the Anger camera. Exercise loads were increased by 25-W increments every 2 minutes until the development of 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 corresponding to the final 2–2.5 minutes of maximal exercise was selected for analysis.

**Serial Follow-up Studies**

After completion of initial studies, patients were followed by their referring physicians and by the Cardiology Clinic of the National Heart, Lung, and Blood Institute (NHLBI). Outpatient reevaluations at the NHLBI were performed on a yearly basis in most patients. When possible, patients with more severely dilated left ventricles (end-diastolic dimension >75 mm or end-systolic dimension >50 mm) were reevaluated every 6 months. The frequency of repeat evaluations varied in many patients and was often individualized, depending upon the severity of left ventricular dilatation and the level of systolic function, as well as upon personal hardships encountered in travelling repeatedly to our clinic. At each evaluation, a history and cardiac physical examination, chest radiograph, electrocardiogram, echocardiogram, and radionuclide angiogram were obtained.
with the exception that radionuclide angiography was performed on a yearly basis in those patients who were reevaluated at 6-month intervals. Serial studies in the 104 patients included a total of 815 echocardiograms (average, 7.8 per patient) and 515 radionuclide angiograms (average, 5.0 per patient) over a follow-up period ranging from 2 to 16 years (mean, 8 years). All 104 patients had at least three echocardiographic (range, 3–32) and three radionuclide angiographic (range, 3–15) studies, with the exception of the two patients noted above in whom only a single radionuclide study was performed on a preoperative basis.

Initial echocardiographic and radionuclide angiographic studies were performed while patients were taking no cardiac medications, except for one patient who was studied while receiving digoxin and propranolol. During the course of the study, we recommended that patients receive no cardiac drugs except for antiarrhythmic drugs in those patients with evidence of ventricular or supraventricular tachyarrhythmias. After entry into the study, five patients were placed on digoxin by their referring physicians and another two patients were placed on hydralazine. In these seven patients, follow-up data over 7–61 months were obtained before these drugs were instituted; late studies over 34–100 months were repeated while these patients were on either digoxin or hydralazine.

**Indications for Aortic Valve Replacement**

During the course of this study, there were only two indications for aortic valve replacement. Valve replacement was performed if the patients 1) developed symptoms of angina, syncope, overt evidence of left ventricular failure (paroxysmal nocturnal dyspnea, orthopnea, or dyspnea at rest), or exertional dyspnea severe enough to interfere greatly with the patient’s quality of life, or if patients 2) developed evidence of left ventricular systolic dysfunction at rest while asymptomatic, with consistent reductions in both fractional shortening and resting ejection fraction below normal. Patients who were believed to have developed left ventricular dysfunction in the absence of symptoms, and who might therefore be candidates for operation, were reevaluated within 1–3 months to reproduce these findings and then underwent cardiac catheterization to confirm left ventricular dysfunction.

There were two patients who represented exceptions to these indications for operation. One was a man who developed chronic renal insufficiency requiring chronic hemodialysis. This patient remained asymptomatic with normal left ventricular systolic function but underwent aortic valve replacement before surgical creation of an arteriovenous fistula, because there was concern that the fistula might create an acute increase in the severity of the ventricular volume overload. For purposes of data analysis, this patient is censored at the time of his operation, as operation was performed for prophylactic reasons, and he did not achieve either of the two cardiac end points of the study. The other exception was a man who developed infective endocarditis after 117 months of follow-up, resulting in an acute and severe increase in left ventricular cavity dimensions. For purposes of data analysis, this patient is censored at the time on endocarditis. 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 operation at another institution without catheterization.

**Postoperative Studies**

Patients who underwent aortic valve replacement returned 6–8 months after operation for repeat cardiac catheterization, echocardiography, and radionuclide angiography. Left heart catheterization was performed with either the transseptal or left ventricular puncture technique. Two patients who underwent operation at other institutions returned for postoperative echocardiograms and radionuclide angiograms but did not undergo postoperative catheterization. Echocardiographic left ventricular end-diastolic dimension and fractional shortening were not analyzed because of abnormal septal motion in many patients after operation.5,16,17

**Statistical Methods**

**Initial data.** The relation between initial echocardiographic measurements and radionuclide angiographic data was assessed using linear regression analysis. The association between individual echocardiographic and radionuclide angiographic variables obtained at initial study and subsequent clinical course was tested using the univariate Cox regression model.18 Multivariate Cox regression analyses of these data were also performed. Two separate sets of computations were performed. In one, the end point evaluated was death or the development of symptoms; in the other, the end point was defined as death, the onset of symptoms, or the onset of left ventricular dysfunction without symptoms.

