Mitral regurgitation: relationship of noninvasive descriptors of right and left ventricular performance to clinical and hemodynamic findings and to prognosis in medically and surgically treated patients

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ABSTRACT  To determine objective predictors of survival, 53 patients with chronic, hemodynamically severe mitral regurgitation underwent rest and exercise radionuclide cineangiography, echocardiography, treadmill exercise testing, and ambulatory electrocardiographic monitoring before prospective (average 30 month) follow-up. At entry, symptom status correlated best with radionuclide-based right ventricular ejection fraction (RVEF) and left atrial size, while treadmill exercise tolerance correlated best with RVEF during exercise (r = .48, p < .005). Correspondingly, in 23 patients who underwent cardiac catheterization, pulmonary arterial systolic and wedge pressures were significantly inversely related to RVEF. On the 24 hr ambulatory electrocardiogram, nonsustained ventricular tachycardia was present in 29% of patients, most frequently when both RVEF and left ventricular ejection fraction (LVEF) were subnormal (p = .03 vs other patients). Since entry, 35 patients have been managed without surgery for 9 to 57 months (average 28); three of these who subsequently underwent operation also are among the 21 patients who have undergone mitral valve replacement (MVR). During the average 28 months of observation under medical treatment five of 35 nonoperated patients have died; all five were among the six nonoperated patients with RVEFs of 30% or less at entry, a descriptor that significantly identified those at high mortality risk (p < .0001 vs patients with RVEFs greater than 30%). All five also were among the eight nonoperated patients with LVEFs of 45% or less (lower limit of normal), a descriptor that also significantly predicted mortality. Three of the 21 patients who underwent surgery have died, all late after MVR. Among operated patients, only age was a predictor of postoperative survival. A trend toward improved survival was found in the patients with depressed right or left ventricular ejection fraction who underwent surgery compared with those who did not.


SEVERE chronic mitral regurgitation represents a particularly difficult problem in patient management. Although several studies\textsuperscript{1-3} indicate that mitral valve replacement can reduce symptoms and prolong life, long-term survival and symptom relief after valve replacement remain disappointing.\textsuperscript{4,5} Because operative outcome may be partially attributable to selection of patients by relatively inadequate symptom-based criteria, definition of objective prognostic indexes that might beneficially modify patient selection is clinically important. Hemodynamic and functional parameters, including pulmonary arterial and wedge pressures, cardiac output, left ventricular volume, and ejection fraction, and the ratio of left ventricular wall stress to volume at end-systole, have been demonstrated to provide prognostic information on patients with mitral valve disease.\textsuperscript{2,4,6-8} Of these, only left ventricu-
lar ejection fraction has been readily measurable by accurate noninvasive methods, an important consider-

ation in evaluating the course of patients with chronic mitral regurgitation, in whom clinically important car-
diac dysfunction may develop over many years. In this setting, serial assessment to identify important prog-
nostic descriptors is impracticable by invasive meth-
ods. Moreover, while ejection phase indexes are easily measured noninvasively, their value as indicators of
appropriate timing of mitral valve replacement would
appear to be intrinsically limited: with mitral regurgita-
tion, left ventricular ejection occurs in part into the low
impedance left atrium, somewhat mitigating the bur-
den associated with volume loading, but potentially
confounding inferences about the severity of myocar-
dial damage derived from the left ventricular ejection
fraction. However, the left ventricle is not the only
“shock organ” in patients with mitral regurgitation: the
supranormal left atrial volumes and pressures increase
impedance to pulmonary artery and right ventricular
outflow, thereby affecting right ventricular perfor-
amce. Thus, mitral regurgitation inexorably is a bi-
ventricular disease, potentially affecting left and right ven-
tricular myocardium to different degrees. The recent
availability of noninvasive radionuclide-based meth-
ods\(^8\)\(^9\)\(^\text{10}\) for assessing right ventricular performance
permits evaluation of the relationship of right and left
ventricular function to clinical and hemodynamic find-
ings and to prognosis. To elucidate these relationships,
we have used noninvasive and invasive modalities in
the study of 53 patients enrolled in a prospective study
of the prognostic value of objective indexes in chronic
mitral regurgitation.

