Prediction of Indications for Valve Replacement Among Asymptomatic or Minimally Symptomatic Patients With Chronic Aortic Regurgitation and Normal Left Ventricular Performance

Jeffrey S. Borer, MD; Clare Hochreiter, MD; Edmond McM. Herrold, MD, PhD; Phyllis Supino, EdD; Michael Aschermann, MD; Detlef Wencker, MD; Richard B. Devereux, MD; Mary J. Roman, MD; Massimiliano Szulc, PhD; Paul Kligfield, MD; O. Wayne Isom, MD

Background—Optimal criteria for valve replacement are unclear in asymptomatic/minimally symptomatic patients with aortic regurgitation (AR) and normal left ventricular (LV) performance at rest. Moreover, previous studies have not assessed the prognostic capacity of load-adjusted LV performance (“contractility”) variables, which may be fundamentally related to clinical state. Therefore, 18 years ago, we set out to test prospectively the hypothesis that objective noninvasive measures of LV size and performance and, specifically, of load-adjusted variables, assessed at rest and during exercise (ex), could predict the development of currently accepted indications for operation for AR.

Methods and Results—Clinical variables and measures of LV size, performance, and end-systolic wall stress (ESS) were assessed annually in 104 patients by radionuclide cineangiography at rest and maximal ex and by echocardiography at rest; ESS was derived during ex. During an average 7.3-year follow-up among patients who had not been operated on, 39 of 104 patients either died suddenly (n = 4) or developed operable symptoms only (n = 22) or subnormal LV performance with or without symptoms (n = 13) (progression rate = 6.2%/y). By multivariate Cox model analysis, change (Δ) in LV ejection fraction (EF) from rest to ex, normalized for ΔESS from rest to ex (ΔLVEF-ΔESS index), was the strongest predictor of progression to any end point or to sudden cardiac death alone. Unadjusted ΔLVEF was almost as efficient. Symptom status modified prediction on the basis of the ΔLVEF-ΔESS index. The population tercile at highest risk by ΔLVEF-ΔESS progressed to end points at a rate of 13.3%/y, and the lowest-risk tercile progressed at 1.8%/y.

Conclusions—Currently accepted symptom and LV performance indications for valve replacement, as well as sudden cardiac death, can be predicted in asymptomatic/minimally symptomatic patients with AR by load-adjusted ΔLVEF-ΔESS index, which includes data obtained during exercise. (Circulation. 1998;97:525-534.)

Key Words: valves ■ heart failure ■ regurgitation ■ ventricles

Among patients with AR, appropriate criteria for valve replacement in the asymptomatic or minimally symptomatic patient are controversial despite publication of several prospective prognostic studies during the past 15 years.1–16 Baseline variables for the purpose of inclusion in these populations, application of predictors of postoperative results (measured immediately before operation in patients sent to valve replacement for other reasons) to patients who may be relatively early in the natural course of their disease, and possible alteration in the natural history of the disease itself associated with use of prophylactic drug therapy,17–19 In addition, most studies have based prediction on objective descriptors of LV size and performance, which reflect the impact of extrinsic and varying loading factors as well as intrinsic myocardial characteristics.20–24 Indeed, currently accepted criteria for operation include both subnormal LV performance at rest and symptoms of early pulmonary vascular congestion,16 which often occurs with normal resting LV systolic performance.

In AR, the stress of exercise can unmask subnormal performance not apparent at rest.2,6,10,11,13,14 In addition, intrinsic myocardial impairment is presumed to be a fundamental basis of clinical debility.3,12–24 Eighteen years ago, we began a prospective study of clinical and noninvasive prognostication in regurgitant...
Prognostication in Chronic Aortic Regurgitation

Selected Abbreviations and Acronyms

| AR | = | aortic regurgitation |
| Δ | = | change |
| EF | = | ejection fraction |
| ESS | = | end-systolic stress |
| FC | = | functional class |
| IVS | = | interventricular septal thickness |
| LV | = | left ventricular |
| LVEDV | = | end-diastolic volume |
| LVEF-ESS index | = | ESS-adjusted LV performance variables |
| LVEFex | = | unadjusted LVEF during exercise |
| ΔLVEF-ΔESS index | = | ΔLVEF normalized for ΔESS |
| LVIDd | = | LV internal dimension in diastole |
| LVIDs | = | LV internal dimension in systole |
| PWT | = | posterior wall thickness |

valvular diseases that included measurement of loads and performance, at rest and with exercise, allowing definition of load-adjusted variables. We have now determined the absolute and relative strengths of association between these descriptors and clinical outcome in 104 initially asymptomatic or minimally symptomatic patients who, at entry, had normal LVEF at rest and thus were not considered candidates for valve replacement. In addition, we tested the hypothesis that objective assessment could identify patients who, although currently not candidates for valve replacement, would develop characteristics known to confer relatively high postoperative risk by the time they satisfied conventional criteria for operation.