To further assess the influence of baseline variables on subsequent outcome, patients were divided into subgroups using threshold values of end-diastolic dimension, end-systolic dimension, and the magnitude of change in ejection fraction during exercise, as previously described.14 Life table curves were plotted for all patients and for these subgroups of patients using a modification of the method of Kaplan and Meier.19 Annualized event rates were calculated based on long-term Kaplan-Meier results, using an exponential model. Differences between subgroups were tested by the method of Mantel and Haenszel.20

**Serial follow-up data.** To evaluate the impact of changes in left ventricular size and function upon subsequent clinical course, the average rate of change in each echocardiographic or radionuclide angiographic index was computed for each patient. This was performed by assuming a linear rate of change in each variable with time; the data were fit to
a linear model, and the slope of the regression line was calculated to represent the average rate of change. This particular analysis was performed only in those patients with data obtained at a minimum of three points in time, with a subset analysis involving only those patients with a minimum of four data points. The rate of change in each variable was first tested individually for its association with subsequent clinical outcome using a univariate Cox regression analysis. Finally, a multivariate Cox regression analysis incorporating the rates of change along with the initial values of all variables was performed. In these analyses of serial follow-up data, the end point evaluated was defined as death or the development of symptoms. The onset of asymptomatic left ventricular dysfunction was not included in the end point, as some of the same variables involved in this analysis (fractional shortening and ejection fraction at rest) were those used to define left ventricular dysfunction. For example, it was self-evident that patients with a greater rate of decrease in ejection fraction with time might be more likely to develop a subnormal ejection fraction than those in whom the ejection fraction did not change with time.

Results

Patient Experience

During the mean 8-year follow-up period, two patients died suddenly and 23 patients underwent aortic valve replacement. Nineteen of these latter patients underwent operation because of the development of symptoms and four patients because of reproducible evidence of left ventricular dysfunction at rest in the absence of symptoms. Among the 19 patients who developed symptoms warranting operation, 11 (58%) also manifested evidence of left ventricular dysfunction with subnormal ejection fraction and fractional shortening at the time of preoperative studies. Seventy-nine patients remained asymptomatic with normal left ventricular systolic function under resting conditions. By Kaplan-Meier life table analysis, 58±9% of patients remained asymptomatic with normal left ventricular function at 11 years (Figure 1), an average attrition rate less than 5% per year. This confirms our previous observations, made in a smaller group of patients with shorter follow-up periods, regarding the clinical outcome of patients with asymptomatic aortic regurgitation.14 The two deaths in our current series represent an annual mortality rate of 0.4% per year.

Determinants of Clinical Outcome

Initial data. By univariate Cox regression analysis, several variables at the time of initial study were associated significantly with subsequent clinical course (Table 1). These included the left ventricular dimensions at end diastole and end systole and the fractional shortening by echocardiography and the ejection fraction, both at rest and during maximum exercise, by radionuclide angiography. Left ventricular wall thickness was not associated with outcome. As age was also a significant determinant of clinical course, these variables were reanalyzed with age as a covariate. All baseline variables identified on univariate analysis as significantly related to clinical outcome remained so after age correction, except for the ejection fraction at rest.

On the basis of these data, patients were divided into subgroups to assess the influence of baseline variables on subsequent clinical outcome (Table 2). By Kaplan-Meier life table analyses, the likelihood of death, symptoms, or left ventricular dysfunction, which was less than 5% per year for the entire population, increased to 19% per year in patients with initial left ventricular end-systolic dimensions of 50 mm or greater but was negligible in the subgroup with an end-systolic dimension less than 40 mm. Similarly, the risk of a cardiac end point increased to 10% per year in patients with initial end-diastolic dimensions of 70 mm or greater and to 12% per year in those in whom the ejection fraction decreased with exercise greater than 5% compared to the resting
value. The risk was negligible in patients in whom the ejection fraction increased during exercise.

Using multivariate Cox regression analysis of the initial variables, only age and left ventricular end-systolic dimension were significantly associated with clinical outcome (Table 3). After adjustment for age and end-systolic dimension, neither the ejection fraction during exercise nor the magnitude of change in ejection fraction with exercise provided independent prognostic information. When the end-systolic dimension was removed from this analysis, age (p<0.01) and the end-diastolic dimension (p<0.01) were significantly associated with outcome, but the ejection fraction during exercise and the ejection fraction change with exercise remained insignificant variables.