**Methods**

**Population characteristics (Table 1).** The study population comprised 53 patients (26 men, 27 women; 20 to 76 years old, mean 53) with clinical and noninvasive evidence of hemody-
namically important nonischemic chronic mitral regurgitation who were enrolled in a prospective study of the prognostic value of noninvasively determined objective indexes in patients with regurgitant valve disease. A concerted effort was made to enroll
all patients with mitral regurgitation who met study admission criteria and who presented in the catheterization laboratory, echocardiography laboratory, or nuclear cardiology laboratory or who were referred directly for valve replacement at The New York Hospital or who were referred to study investigators in response to telephone and letter appeals to the New York Hospita-

tal staff. Refusals of patients to participate were rare, and no patient was excluded from analysis because of incomplete data. All protocol studies were performed after informed consent was


<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Patients with mitral regurgitation: characteristics of group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>53</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
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</tr>
<tr>
<td>Male/female</td>
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<tr>
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<tr>
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<td>NYHA class II</td>
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<td>1</td>
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<td><strong>Cause</strong></td>
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<td>Mitral valve prolapse</td>
<td>26</td>
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<tr>
<td>Rheumatic heart disease</td>
<td>8</td>
</tr>
<tr>
<td>Ruptured chordae</td>
<td>8</td>
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<tr>
<td>Mitral annular calcification</td>
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</tr>
<tr>
<td>Bacterial endocarditis</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
</tr>
<tr>
<td>Coronary artery disease at cardiac catheterization</td>
<td>3</td>
</tr>
<tr>
<td>Mitral valve replacement</td>
<td>22</td>
</tr>
</tbody>
</table>

who entered this study between December 1980 and July 1984, were included in the analysis. Patients with mitral regurgitation were excluded from the study if they manifested evidence of previous myocardial infarction or typical angina pectoris, if stenosis of any valve or regurgitation of the aortic valve was more than mild, as noted below, or if valve replacement had been previously performed or consent was refused. The diagnos-
sis of hemodynamically important mitral regurgitation was con-

firmed at cardiac catheterization in 26 of the 53 patients who had
3 + or 4 + /4 + mitral regurgitation according to results of con-
test cineangiography.\(^11\) Clinically unexpected coronary artery
disease causing a greater than 50% reduction in luminal diam-
ter of at least one coronary artery was found in three of these
patients. However, none of these had suffered prior myocardial
infarction or angina, and each had a clear nonischemic cause
(rheumatic or prolapse) accounting for the mitral regurgitation.

Mild mitral stenosis was present in one patient, and mild
1 + /4 + aortic regurgitation was present in two patients. In

addition, three patients had evidence of moderate tricuspid regu-
r\ Formulation on atrial pressure tracings. In patients who did not under-
go catheterization, the diagnosis of hemodynamically important
isolated mitral regurgitation was based on the following criteria: (1) On physical examination the left ventricular apex

was laterally displaced and heaving, and a grade II/VI or greater holosystolic or late systolic apical murmur was present. (2)

Echocardiographic examination revealed left ventricular dilata-
tion and/or left atrial enlargement (with dimensions exceeding the 97th percentile of 225 normal subjects studied in our labora-
tory),\(^13\) including left ventricular internal dimension in diastole
of 5.9 cm or more in men or 5.5 cm or more in women. (4) Left
atrial dimension was 4 cm or more. (5) There was no clinical or
M mode or two-dimensional echocardiographic evidence of sig-
ificant mitral stenosis or aortic valve disease.

**Cause of mitral regurgitation (Table 1).** In 26 patients mitral
valve prolapse was evident on the echocardiogram, based on
criteria previously reported from our laboratory.\(^13\) Rheumatic
mitral disease without significant mitral stenosis was diagnosed
in eight patients based on historical, echocardiographic, and
hemodynamic data. Eight patients had known or suspected rup-
tured chordae without a clearly defined underlying cause, three
had extensive mitral annular calcification, three had had bac-
terial endocarditis in the past but the preexisting valve status
was unknown, and in five patients no cause could be deter-
mined. This distribution of causes parallels that of the larger

Vol. 73, No. 5, May 1986
series of patients with mitral regurgitation recently reported by Waller et al.14

Clinical status. At entry into the study, of the 53 patients, 20 (16 men, 4 women; mean age 49 years) were asymptomatic, i.e., they were in New York Heart Association (NYHA) functional class I, and 33 were symptomatic (10 men, 23 women; mean age, 56 years). Of the symptomatic patients, 19 were in NYHA class II, and 14 were in NYHA class III or IV.