Methods

Study Population

In 1979, entry began into our ongoing prospective study of prognostication among patients with regurgitant valvular diseases. Study details, including entry criteria for patients with AR, have been described previously.29–35 The present analysis involves the cohort of patients who, at study entry, manifested hemodynamically severe, isolated, pure AR; were asymptomatic or minimally symptomatic; had normal LVEF at rest; and had at least 1 year of objective follow-up after study entry. In all patients, AR was confirmed as hemodynamically severe either at cardiac catheterization (n = 5) or by physical and echocardiographic evidence of severe AR, including supranormal LV diastolic dimension, LV diastolic diameter exceeding >2 or Doppler echocardiographic AR.29,35 Patients were excluded if at entry they had evidence of previous myocardial infarction, a history of typical angina pectoris (unless coronary arteriography revealed normal coronary arteries), more than minimal mitral regurgitation or mild aortic stenosis, or any mitral stenosis.

Our study plan requires clinical evaluation supplemented at study entry by several objective tests, including radionuclide cineangiography at rest and during exercise and echocardiography at rest. Decisions regarding medications and surgery are not influenced by study protocol. Repetitions of entry evaluations are planned annually, but some annual evaluations were not performed in the reported patients because of logistic difficulties or patient inconvenience. This fact did not affect the primary analysis, because the development of symptom-based criteria for operation was obtained by history in all patients and objective evaluations of LV function were available within 1 year of the last follow-up or of surgery in all but 3 patients. In addition, catheterization data were available to supplement previous noninvasive determinations in all but 1 patient who underwent surgery.

As of July 1994, when data entry for this analysis was closed, 165 patients with severe, isolated AR had entered our study and had at least 1 year of potential follow-up. Of these, 23 had reached symptom-based criteria for valve surgery at study entry, despite normal LV performance at rest; 29 had subnormal LV performance at rest at study entry despite absence of symptoms and consequently were referred for operation; and 5 others had both operable symptoms and subnormal LV performance at rest at study entry. Four additional patients were lost to follow-up shortly after study entry; for these patients, no follow-up was available, and they were not included in the analyses presented here. The remaining 104 patients had severe AR with normal LV performance at rest and were asymptomatic (83 patients) or minimally symptomatic (at most, early NYHA FC II, 21 patients) at study entry. Each had normal LVEF (≥45% by radionuclide cineangiography).36 These 104 patients compose the cohort for the present analysis. (Three of these patients subsequently underwent operation without symptoms or subnormal LV performance on the basis of their personal physicians’ directives; their follow-up was censored at operation, and they were not considered to have reached end points.)

Demographic characteristics at baseline are presented in Table 1. For patients who had not yet died or reached an end point, the time from study entry to the last evaluable follow-up averaged 7.4 ± 3.7 years (1 to 12.9 years). No patients entered the study with known ischemic heart disease. However, by the time of operation several years later, 9 patients had clinically unsuspected coronary luminal diameter narrowing of ≥50% at coronary angiography, affecting 1 artery in 5 patients, 2 arteries in 3 patients, and 3 arteries in 1 patient. In 7 of these 9 patients, coronary artery bypass graft surgery was performed at the time of valve replacement. None evidenced functional aortic stenosis by clinical and echocardiographic evaluation at entry, but 3 had developed aortic stenosis by the time of operation (2 among the 9 with coronary disease); 2 additional patients had developed mild to moderate mitral regurgitation. Among the 104-patient cohort, 35 had severe AR confirmed at cardiac catheterization. All others had physical and study-managed entry echocardiographic findings of severe AR. Definable cause of disease was predominantly non-Marfan’s idiopathic aortic root dilatation (26 patients), although in 36 patients, no cause could be defined (Table 1).

At entry, long-term therapy included digoxin (20 patients), diuretics (13 patients), β-blockers (6 patients), antiarrhythmics (5 patients), calcium channel blockers (1 patient), and vasodilators (13 patients; ACE inhibitor in 7); 65 were taking no medications, 9 were receiving combination therapy, and in 1 patient medication information was not available. During follow-up, 3 of the 38 patients receiving medication at entry stopped their drugs; 26 patients who, at entry, were not receiving medications began such therapy; and 25 who had been taking single agents at entry received combination therapy at some time subsequently. According to the study plan, medications were stopped before yearly evaluations, although at the primary physician’s direction, drugs could be continued during testing.