**Serial follow-up data.** The rate of increase in end-diastolic dimension did not differ between patients who remained stable and patients who developed a cardiac end point (0.3±0.8 versus 0.4±0.8 mm/year). However, patients who developed a cardiac end point had a significantly greater rate of increase in end-systolic dimension (1.1±1.3 versus 0.2±0.7 mm/year, p<0.005) and greater rate of decrease in ejection fraction at rest (−3.4±4.9 versus 0.2±1.3%/year, p<0.005) and during exercise (−3.5±5.6 versus −0.7±1.8%/year, p<0.05) than those who remained stable during the course of serial studies.

The rates of change in several echocardiographic and radionuclide angiographic variables during serial follow-up studies were significantly associated with subsequent death or symptoms when each variable was assessed individually by univariate Cox regression analysis. These included the rate of increase in end-diastolic dimension (p<0.05) and end-systolic dimension (p<0.001) and the rate of decrease in ejection fraction both at rest and during maximum exercise (both p<0.001). The rate of change in the magnitude of the ejection fraction response from rest to exercise was not significantly related to subsequent outcome.

When tested in a multivariate Cox analysis, in which the rates of change in left ventricular dimensions and function were tested along with all other variables (Table 3), only age (p<0.05), baseline end-systolic dimension (p<0.001), and the rates of increase in end-systolic dimension (p<0.05) and decrease in resting ejection fraction (p<0.05) provided significant prognostic information. Examples of the relation between serial changes in left ventricular dimensions and ejection fraction and subsequent clinical course are illustrated for two representative patients in Figure 2.

**Serial data in patient subgroups.** The impact of serial changes in end-systolic dimension and rest ejection fraction was further assessed within patient subgroups defined by the magnitude of the baseline end-systolic dimension. In the subgroup of patients with an end-systolic dimension 50 mm or more on

---

**Table 1. Determinants of Outcome by Cox Regression Analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Age-corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t</td>
<td>p</td>
</tr>
<tr>
<td>Age</td>
<td>2.24</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV diastolic dimension</td>
<td>4.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV systolic dimension</td>
<td>4.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV fractional shortening</td>
<td>−2.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV wall thickness</td>
<td>1.12</td>
<td>NS</td>
</tr>
<tr>
<td>Radionuclide angiogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EF at rest</td>
<td>−1.99</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV EF during exercise</td>
<td>−4.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV EF exercise response</td>
<td>−3.92</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LV, left ventricular; EF, ejection fraction; NS, not significant.

---

**Table 2. Risk Stratification Based on Kaplan-Meier Life Table Analysis of Measurements at Initial Study**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Likelihood of death, symptoms, or LV dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-systolic dimension</td>
<td>&gt;50 mm</td>
<td>19% per year</td>
</tr>
<tr>
<td></td>
<td>40-49 mm</td>
<td>6% per year</td>
</tr>
<tr>
<td></td>
<td>&lt;40 mm</td>
<td>0% per year</td>
</tr>
<tr>
<td>LV end-diastolic dimension</td>
<td>≥70 mm</td>
<td>10% per year</td>
</tr>
<tr>
<td></td>
<td>&lt;70 mm</td>
<td>2% per year</td>
</tr>
<tr>
<td>LV ejection fraction response to exercise</td>
<td>Decrease &gt;5%</td>
<td>12% per year</td>
</tr>
<tr>
<td></td>
<td>Decrease 0–5%</td>
<td>4% per year</td>
</tr>
<tr>
<td></td>
<td>Increase &gt;0%</td>
<td>1% per year</td>
</tr>
</tbody>
</table>

LV, left ventricular.
TABLE 3. Multivariate Cox Regression Analysis of Variables on Serial Studies Associated With Death or Symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initial value</th>
<th>Rate of change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>p &lt; 0.05</td>
<td>...</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic dimension</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LV end-systolic dimension</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>LV fractional shortening</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Radionuclide angiogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EF at rest</td>
<td>NS</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>LV EF during exercise</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LV EF response to exercise</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

LV, left ventricular; EF, ejection fraction; NS, not significant.