Medical follow-up group. The medical group comprised 31 patients who had not undergone mitral valve replacement and four patients who were followed medically for 13 to 41 months before valve replacement was recommended due to increased symptomatic debility. In three of these four, studies were repeated shortly before operation, after development of the increased symptomatic debility; these three patients were then followed as part of the surgical group (described below). Average follow-up in the medical group was 28 ± 13 months.

Surgical follow-up group. Twenty-two of the 53 patients underwent mitral valve replacement 0 to 41 (mean 7) months after entry into the study, and had undergone 6 to 65 (mean 32 ± 19) months of follow-up at the time of this evaluation. Twenty-one of these patients underwent preoperative noninvasive studies, and thus make up the surgical group. (The lone exception, noted above, was the patient originally followed medically who did not undergo repeated study shortly before operation.) Surgical technique for cardioplegia involved hypothermic, hyperkalemic (blood or crystalloid) arrest in all cases. Ten mechanical mitral valve prostheses (eight Björk-Shiley, one Starr-Edwards, one St. Jude) and 12 bioprostheses (Carpentier-Edward) were used. All but one patient were symptomatic before operation. There were no operative or perioperative deaths; three late postoperative deaths (5, 11, and 19 months after operation) have occurred. Follow-up was complete in all patients.

Normal control subjects for objective testing. For determination of the normal range of echocardiographic values at rest, 18 healthy volunteers (age 23 to 57 years) without clinical evidence of coronary or other heart disease were studied. To determine normal radionuclide cineangiographic results, 23 healthy male volunteers (age 23 to 76 years, mean 33 years) with no clinical evidence of cardiac disease and with normal exercise electrocardiograms and normal echocardiographic measurements (according to previously defined standards12) were studied. All normal subjects were volunteers who underwent study specifically for the purpose of defining normal values. Of note is the fact that the values recorded in the 23 healthy subjects involved in the radionuclide cineangiographic studies agreed well with those previously obtained by one of the investigators in our group using similar methods to define left ventricular function in 30 normal volunteers, age 19 to 63 years.13 Also, the echocardiographic values were similar to those previously reported from this laboratory in a study of 225 clinically normal subjects.12

Objective testing. According to the study protocol, at entry patients undergo M mode, two-dimensional, and Doppler echocardiographic examinations at rest, radionuclide cineangiography at rest and during exercise, treadmill exercise tolerance testing, and 24 hr ambulatory electrocardiographic monitoring. Studies are repeated annually, and, if possible, immediately before intercurrent operation, approximately 6 months after operation, and annually thereafter. On occasion, individual studies have not been performed at every assessment point because of logistic difficulties or patient inconvenience; similarly, variation in timing of studies on occasion has occurred to accommodate patient needs.

At the time of initial noninvasive testing medications were as follows: long-term therapy with digoxin was administered to 32 of the 53 patients; the drug was discontinued for 4 days before testing in the nine patients who could tolerate such discontinuation, and was continued in 23 patients (14 in atrial fibrillation, seven with intermittent supraventricular arrhythmias, two with poorly compensated heart failure). Diuretics were administered over the long term and continued during study in 23 patients. β-Blocker therapy was started as soon as possible after valve replacement and continued in the six patients in whom they were used: Vasodilators were discontinued 18 to 24 hr before testing in the six patients to whom they were administered over the long term. Three patients were on antirhythmic agents, two on quinidine and one on disopyramide.

Echocardiography. Standard M mode and two-dimensional echocardiograms were obtained at entry of 52 of the 53 patients and all of the 18 normal subjects into the study. The remaining patient underwent echocardiography at another laboratory with interpretation confirmed in our laboratory. Optimal positioning of the M mode beam at the level of the left ventricular minor axis was ensured by use of two-dimensional echocardiography. M mode left ventricular measurements were made according to the recommendations of the American Society of Echocardiography.16 For comparison between groups with differing proportions of men and women, echocardiographic measurements were indexed by body surface area. Measurements of interventricular septal thickness (IVSd), left ventricular internal dimension at end-diastole (LVIDd), and left ventricular posterior wall thickness (PWTd) were made by an investigator who was blinded to all patient data. Measurements of up to six cycles (at least three in all patients with atrial fibrillation) were averaged. Calculation of left ventricular mass (LVM) from American Society of Echocardiography measurements was based on the following equation:

\[
LVM = 0.8 \times \left(1.04 \times (IVSd + LVIDd + PWTd) - LVIDd^2\right) + 0.6 \, \text{g}
\]