To define normal radionuclide cineangiographic variables, studies identical with those performed in patients also were performed in 26 normal subjects, 23 to 61 years old (average, 37 years), who showed no clinical and rest stress ECG abnormalities; most of these have been reported previously.29,32,33

End Points and Predictors

Clinical and objective data were analyzed to define rate of progression from study entry to the development of one or more of the following end points: (1) “operable symptoms,” defined as well-established NYHA FC II or worse dyspnea, angina, or fatigue; (2) “operative LV performance descriptors,” defined as subnormal LVEF at rest (<45%) determined by radionuclide cineangiography34 or, among patients who became operably symptomatic, subnormal LVEF at preoperative contrast angiography at catheterization1; and (3) cardiac death in the absence of operable symptoms or subnormal LV performance. Descriptors assessed for predictive capacity included those previously reported to be prognostically valid in populations who either had or had not undergone surgery (LVEF [rest or exercise]26,32,33, change in EF from rest to exercise13,14, fractional shortening, LVIDd, and LVMI.22,23,24 LVEF-ESS indices, effective prognostically in our preliminary studies,13,30 and clinical symptoms26,27).
Procedures

Echocardiography

Standard M-mode and two-dimensional echocardiograms were performed as previously described.27–29 M-mode measurements of end-diastolic and end-systolic LV wall thicknesses and internal dimensions (LVIDd and LVIDs) and of left atrial dimensions were obtained according to American Society of Echocardiography recommendations.38 LV mass was calculated by an anatomically validated formula.39 ESS at rest was calculated according to the method of Reichek et al40:

\[
ESS = \frac{0.334 \times SBP \times LVIDs}{(PWTs (1 - PWTs/LVIDs))}
\]

where SBP is systolic blood pressure and PWTs is posterior wall thickness in systole. LV end-systolic volume and LVEDV were calculated from LVIDs and LVIDd according to the angiographically validated formula of Teichholz et al.41 LVIDs, LVIDd, ESV, LV mass, and left atrial dimension were indexed for body surface area; in alternative analyses, the linear dimensions of LV and left atrial diameters also were indexed by body height. Doppler echocardiography, from the time this procedure became available in our patients, was evaluated by standard methods we have previously identified for this study.27

Radionuclide Cineangiography

Radionuclide cineangiography was performed with the patient in the supine position at rest and during maximal, symptom-limited bicycle exercise by an ECG-gated equilibrium method analogous to one we have previously described,25,42 after in vivo labeling of red blood cells with intravenous injection of stannous pyrophosphate and 15 to 25 mCi of 99mTc. In our laboratory, exercise is performed beginning at a load of 25 W; load generally is increased by 25 W at 2-minute intervals until limited by fatigue, dyspnea, or hemodynamically important arrhythmias. Exercise EF is determined at peak exercise, generally involving at least the last 90 seconds of data collection. LVEF was determined by a method analogous to our previously reported count-based procedure,25,42–44 validated by comparison with contrast angiography at rest and exercise.43,44

ESS During Exercise

ESS during exercise was determined by combining exercise systolic blood pressure with derived exercise echocardiographic wall thicknesses and chamber dimensions calculated from these measurements made at rest by taking into account the changes in LV chamber volumes from rest to exercise determined by radionuclide cineangiogram.