For the initial study, a separate Cox regression analysis (in which age was used as a covariate) revealed that the rate of increase in end-systolic dimension (p = 0.03) and the rate of decrease in rest ejection fraction (p = 0.04) were both predictive of outcome. When a similar analysis was performed in the subgroup with a baseline end-systolic dimension measuring 40–49 mm, the rate of change in end-systolic dimension (p = 0.05) and in rest ejection fraction (p = 0.02) were again both significantly related to outcome. The rate of change in neither variable was related to outcome in the subgroup with an initial end-systolic dimension less than 40 mm, as no patient in this subgroup had a cardiac end point (Table 2).

The impact of progressive increases in left ventricular end-systolic dimension on the rate of cardiac events was further examined by performing Kaplan-Meier life table analyses within these patient subgroups. Patients stratified according to baseline end-systolic dimension were further subdivided into those with progressive increases in end-systolic dimension (rate of increase more than 1 mm/yr) and those with no progressive increase in end-systolic dimension (rate of increase ≤ mm/year). In patients with baseline end-systolic dimensions equal to or more than 50 mm, in whom the overall risk of a cardiac end point was 19% per year (Table 2), this risk increased to 27% per year if there was a progressive increase in end-systolic dimension but was reduced to 11% per year if there was no progressive increase in end-

Initial study, a separate Cox regression analysis (in which age was used as a covariate) revealed that the rate of increase in end-systolic dimension (p = 0.03) and the rate of decrease in rest ejection fraction (p = 0.04) were both predictive of outcome. When a similar analysis was performed in the subgroup with a baseline end-systolic dimension measuring 40–49 mm, the rate of change in end-systolic dimension (p = 0.05) and in rest ejection fraction (p = 0.02) were again both significantly related to outcome. The rate of change in neither variable was related to outcome in the subgroup with an initial end-systolic dimension less than 40 mm, as no patient in this subgroup had a cardiac end point (Table 2).

The impact of progressive increases in left ventricular end-systolic dimension on the rate of cardiac events was further examined by performing Kaplan-Meier life table analyses within these patient subgroups. Patients stratified according to baseline end-systolic dimension were further subdivided into those with progressive increases in end-systolic dimension (rate of increase more than 1 mm/yr) and those with no progressive increase in end-systolic dimension (rate of increase ≤ mm/year). In patients with baseline end-systolic dimensions equal to or more than 50 mm, in whom the overall risk of a cardiac end point was 19% per year (Table 2), this risk increased to 27% per year if there was a progressive increase in end-systolic dimension but was reduced to 11% per year if there was no progressive increase in end-

Figure 2. Left panel: Plot of serial changes in left ventricular (LV) function in two patients. In each patient, the end-diastolic (DD) and end-systolic (SD) dimensions (top), the fraction shortening (FS, bottom), and radionuclide angiographic ejection fraction (EF, middle) are plotted serially as functions of time. The exercise (Ex) ejection fraction data are shown in open circles. Dashed lines at 45% and 29% indicate the lower limit of normal for resting ejection fraction and fractional shortening, respectively. Despite ventricular dilatation, the patient illustrated in the left panel has remained asymptomatic with normal resting ejection fraction and fractional shortening for over 12 years. Right panel: The initially asymptomatic patients in the right panel, who developed symptoms and underwent operation after 8 years, manifested consistent and progressive, although gradual, increases in end-systolic dimension and decreases in both ejection fraction and fractional shortening preceding the development of symptoms.
systolic dimension. In comparison, among patients with baseline end-systolic dimensions of 40–49 mm, in whom the overall risk was 6% per year (Table 2), this risk increased to 10% per year in those with progressive increases in end-systolic dimension but decreased to 1% per year in those with no progressive changes in end-systolic dimension during the course of serial studies.

**Effect of medications.** Among the seven patients who were treated with digoxin or hydralazine after 7–61 months of follow-up, two patients developed symptoms after treatment with digoxin. Neither of the two patients treated with hydralazine experienced a cardiac end point, but neither had an end-systolic dimension equal to 50 mm or more or an end-diastolic dimension equal to 70 mm or more. Because of the small numbers of such patients, the effect of drug therapy was not subjected to a separate analysis.