We have previously found this equation to produce results that correlate closely (r = 0.90) with measurements of left ventricular mass obtained at autopsy.17

Radionuclide cineangiography. This procedure was performed in patients in the supine position at rest and during maximal, symptom-limited bicycle exercise with the use of a procedure analogous to our previously described electrocardiographically gated equilibrium method.18 Red blood cells were labeled in vivo by intravenous administration of stannous pyrophosphate followed by intravenous injection of 10 to 20 mCi of technetium 99m. Both rest and exercise scans were done with an Anger camera in the modified left anterior oblique view (left anterior oblique angulation visually provides right and left ventricular separation, with approximately 15 degree caudal tilt for separation of atrial and ventricular counts). Exercise was performed according to our previously described protocol19 (spine bicycle ergometry beginning at a load of 25 W and increasing by 25 W at 2 min intervals with exercise continued until limited by fatigue or dyspnea). Imaging was performed in patients at rest and during maximal exercise, including at least the final 1½ to 2 min of exercise. Heart rate was monitored and recorded every minute and arterial pressure (arm cuff sphygmomanometry) was measured and recorded every 2 min.

Resting and exercise left ventricular ejection fractions were determined according to standard count-based methods validated in our laboratories by comparison with results of contrast angiography.19, 20 Resting and exercise right ventricular ejection fractions were determined by the method of Maddahi et al.,9 in which the background region is used for determination of left ventricular ejection fraction and separate determination of end-
diastolic and end-systolic right ventricular regions of interest is performed to exclude right atrial counts at end-systole. This method, initially validated by demonstration of excellent correlation between its results and first-pass radionuclide angiographic results, has been further validated in our laboratory by comparison with videodensitometrically determined right ventricular ejection fractions calculated by contrast angiography by digital subtraction techniques. Analysis of radionuclide studies was done by an investigator who was unaware (except in two cases) of the clinical, hemodynamic, and other noninvasive data on each patient.

**Exercise treadmill testing.** Forty patients underwent evaluation of upright exercise tolerance by a modified Bruce protocol incorporating an initial low-level stage (3 min at 1.7 mph and 0 degree grade) and continuing until limited by symptoms (dyspnea in 19 patients, fatigue in 14 patients, and a fall in systolic blood pressure in one patient, knee pain in one patient). The reported duration of exercise includes this initial period in addition to the standard 3 min Bruce stages. Treadmill tests were not available in 13 patients. In most cases this was due to logistic problems in scheduling both treadmill and supine radionuclide exercise studies in the short period of time between presentation, cardiac catheterization, and surgical intervention. In one patient congenital deafness prompted deferment of treadmill exercise. Exercise was terminated before symptoms occurred because of complex ventricular ectopy in three sequential ventricular premature complexes) in three patients and paroxysmal supraventricular tachycardia in two patients. In those patients in whom exercise was stopped because of arrhythmias, treadmill time was not considered to reflect exercise tolerance, and data from these patients were excluded from analyses of exercise tolerance.

**Ambulatory electrocardiographic monitoring.** Twenty-four hour ambulatory electrocardiograms were available for 49 patients at study entry. Two-channel continuous ambulatory electrocardiograms were obtained according to previously reported methods, and all recordings were reviewed by two cardiologists. Arrhythmia analysis included quantification of the mean number of ventricular premature complexes per 1000 total beats and quantitative tabulation of the peak ventricular complexity grade according to previously reported modification of the Lown method. In the present study, any frequency of single ventricular premature complexes was considered a “simple” ventricular arrhythmia, even when monomorphic ectopic morphology was present. Since the hierarchical position of early-cycle ventricular premature complexes is unclear in patients with valvular regurgitation, each of the three patients having early-cycle forms was ranked according to the next highest complexity grade present. In each case, patients with early-cycle ectopy also had either ventricular couplets or salvos. Ventricular couplets, salvos, and runs of ventricular tachycardia were considered “complex” ventricular arrhythmias. Thus, in our study, “simple” ventricular arrhythmias correspond to Lown grades 0 to 3, while “complex” ventricular arrhythmias correspond to Lown grades 4A and 4B.