### TABLE 1. Baseline Characteristics of the Study Population and Normal Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Population</th>
<th>Normal Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean±SD (Range)</td>
</tr>
<tr>
<td>LVEFr, %</td>
<td>104</td>
<td>55±5 (45-70)</td>
</tr>
<tr>
<td>LVEFex, %</td>
<td>103</td>
<td>53±9 (29-72)</td>
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<tr>
<td>ΔEF, %</td>
<td>103</td>
<td>-2±7 (-22-15)</td>
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<td>ESSr, dyne/cm²</td>
<td>94</td>
<td>103±37 (33-269)</td>
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<tr>
<td>ESSex, dyne/cm²</td>
<td>88</td>
<td>127±68 (28-488)</td>
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<tr>
<td>LVEF index, %</td>
<td>94</td>
<td>4±6 (-6-25)</td>
</tr>
<tr>
<td>LVEFex index, %</td>
<td>88</td>
<td>-9±7 (-25-5)</td>
</tr>
<tr>
<td>ΔLVEF/Δ ln ESS index, %</td>
<td>88</td>
<td>-15±6 (-34-1)</td>
</tr>
<tr>
<td>FS, %</td>
<td>98</td>
<td>33±6 (18-57)</td>
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<tr>
<td>FS, index, %</td>
<td>94</td>
<td>4±4 (-9-18)</td>
</tr>
<tr>
<td>LVIDd, cm</td>
<td>98</td>
<td>6.7±0.9 (4.5-8.7)</td>
</tr>
<tr>
<td>LVIDs, cm</td>
<td>98</td>
<td>4.5±0.8 (2.3-6.7)</td>
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<td>LVM, g</td>
<td>88</td>
<td>327±105 (622-114)</td>
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<tr>
<td>SBPr, mm Hg</td>
<td>103</td>
<td>138±20 (105-200)</td>
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<td>DBPr, mm Hg</td>
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<td>61±15 (0-90)</td>
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<tr>
<td>DBPex, mm Hg</td>
<td>102</td>
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<td>HRr, bpm</td>
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<tr>
<td>HRex, bpm</td>
<td>103</td>
<td>130±19 (91-187)</td>
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<tr>
<td>Duration of exercise</td>
<td>104</td>
<td>9.5±2.7 (4-18)</td>
</tr>
<tr>
<td>Age, y</td>
<td>104</td>
<td>46±15 (17-73)</td>
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<tr>
<td>Gender, male: female</td>
<td>104</td>
<td>82:22</td>
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<tr>
<td>NYHA FC I: early II</td>
<td>104</td>
<td>83:21</td>
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<td>26</td>
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<tr>
<td>Congenital abnormalities</td>
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<td>10</td>
</tr>
<tr>
<td>Degenerative and others</td>
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</table>

FS indicates fractional shortening; LVM, LV mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; and HR, heart rate.
raphy. Logistic difficulties preclude concurrent performance of echocardiography and radionuclide cineangiography; therefore, data for the calculation were obtained from studies performed sequentially during the same visit. ESS at peak exercise was estimated from the formulas below on the basis of the following assumptions: (1) The ratio of rest and peak exercise LVEDV determined by radionuclide cineangiography is the same as this ratio determined from echocardiographic measurements of LVEDV; (2) LV mass and density remain constant from rest to exercise; (3) the ratio of PWT to IVS is identical at rest and during exercise. The standard echocardiographic independent predictive formulas for LV mass\textsuperscript{13} and for LV chamber volume were used to develop the formula for exercise ESS.

(1a) \( LVM = 0.80 \times (1.04 \times [LVIDV + IVS + PWT^2] - LVID^3) + 0.6 \)

(1b) Mean wall thickness (MWT) = (IVS + PWT)/2

(2) LV volume (ESV or EDV) = \( \left[ 7 \times (2.4 + LVID) \times LVID^3 \right] \)

(3) ESS = \( \left[ (0.33 \times SBP \times LVID_c) / PWT \times \right] \times \left[ 1 + (PWT/LVID_c) \right] \)

By calculating the ratio of the rest (r) and exercise (ex) LVEDV from radionuclide cineangiography, echocardiographic (echo) dimensions at peak exercise were estimated on the basis of assumption 1 and the relationship between the measured resting echo variables and resting echo LVEDV. Thus,

(4) \( LVEDV_{echo,ex} = \frac{LVEDV_{echo,r}}{LVEDV_{echo,ex}} \times \frac{LVEDV_{RNCA,r}}{LVEDV_{RNCA,ex}} \)

or

(5) \( LVEDV_{echo,ex} = \frac{LVEDV_{echo,ex}}{LVEDV_{echo,r}} \times \frac{LVEDV_{RNCA,ex}}{LVEDV_{RNCA,r}} \)

LVID\textsubscript{c} was determined from LVID\textsubscript{echo,ex} from Equation 2 solved by iterative estimation of the LVID that produced the LVEDV\textsubscript{echo,ex} within 0.001 mL of the LVEDV from Equation 4. With LVID\textsubscript{c} known, MWT\textsubscript{c} was calculated from LVID\textsubscript{echo,ex} from Equations 1a and 1b and assumption 2 (ie, LV myocardial volume is identical at rest and exercise). Given assumption 3, the two unknowns, PWT and IVS, were determined from Equations 1a and 1b for the sum and the ratio of PWT and IVS. Exercise ESS was calculated from Equation 3 by entering the SBP (measured by cuff sphygmomanometry) and calculated values of PWTs and LVIDs at peak exercise.