**Ejection Fraction Response to Exercise**

The ejection fraction during exercise and the magnitude of change in ejection fraction with exercise compared to resting values were associated with outcome when tested in univariate analyses (Table 1) but were not significant determinants of clinical course when tested in a multivariate analysis along with the echocardiographic data (Table 3). This observation may be explained by the significant relation between these exercise indexes and the severity of left ventricular cavity dilatation under resting conditions (Figure 3). Both the end-diastolic dimension and the end-systolic dimension correlated with the exercise ejection fraction $(r=-0.49$ and $r=-0.61$, respectively, both $p<0.001)$ and the change in ejection fraction from resting values $(r=-0.44$ and $r=-0.46$, respectively, both $p<0.001)$. Although serial decreases in the ejection fraction at rest were significantly associated with subsequent cardiac events, serial changes in the exercise ejection fraction response were not (Table 3).

**Asymptomatic Left Ventricular Dysfunction**

The data in the four patients who underwent operation because of the development of left ventricular dysfunction in the absence of symptoms are shown in Table 4. These four patients manifested reductions in fractional shortening and resting ejection fraction during serial studies, which were associated with an increase in left ventricular end-systolic dimension, during follow-up periods ranging from 28–80 months. After operation, substantial reductions in left ventricular end-diastolic dimension and increases in ejection fraction were observed in all four patients.

**Sudden Death**

The two patients who died during the course of this study were both young men (ages 32 and 40 years at the time of death), in whom sudden death occurred during sedentary activities after 31 and 84 months of follow-up. Postmortem examination revealed no evidence of coronary artery disease. In both patients, fractional shortening and ejection frac-

**TABLE 4. Patients Developing Asymptomatic Left Ventricular Dysfunction**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>EDD (mm)</th>
<th>ESD (mm)</th>
<th>FS (%)</th>
<th>EF$_R$ (%)</th>
<th>EF$_{Ex}$ (%)</th>
<th>Follow-up period (mo)</th>
<th>Late (preoperative) data</th>
<th>Postoperative data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>70</td>
<td>43</td>
<td>39</td>
<td>59</td>
<td>62</td>
<td>80</td>
<td>75</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>76</td>
<td>54</td>
<td>29</td>
<td>46</td>
<td>37</td>
<td>28</td>
<td>78</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>62</td>
<td>42</td>
<td>32</td>
<td>47</td>
<td>33</td>
<td>44</td>
<td>72</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>74</td>
<td>51</td>
<td>31</td>
<td>61</td>
<td>45</td>
<td>36</td>
<td>77</td>
<td>58</td>
</tr>
</tbody>
</table>

EDD, end-diastolic dimension; ESD, end-systolic dimension; FS, fractional shortening; EF$_R$, ejection fraction at rest; EF$_{Ex}$ ejection fraction during exercise.
tion were consistently maintained in the normal range before death. These data and echocardiographic dimensions remained stable without serial change during multiple serial studies (Figure 4). The exercise ejection fraction response was not distinctly abnormal before death in either patient, increasing by 1% and 2% compared to the resting value in the last exercise radionuclide angiogram before death.

The data obtained at the initial evaluation of these two patients are presented in Figure 5 in comparison with the other 102 patients. Regarding the initial ejection fraction data, the two patients who ultimately died did not differ from the other patients with respect to either the ejection fraction at rest or its change with exercise. On the other hand, the left ventricular cavity dimensions in these two patients were at the extreme end of the spectrum. Both had end-diastolic dimensions that were consistently 80 mm or greater and end-systolic dimensions that were 55 mm or greater. Only one other surviving patient in this series had ventricular dimensions in this range.

**Postoperative Studies**

Among the 23 patients who underwent aortic valve replacement, there were no perioperative or postoperative deaths. Despite subnormal ejection fractions at rest in 15 patients (65%) preoperatively, ejection fractions were normal in all patients at the 6–8-month postoperative reevaluation, and for the group ejection fraction increased significantly after operation both at rest (from 45±5 to 60±11%, p<0.001) and during exercise (from 36±8 to 57±13%, p<0.001). In concert with the increases in left ventricular systolic function, there was a concomitant decrease in left ventricular end-diastolic dimension after operation (from 74±4 to 52±6 mm, p<0.001).
Discussion
Determinants of Outcome in Chronic Aortic Regurgitation

Numerous studies indicate that long-term prognosis in patients with chronic aortic regurgitation is influenced importantly by left ventricular systolic function and the severity of left ventricular dilatation. In patients undergoing aortic valve replacement, preoperative ejection phase measures of left ventricular systolic performance and indexes of left ventricular end-systolic volume are predictive of both short-term and long-term survival and left ventricular function after operation.1-13 Similarly, we have previously reported that these same variables also identify asymptomatic patients with severe aortic regurgitation and normal left ventricular systolic function who are likely to require aortic valve replacement over the course of the next 4 years because of the development of symptoms or left ventricular dysfunction.14 These latter data have recently been supported by a separate natural history study by other investigators.21