**Cardiac catheterization.** Cardiac catheterization data were available for 26 patients who underwent catheterization by standard techniques for clinical purposes including measurement of right ventricular, pulmonary arterial, pulmonary capillary wedge, and left ventricular pressures at rest. Single-plane left ventriculography in the right anterior oblique position and coronary arteriography were performed by the Judkins technique. In 23 instances catheterizations were done within 7 months of noninvasive evaluation of ventricular function (mean 1.1 months; in 13 patients studies were done within 1 week), with no intervening change in status between the noninvasive and invasive studies. Noninvasive and hemodynamic variables were compared only in these 23 instances. Tricuspid regurgitation was moderate to severe in three patients in whom the right atrial pressure tracing showed an early V wave with elevated mean pressures (≥9 mm Hg). As noted above, coronary artery disease was found unexpectedly in three patients, but no evidence of myocardial infarction or segmental wall motion abnormality was present in these patients.

**Statistical analysis.** Group data are expressed as mean ± SD. Group means were compared with the use of paired and unpaired Student’s t tests. The strength of linear correlations was assessed by the least squares method and expressed as a correlation coefficient. Statistical significance of correlations was determined by two-tailed t test. Differences in group proportions were assessed by a chi-square test with Yates’ correction or a Fisher’s exact test when cell size was less than 5.

Stepwise logistic regression analysis, multiple linear regression analysis, and Cox multivariate models for analysis of factors related to survival were provided through use of the BMDP statistical software package.

**Results**

**Findings at entry into study**

*Left and right ventricular function (table 2)*

**Radionuclide cineangiography.** At rest, left ventricular ejection fraction did not differ significantly from normal in either the asymptomatic (NYHA class I) patients or symptomatic (functional class ≥ II) patients, but the asymptomatic patients on average manifested lower left ventricular ejection fraction than the asymptomatic group. During exercise, left ventricular ejection fraction was subnormal in both asymptomatic and symptomatic groups, as was the change in left ventricular ejection fraction from rest to exercise, but no significant differences existed between these groups. Distinction between asymptomatic and symptomatic patients was more evident on assessment of right ventricular ejection fraction: at rest right ventricular ejection fraction was indistinguishable from normal in asymptomatic patients, but was significantly lower in symptomatic patients than in normal subjects or asymptomatic patients. There was a stepwise decrease in exercise right ventricular ejection fraction from normal subjects to asymptomatic patients and from this group to symptomatic patients with mitral regurgitation.

**Echocardiography.** As expected from patient selection criteria, left ventricular internal dimensions at end-diastole and end-systole, left atrial index, and left ventricular mass index were all significantly greater in patients with mitral regurgitation than in normal subjects. Left ventricular end-systolic dimension and left atrial index were larger in asymptomatic patients than in normal subjects, and larger in symptomatic than in asymptomatic patients.

Stepwise multiple logistic regression analysis (including resting left ventricular ejection fraction, right
TABLE 2
Comparison of normal subjects, asymptomatic patients, and symptomatic patients with mitral regurgitation

<table>
<thead>
<tr>
<th></th>
<th>I, asymptomatic mitral regurg. (n = 20)</th>
<th>II, symptomatic mitral regurg. (n = 33)</th>
<th>III, symptomatic mitral regurg. (n = 33)</th>
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</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td>p value, I vs II</td>
<td>p value, II vs III</td>
<td>p value, III vs I</td>
</tr>
<tr>
<td>Rest</td>
<td>52 ± 5 (n = 23)</td>
<td>53 ± 6 &lt;.05</td>
<td>46 ± 14 (n = 33)</td>
</tr>
<tr>
<td>Exercise</td>
<td>67 ± 8 (n = 23)</td>
<td>54 ± 11</td>
<td>47 ± 16 (n = 33)</td>
</tr>
<tr>
<td>∆LVEF</td>
<td>16 ± 5 (n = 23)</td>
<td>2 ± 8</td>
<td>1 ± 5 (n = 33)</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>p value, I vs II</td>
<td>p value, II vs III</td>
<td>p value, III vs I</td>
</tr>
<tr>
<td>Rest</td>
<td>45 ± 5 (n = 18)</td>
<td>42 ± 7 &lt;.005</td>
<td>35 ± 9 (n = 33)</td>
</tr>
<tr>
<td>Exercise</td>
<td>58 ± 5 (n = 17)</td>
<td>42 ± 11 &lt;.005</td>
<td>33 ± 10 (n = 32)</td>
</tr>
<tr>
<td>∆RVEF</td>
<td>13 ± 6 (n = 17)</td>
<td>0 ± 7</td>
<td>−2 ± 4 (n = 32)</td>
</tr>
<tr>
<td>LVIDd (cm/m²)</td>
<td>2.8 ± 0.2 (n = 18)</td>
<td>3.4 ± 0.5 &lt;.001</td>
<td>3.6 ± 0.6 (n = 33)</td>
</tr>
<tr>
<td>LVIDs (cm/m²)</td>
<td>1.8 ± 0.2 (n = 17)</td>
<td>2.1 ± 0.4 &lt;.005</td>
<td>2.4 ± 0.6 (n = 32)</td>
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<tr>
<td>FS%</td>
<td>35 ± 4 (n = 17)</td>
<td>38 ± 5 &lt;.005</td>
<td>33 ± 10 (n = 32)</td>
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<td>LAI (cm²/m²)</td>
<td>1.6 ± 0.3 (n = 16)</td>
<td>2.5 ± 0.5 &lt;.005</td>
<td>3.0 ± 0.6 (n = 33)</td>
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<tr>
<td>LVMI (g/m²)</td>
<td>83 ± 23 (n = 18)</td>
<td>146 ± 43 &lt;.001</td>
<td>147 ± 37 (n = 32)</td>
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<tr>
<td>Age (yr)</td>
<td>33 ± 14 (n = 23)</td>
<td>49 ± 15</td>
<td>56 ± 14 (n = 33)</td>
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</tbody>
</table>