**Calculation of LVEF-ESS Indices**

For each of the three indices (LVEF\textsubscript{ex} normalized for ESS\textsubscript{ex}, LVEF\textsubscript{ex} normalized for ESS\textsubscript{ex}, and \( \Delta \)LVEF from rest to exercise normalized for change in ESS from rest to exercise [\( \Delta \)ESS]), the normal relation between the LVEF variable and the natural log of the ESS variable was defined by least-squares linear regression analysis. Logarithmic transformation of ESS previously has been found to improve prediction of LV chamber function.\textsuperscript{43} The relations between rest, exercise, and \( \Delta \)LVEF and the corresponding ESS variable in the 26 normal subjects were used to develop regression equations to predict the average value of each performance variable expected in normal subjects for a given value of ESS, as previously reported for functional stratification by echocardiography alone and combined with radionuclide cineangiography.\textsuperscript{38-40} The LVEF variable recorded for each patient then was subtracted from the normally expected LVEF variable. The difference, the LVEF-ESS index variable, was used in statistical analyses, as noted below (Fig 1).

**Statistical Analysis**

Baseline variables screened for prognostic significance are denoted in Table 1. The Kaplan-Meier product limit estimate method\textsuperscript{50} was used to determine rate of progression from study entry to the initial primary end points. These end points included (1) operable symptoms alone, (2) operable symptoms or LV dysfunction (determined by radionuclide cineangiography or cardiac catheterization), (3) operable symptoms or cardiac death, and (4) all cardiac events (symptoms, LV dysfunction, death). When an end point was reached, or when operation was performed for reasons other than development of symptoms or LV dysfunction (3 patients), or when documented noncardiac death occurred (3 patients), the patient was censored from further analysis. Kaplan-Meier product limit estimate curves were compared by the log-rank test to provide univariate assessment of the relation of selected clinical risk factors, hemodynamic variables, and functional and other descriptors measured during index radionuclide study or echocardiography to each of the primary end points both for the patient population of 104 and among the 88 patients for whom echocardiographic data were sufficiently complete to support ESS-based analysis. Because of the limited number of end points, analyses of the relation of prognostic indices to two additional end points, (5) cardiac death and (6) LV dysfunction alone, were undertaken on a univariate, exploratory basis only. For all but the exploratory analyses, continuous variables were partitioned according to statistical terciles (ie, the group was divided into thirds according to the distribution of the variable of interest, with no a priori assumptions or biases relative to cut points). Variables that were significantly (P<.05) related to end points were entered into a series of multivariate Cox proportional hazards models\textsuperscript{50} to confirm their independent predictive value for each end point. Separate Cox models were constructed for baseline clinical descriptors and for LV function or size predictors. Variables found to be independently predictive in these separate models then were entered into a final, summative multivariate Cox model.

**Results**

Objective measures of LV size and performance at index study are presented in Table 1. During follow-up (average, 7.4 years for patients remaining alive and not operated on), 39 of 104 patients reached a “surgical” end point or died suddenly without indications for operation. Of these, 22 developed a symptomatic indication for surgery (dyspnea FC II, III, IV [n=9, 3, 6], angina FC II [n=3], fatigue FC II [n=1]) without LV dysfunction; 7 developed LV dysfunction without symptoms; 6 developed symptoms (dyspnea FC II, III, IV [n=1, 2, 2], fatigue FC II [n=1]) and evidenced concomitant LV dysfunction for the first time when studied immediately before operation; and 4 died suddenly without LV dysfunction or operable symptoms at their last evaluation 6 to 10 months before death. Three additional patients died of documented noncardiac cause (infection in 1, cancer in 2) and were censored from analysis at the time of this event. The annual risk
of reaching a surgical end point or cardiac death was 6.2% (Fig 2), and for a surgical end point alone, 6.0%. At 5 years, 75% of patients had not yet died of cardiac cause or developed indications for valve replacement; the 5-year risk of cardiac death alone was 2.4%. Half the patients were projected to reach cardiac end points by ≈10 years after study entry (Fig 2).

Univariate Predictors of Single and Combined End Points

**Clinical Variables**

When clinical variables were considered by univariate analysis for the 88 patients with complete data, NYHA FC and age were significantly associated with development of operable symptoms alone and of symptoms and/or subnormal LV performance, although not with subnormal LV performance alone. FC, but not age, was associated with cardiac death (Table 2). FC and age similarly were significantly related to most end points among the entire 104-patient cohort. Conversely, assessment for the impact of AR cause on outcome revealed no association between cause and cardiac end points.