In the current investigation, we have extended our previous observations by studying a larger number of patients with a longer mean follow-up period. The results not only confirm our previous observations14 and those of Siemienczuk et al21 but also provide new insights. First, our findings confirm that the majority of asymptomatic patients with chronic severe aortic regurgitation and normal left ventricular systolic performance do well with conservative, nonoperative management. At 11 years, 58% of our patients were alive and asymptomatic, with maintenance of normal systolic function (Figure 1), which represents an average attrition rate of less than 5% per year by life table analysis. This rate of attrition is identical to earlier series.14,21 Second, as in previous reports, patients in the current study could be stratified according to the risk of developing symptoms or left ventricular dysfunction during the subsequent follow-up period on the basis of echocardiographic and radionuclide angiographic measurements made at the time of initial study. These included, after correction for the effects of age, the left ventricular end-systolic dimension, end-diastolic dimension and fractional shortening by echocardiography, and the radionuclide angiographic indexes of left ventricular function during exercise (Table 1). As in our previous experience,14 the end-systolic dimension provided the greatest discrimination; no patient with an initial end-systolic dimension less than 40 mm died, experienced symptoms, or developed left ventricular dysfunction, whereas patients with an end-systolic dimension of 50 mm or greater had a 19% likelihood per year of incurring one of these cardiac events. Finally, our data confirm that when aortic valve replacement is delayed until the onset of either symptoms, left ventricular dysfunction, or both, death prior to surgery is rare (and limited only to patients with marked ventricular dilatation), and postoperative survival is excellent with substantial improvement in left ventricular dilatation and function.

The current study also provides several new observations on the natural history of asymptomatic chronic aortic regurgitation that were not possible in previous studies. The larger sample size (with a greater number of cardiac end points) in the current study compared to our previous experience permitted a multivariate Cox regression analysis of the initial functional measurements relative to outcome, and the longer duration of follow-up permitted analysis of the importance of serial changes in left ventricular dimensions and function.

Left ventricular dimensions versus exercise ejection fraction. These analyses confirm the importance of echocardiographic estimates of the severity of left ventricular cavity dilatation in the risk stratification of such patients. However, the measurements of left ventricular systolic function during exercise, although significantly associated with outcome when assessed in a univariate Cox regression analysis, were not independent predictors of outcome when subjected to a multivariate analysis that also incorporated the left ventricular cavity dimensions determined at rest by echocardiography (Table 3). The explanation for this effect appears to be the significant correlation between left ventricular dilatation and the exercise functional measurements: both the ejection fraction during exercise and the magnitude of change in ejection fraction from rest to exercise were significantly related to the severity of left ventricular dilatation as reflected by the left ventricular dimensions at end diastole and end systole (Figure 3). The ejection fraction may be influenced dramatically by sudden changes in ventricular loading that develop during exercise22,23 as the regurgitant volume decreases with exercise in response to peripheral vaso-dilation and reduced diastolic filling periods,23,24 and patients with the most severe volume overload may also be subject to the greatest alteration in loading with exercise.23,24 With these considerations in mind, we do not believe that serial measurement of the ejection fraction during exercise is warranted in asymptomatic patients.

Serial changes in left ventricular function. During the course of serial studies, the rate of change of virtually every measure of left ventricular function was significantly associated with death or the development of symptoms when these changes were assessed in a univariate analysis. When subjected to a multivariate Cox regression evaluation, which also included those measurements made on initial study, both the rate of increase in end-systolic dimension and the rate of decrease in resting ejection fraction provided additional independent predictive information beyond that provided by age and the baseline end-systolic dimension (Table 3).

From our data it is difficult to define a specific rate of change in either end-systolic dimension or rest ejection fraction that identifies a patient at high risk of developing symptoms. The errors inherent in
echocardiographic and radionuclide angiographic measurements, as well as physiological variability in left ventricular function, would make such rate calculations difficult to apply in practice. We also do not believe that evidence of a progressive change in left ventricular function, in and of itself, should be used as an indication for operation in the absence of symptoms or overt left ventricular systolic dysfunction. Instead, we interpret our data as indicating more generally that the likelihood that an individual patient will develop symptoms and require operation over the course of time is higher if there is evidence of a progressive decline in left ventricular systolic function at rest on serial studies. Thus, evidence of deteriorating ventricular function, if consistent, is helpful in identifying patients who require more frequent and more careful reevaluation.