LVEF, RVEF = left ventricular and right ventricular ejection fractions; ∆ = change in ejection fraction rest to exercise; LVIDd, LVIDs = left ventricular internal dimension index at diastole and systole; FS% = fractional shortening; LAI = left atrial index; LVMI = left ventricular mass index.

ventricular ejection fraction, diastolic left ventricular dimension, and left atrial size) was employed to determine which variables were independently associated with the presence of symptoms. Only right ventricular ejection fraction at rest and left atrial size were found to be independently associated with the presence of symptoms.

Exercise tolerance (table 3). Upright exercise tolerance varied widely among our patients but was significantly greater in asymptomatic (11 ± 4 min) than symptomatic patients (6 ± 3 min, p < .001). Univariate analysis revealed a moderate relationship between exercise duration and right ventricular exercise ejection fraction, and a weaker but still significant relationship to left ventricular ejection fraction and left atrial size. When a stepwise multiple linear regression model (including exercise left ventricular ejection fraction, exercise right ventricular ejection fraction, left atrial size, and age) was used, exercise right ventricular ejection fraction was selected first by the model as an important predictor of exercise tolerance. No other variable then contributed independently in predicting variability of exercise tolerance.

Hemodynamics (table 4). An explanation for the observed relationship of right ventricular ejection fraction to symptoms and to exercise tolerance may be apparent from the hemodynamic findings in our catheterized patients. Thus, by univariate analysis right ventricular ejection fraction (rest or exercise) was inversely proportional to pulmonary arterial systolic pressure and to pulmonary capillary wedge pressure (figure 1, A and B), variables which, when elevated, generally are associated with the development of exertional dyspnea. Right ventricular ejection fraction (exercise) was inversely related to right ventricular end-diastolic pressure (figure 1, C). Left ventricular ejection frac-

TABLE 3
Relationship between exercise duration and radionuclide and echocardiographic findings*  

<table>
<thead>
<tr>
<th></th>
<th>r value</th>
<th>p value</th>
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<tr>
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<tr>
<td>FS%</td>
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<tr>
<td>LAI (cm²/m²)</td>
<td>−.44</td>
<td>&lt;.01</td>
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<tr>
<td>LVMI (g/m²)</td>
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</table>

Abbreviations are as in table 2.

*This analysis involved results in 35 patients. Five additional patients underwent treadmill exercise tests but their tests were limited by arrhythmia and therefore their results were not included in analysis (see text).
tion was not related to pulmonary arterial or pulmonary wedge pressure.