**LV Size, Performance, or Function**

Univariate analysis of LV function or size descriptors revealed significant associations between several variables and ≥1 of the 6 single or combined morbidity and mortality end points (Table 2). The only variables that significantly predicted all end points were ΔLVEF alone (P = .0006) and ΔLVEF–ΔESS index (P = .0002). Significant univariate associations also existed between at least 1 but not all end points and LVEF at rest normalized for ESS at rest (LVEFrest–ESSrest index), exercise LVEF normalized for exercise ESS (LVEFex–ESSex index), unadjusted LVEFex, and fractional shortening, LVIDd, and LVIDs at rest (Table 2).

**Multivariate Analysis for Independent Contribution to End Point Prediction**

Although several variables provided significant prediction by univariate analysis, when a multivariate Cox proportional hazards model was constructed, the only independent objective predictor of risk of end points was the ΔLVEF–ΔESS index (Table 2). When this complex variable was not consid-
FIGURE 3. Relation of ΔLVEF–ΔESS index at study entry to occurrence of any cardiac end point (cardiac death, operable symptoms, and/or subnormal LV performance at rest) during follow-up. Population of 88 patients with evaluable data for this analysis has been divided statistically into terciles. ΔLVEF–ΔESS index boundaries for each tercile are boxed.

FIGURE 4. Relation of ΔLVEF–ΔESS (stress) index at study entry to occurrence of subnormal LV performance at rest during subsequent follow-up. The 88 patients evaluable for this purpose have been divided into statistical terciles, as in Fig 3.

lower ΔLVEF–ΔESS index of −11%. Patients with higher indices evidenced a 1.8%/y annual rate of progression to any cardiac end point. The corresponding “low-risk” unadjusted ΔLVEF lower bound was +3%; higher values predicted a 1.9%/y annual rate of progression to any cardiac end point.

Predictors of Subnormal LV Performance and Cardiac Death

Subnormal LV performance at rest and cardiac death occurred too infrequently to permit stable multivariate analyses and were evaluated only for univariate association with predictors. For subnormal LV performance, the strongest univariate association was with absolute LVEFex, followed closely by ΔLVEF–ΔESS index (Fig 4); other, less prominent but significant associations also were apparent (Table 2). The highest-risk tercile, bounded by LVEFex ≤49%, evidenced an 8.8%/y likelihood of developing subnormal LV performance at rest, whereas the low-risk tercile (LVEFex ≥57%) had a 0%/y likelihood of developing this end point during our follow-up. For the previously defined high- and low-risk ΔLVEF–ΔESS terciles, the rates of progression to subnormal LV performance were 6.7%/y and 0%, respectively. For cardiac death, the strongest association was with ΔLVEF–ΔESS index; the 5-year sudden death risk was 3.3% in the high-risk tercile (Fig 5). The only other significant objective prognosticator was ΔLVEF alone, which predicted this outcome almost as well. Although less strongly associated with death than ΔLVEF–ΔESS index, early FC II symptoms also bore a significant relation to subsequent sudden death.

Effect of Cardioactive Drugs

By univariate analysis, adverse outcomes were associated with use of any drug at entry (all cardiac end points, symptoms alone, and symptoms and/or subnormal LV performance); antiarrhythmic drugs or digoxin alone at entry predicted development of cardiac end points. However, in multivariate Cox models, neither use of specific agents nor of any cardioactive drug added independently to prediction by ΔLVEF–ΔESS index.
Among patients studied immediately before operation, systolic wall stress was the best and only independent predictor of survival alone. Similarly, Gaasch et al found that a combination of preoperative end-systolic dimension and an index of systolic wall stress was the most useful predictor of poor postoperative outcome among 32 patients with aortic AR.

Our results are consistent with our experimental studies, which indicate the presence of profound abnormalities in myocardial contractile protein metabolism in a model of chronic moderate to severe AR, with markedly subnormal myocardial protein degradation rate associated with heart failure and LV dysfunction. These studies have suggested the possible relation between disordered contractile protein metabolism, subnormal LV contractility, and clinical outcome, a relation mirrored in our clinical findings.

Our data demonstrate that subnormal LV performance and cardiac death can be predicted objectively. Previous series included relatively few patients with subnormal LV performance at the time of operation which did not specifically assess predictors of this outcome. For example, Bonow et al identified 15 patients who developed LV dysfunction, but they evaluated only their 4 patients who developed LV dysfunction without symptoms and found no clear predictor. However, identification of patients imminently at risk of subnormal LV performance, with or without symptoms, is potentially important: outcome is worse after operation among those with subnormal LV performance at rest than those who undergo operation with symptoms and normal LV performance.