Sudden Death

In our previous experience and that of Siemienzuk et al., no deaths occurred during the conservative management of asymptomatic patients with aortic regurgitation and normal left ventricular systolic function. In the larger experience of the current study, two patients died suddenly with longer-term follow-up, both during sedentary activities. Despite these events, our data continue to indicate that sudden death is a rare occurrence among patients with chronic aortic regurgitation with normal left ventricular systolic function in that the two deaths in this series represent an annual mortality rate of only 0.4% per year.

Although the mechanisms responsible for these deaths cannot be determined with certainty, inferences can nonetheless be made. Left ventricular systolic function was normal in both of these patients, but both had extreme degrees of ventricular dilatation on repeated studies with end-diastolic dimensions of 80 mm or greater and end-systolic dimensions of 55 mm or greater (Figure 4). Only one other patient in this series had left ventricular dimensions in this range (Figure 5). In our experience, preserved systolic performance in such severely dilated ventricles is an uncommon finding, as patients with this degree of ventricular dilatation usually have evidence of left ventricular systolic dysfunction. This presumably occurs because the severely dilated ventricle has exceeded its preload reserve and is unable to maintain normal ejection performance in the setting of heightened afterload. The few patients in whom systolic function is maintained in the normal range despite such severe ventricular dilatation might be at risk of sudden cardiac death on the basis of the inability to compensate for sudden increases in afterload by further chamber dilatation, with resultant acute heart failure. Alternatively, the greatly increased wall stress might predispose to subendocardial ischemia and associated ventricular arrhythmias.

That two of the three asymptomatic patients in our series with the most severe left ventricular dilatation died suddenly appears similar to the experience of Turina et al., who also reported sudden and unexplained deaths in two asymptomatic patients who were awaiting aortic valve replacement, both of whom had severe ventricular dilatation (end-diastolic volume index > 200 ml/m²). It is not certain whether these two latter patients had normal or depressed systolic function before death. The reported deaths in our series and those of Turina et al represent a very small number of patients, and therefore the conclusions that may be drawn are limited in nature. Despite this limitation, we now recommend that asymptomatic patients with reproducible evidence of severe left ventricular dilatation (end-diastolic dimension ≥ 80 mm or end-systolic dimension > 55 mm) undergo aortic valve replacement, even if left ventricular systolic function at rest is within the normal range. Thus, we propose three indications for aortic valve replacement in patients with chronic aortic regurgitation: the development of symptoms, the development of left ventricular systolic dysfunction at rest, or the development of marked left ventricular dilatation.

Asymptomatic Left Ventricular Dysfunction

A final observation of our study is that the development of left ventricular dysfunction in chronic aortic regurgitation in the absence of symptoms is also a relatively uncommon event. The concern that such left ventricular dysfunction may develop in asymptomatic patients arises from numerous studies demonstrating that by the time symptoms sufficiently severe as to warrant operation occur, a subset of patients will have already developed irreversible left ventricular dysfunction and will be at risk of persistent dysfunction and death from congestive heart failure during the long-term postoperative course. Although this concern is well-founded, it reflects the cross-sectional experience of patients referred to tertiary centers for aortic valve replacement. A longitudinal evaluation of asymptomatic patients provides a different perspective. In our longitudinal analysis of asymptomatic patients, none of whom initially were candidates for operation, only four of 104 patients (less than 5%) developed asymptomatic left ventricular dysfunction during the mean follow-up period of 8 years. More commonly, symptoms of dyspnea or angina develop before or coincident with the onset of impaired left ventricular function. Nonetheless, it is important to note that of the 25 patients who developed end points in this study, six end points (24%) occurred without previous warning symptoms, including two patients who died suddenly and four who developed asymptomatic left ventricular dysfunction. This experience, and the finding that patients at risk for these asymptomatic end points can be identified using noninvasive indexes, underscore the importance of echocardiographic and radionuclide angiographic studies, both initially and serially, in the management of asymptomatic patients with chronic severe aortic regurgitation.
References

KEY WORDS • aortic regurgitation • left ventricular function • echocardiography • radionuclide angiography