Our 13 subnormal LVEF end points do not constitute a large series and were not sufficiently numerous to support multivariate analyses. Nonetheless, our analysis indicates the significant capacity of LVEF and of ΔLVEF-ΔESS index to predict development of an important risk factor and represents the first such report of which we are aware.

Previous studies have reported few cardiac deaths without operation among asymptomatic patients: Bonow et al observed 2 among 104 patients during an 8-year follow-up, and Henry et al, Lindsay et al, and Siemienczuk et al saw none among a total of 118 patients followed for shorter periods. For this reason, sudden death generally has not been considered an important risk for patients with AR who are asymptomatic and have normal LV performance at rest. Moreover, Bonow et al were unable to identify potential predictors of the sudden deaths they observed. In the present series, the occurrence of sudden death clearly is related to LV dysfunction during exercise at study entry. Although the absolute frequency of this event in an AR population cannot be defined rigorously from our relatively small series, the prominence of this end point in our group suggests that potential sudden death may require specific consideration when management decisions are made for patients with AR. Subnormal LV performance at rest and

**Figure 5. Relation of ΔLVEF-ΔESS index at study entry to cardiac death during follow-up.** Because of small number of end points, group is divided on basis of a binary split for this figure. For risk values associated with tercile boundaries noted in Figs 3 and 4, see text.

**Discussion**

Our data support our hypothesis that the development of currently accepted indications for aortic valve replacement, including symptoms or subnormal LV performance, can be predicted among patients with AR on the basis of objective descriptors of LV size, performance, and function. This finding is consistent with the results of previous studies of patients not operated on, which also concluded that assessment of LV functional and size characteristics could predict development of indications for operation. Our findings also are consistent with the several series in which preoperative characteristics have significantly predicted late postoperative outcome, thus indicating the prognostic utility of objective LV size and performance assessment in the setting of AR.

Our data add to those of previous investigators of load-adjusted performance indices in patients with chronic AR, first, by demonstrating the relative prognostic power of ESS-normalized LVEF (and specifically, of the ΔLVEF-ΔESS index) in comparison with more conventional descriptors and second, by demonstrating that subnormal LV performance and cardiac death alone can be predicted effectively. Thus, we found that ΔLVEF-ΔESS index was the best single predictor of all cardiac end points, of symptoms alone, of symptoms and/or subnormal LV performance, and of sudden cardiac death and, together with absolute LVEF at rest, was among the two strongest predictors of subnormal LV performance. The relative utility of an LVEF-ESS index is consistent with our previous preliminary report among patients studied immediately before valve replacement, which indicated that exercise LVEF normalized to resting ESS was the best and only independent predictor of asymptomatic survival during prolonged follow-up after operation, whereas ESS-normalized resting LVEF was the best and only independent predictor of survival alone. However, for that study, we could not yet assess ESS during exercise and could not perform all analyses reported here. The value of the LVEF-ESS indices is not surprising, because they are more closely related to myocardial contractility, an intrinsic property of the heart muscle, than is LVEF (or fractional shortening or LVIDd), which is directly and importantly affected by loading conditions as well as by intrinsic contractility. Therefore, it is intuitively reasonable that the load-adjusted performance variable should be more closely related to clinical outcome than the performance variable. Consistent with this premise, Carabello et al demonstrated that another contractility descriptor, ESS/ESV index, when measured immediately before operation, significantly predicts outcome after valve replacement in patients with any valvular disease, although the inclusion of only 9 patients with AR precluded conclusions specifically about prognostication in this disease alone. Similarly, Gaasch et al found that a combination of preoperative end-systolic dimension and an index of systolic wall stress was the most useful predictor of poor postoperative outcome among 32 patients with aortic AR.
cardiac death were relatively uncommon in our population; nonetheless, when the highest-risk terciles are considered alone, it is possible to identify a subgroup with an annual risk of 9.5% for these end points. Thus, it is necessary to consider the appropriateness of prophylactic valve replacement in this group to minimize the risks possibly associated with postponing operation beyond the time at which postoperative results will be optimal. It must be emphasized that the present study did not evaluate the effectiveness of such prophylactic treatment and cannot be the basis for any firm conclusions regarding this important issue; the competing risk-benefit relations of prophylactic operation and of less aggressive therapy can be properly evaluated only in trials specifically designed for this purpose. Our results strongly suggest the need for such studies. Nonetheless, until these studies are performed, the prognostic information available from both the load-adjusted and conventional performance descriptors may be useful in decisions in which the known competing risks of valve replacement are considered.

Our data support those of Bonow et al concerning the rate of progression to end points among asymptomatic patients with AR who have normal LV performance at rest. Our 6.0% rate of progression to currently accepted indications for operation (6.2% including cardiac death) is similar to the 5.0% rate reported by Bonow et al and also is consistent with the 4% annual progression rate reported by Siemienczyk et al in a smaller study with shorter follow-up. These rates all were lower than suggested by the 12 end points over 2.4 years reported by Yousof et al in a study with far fewer end points than the present study, which rendered statistical conclusions less stable, and including a predominance of relatively young patients with presumed rheumatic disease, also in contrast to the present study.

Although LVEF-ESS indices were the best prognosticators among our patients, more easily measured conventional LV performance variables also demonstrated prognostic significance. One of these, ΔLVEF, was almost as efficient as ΔLVEF-ΔESS index and currently may be preferable for practical application. Variation in ΔLVEF among patients with AR was first demonstrated by Borer et al in 1978 and was shown to be prognostically significant by Bonow et al in 1991, although in Bonow’s study, resting echocardiographic and radionuclide cineangiographic variables were more predictive than ΔLVEF. Our best predictor of the development of subnormal LV performance at rest, exercise LVEF, also was the only significant predictor of combined cardiac end points in the study by Lindsay et al, tended to outperform other predictors in the study by Siemienczuk et al, and was significantly predictive of all events in Bonow’s report. The differences in the relative prognostic efficiency of performance variables among these studies may be attributable to patient selection factors, particularly since earlier studies contained fewer patients and/or fewer end points than the present report. However, superiority of ESS-normalized variables is not inconsistent with earlier reports, none of which assessed load-adjusted descriptors.

Although our study supports the principle that load-adjusted performance indices are prognostically useful, the cumbersome procedure used in our measurements may limit practical application. Further study will be needed to determine whether more easily measured indices of intrinsic contractility that are currently available can provide similarly efficient prognostication. More importantly, the results of this study must be approached with caution because of the limitations inherent in the study design and measurements. First, patients were referred for study and follow-up by their primary physicians. Therefore, nonsystematic and unintentional referral bias may have affected our results, although the objective characterization of study participants at entry would tend to minimize the impact of this problem. In addition, although multivariate analysis does not suggest any significant independent influence of pharmacological therapy on outcome, alteration in absolute rates of progression may have been effected in some patients by concomitant therapy, thus confounding the description of natural history presented by our data. The potential for such alteration by drugs is supported by the recent demonstration of differential outcome among patients with AR receiving nifedipine in comparison with those receiving digitalis in the study by Scognamiglio et al. Furthermore, although significant outcome prediction was achieved with conventional performance descriptors, the best predictor in our series was ΔLVEF-ΔESS index, which depends for its accuracy on a measurement of ESS during exercise. Our method, although theoretically sound, may have been relatively imprecise: echocardiographic and radionuclide cineangiographic components were measured on succeeding days, with the potential for intervening biological variation; endocardial surfaces were used to define boundaries for measurement of ESS, although recent data from our group among patients with hypertension suggest that midwall landmarks may optimize such calculations; the method for exercise ESS determination involves a number of assumptions that, while logical and theoretically reasonable, have not been subjected to direct validation with an objective standard. Most importantly, the algorithms we used do not employ direct measurement of the LV long axis when the LV short axis changes. The inclusion of a nonzero slope and intercept in the short axis–based volume equation was developed empirically to correct for this problem but may not be adequate in all cases, particularly if regional dysfunction is marked. However, a study by Tischler et al indicates that the magnitude of independent variation in long axis versus short axis generally is relatively small from diastole to systole and from rest to exercise in patients with LV dysfunction but without AR. In addition, preliminary theoretical and empirical observations in our laboratory (unpublished data) suggest that, at maximum, long-axis variation has a relatively small influence on wall stress measurement variation from rest to exercise. Further studies will be necessary to determine the magnitude of any error introduced by our analysis algorithms and, specifically, by use of short axis–based formulations.

Despite these limitations and concerns, the method allowed highly efficient prognostication and was superior to performance descriptors alone for this purpose (a finding consistent with our earlier preliminary results using ESS-normalized LVEF in a different population, as noted above). This observation suggests that correction of the problems enumerated above may further enhance the prognostic utility of this
References


Prediction of Indications for Valve Replacement Among Asymptomatic or Minimally Symptomatic Patients With Chronic Aortic Regurgitation and Normal Left Ventricular Performance

Jeffrey S. Borer, Clare Hochreiter, Edmond McM. Herrold, Phyllis Supino, Michael Aschemann, Detlef Wencker, Richard B. Devereux, Mary J. Roman, Massimiliano Szulc, Paul Kligfield and O. Wayne Isom

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