**Ambulatory electrocardiography** (table 5). There was a high prevalence of ventricular arrhythmias in the 49 patients with mitral regurgitation who underwent ambulatory electrocardiography at study entry, consistent with our previous report on a smaller group of patients. Complex ventricular arrhythmias (Lown class 4A or 4B) occurred in 30 of 49 (61%) patients. Ventricular tachycardia occurred in 29% (14 of 49) of the mitral regurgitation population. Both right ventricular ejection fraction (rest and exercise) and left ventricular ejection fraction (exercise and change from rest to exercise) were lower in patients with complex ventricular arrhythmias than in those without. Neither symptomatic status, age, echocardiographic dimensions, nor exercise tolerance differed significantly between patients with and without complex ventricular ectopy. The prevalence of ventricular tachycardia was greatest in those with both subnormal right ventricular and left ventricular ejection fractions (five of eight or 63%, compared with nine of 41 or 22% of those with normal resting function of one or both ventricles, p = .033; figure 2). However, stepwise multiple logistic regression analysis (including resting left ventricular ejection fraction, right ventricular ejection fraction, systolic left ventricular dimension, and left ventricular mass) revealed that resting right ventricular ejection fraction was the only variable significantly related to the presence or absence of complex ventricular arrhythmias.

Moreover, no other variables significantly improved the predictive accuracy of resting right ventricular ejection fraction alone for the presence or absence of complex arrhythmias.

In summary, on admission to the study, patients with mitral regurgitation were distinguishable from normal subjects on the basis of several parameters of right and left ventricular performance and left atrial and ventricular size. Symptomatic patients were distinguished from asymptomatic patients not only because of left atrial dilatation and exercise intolerance, but also because of several descriptors of ventricular dysfunction, most strikingly those associated with the right ventricle. Severe ventricular arrhythmias were frequent and were most clearly associated with right ventricular dysfunction, although the incidence of ventricular tachycardia was greatest if both right and left ventricular dysfunction were present.

**Findings during follow-up.** Among the 53 patients, 35 were followed while receiving medical therapy only. Of the 21 patients in the surgical follow-up group, 20 presented with or developed symptoms (at least moderately severe effort dyspnea with exercise intolerance) currently accepted at this institution as indications for valve replacement. One additional patient who was found to have depressed left ventricular function at rest but was asymptomatic underwent valve replacement at the behest of his primary physician.

**Follow-up of medically treated patients.** Of the 35 patients who did not initially undergo operation, this rec-
ommodation was based on lack of symptoms or presence of only minimal symptoms in 32 patients. In one of the remaining three patients, development of moderate symptoms was followed by sudden death before scheduled cardiac catheterization for preoperative evaluation, in one surgery was not recommended despite prominent symptoms because of the fear that coexistent depressed left ventricular function (left ventricular ejection fraction, 21%) precluded surgical benefit, and in the final patient, also with a depressed left ventricular ejection fraction, previously noted symptoms were largely mitigated pharmacologically until shortly before death. As noted earlier, four patients subsequently suffered progression of symptoms and underwent mitral valve replacement. Average follow-up in medically treated patients was 28 ± 13 months, during which time there were five deaths. Four of these five deaths occurred suddenly, and one occurred in the setting of severe, progressive congestive heart failure. Of the five patients who died, one was in NYHA class I, one was in NYHA class II and was not considered sufficiently debilitated by current clinical criteria to warrant operation, one, who had been modestly symptomatic and similarly had not been considered clinically to be an operative candidate, developed some increase in symptoms but died suddenly before planned preoperative evaluation for valve replacement could be undertaken, one had previously reported modest symptoms that had been alleviated by pharmacologic therapy, and one with severe symptoms was denied operation because of severely reduced left ventricular function. Although the number of deaths thus far has been small, these deaths have all clustered in a group defined by at least moderately severe right ventricular dysfunction (right ventricular ejection fraction at rest ≤30%) and at least mild left ventricular dysfunction (left ventricular ejection fraction at rest ≤45%; figure 3, A). As a group, the patients who died also had lower left ventricular fractional shortening and larger echocardiographic systolic dimensions (table 6).

**TABLE 5**

Relationship of complexity of ventricular arrhythmia and ventricular performance and mass and exercise tolerance

<table>
<thead>
<tr>
<th></th>
<th>Lown 0–3 (n = 19)</th>
<th>Lown 4A, 4B (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>49</td>
<td>52 ± 10</td>
</tr>
<tr>
<td>Exercise</td>
<td>49</td>
<td>55 ± 13</td>
</tr>
<tr>
<td>ΔLVEF</td>
<td>49</td>
<td>3 ± 6</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>49</td>
<td>41 ± 7</td>
</tr>
<tr>
<td>Exercise</td>
<td>49</td>
<td>40 ± 9</td>
</tr>
<tr>
<td>ΔRVEF</td>
<td>49</td>
<td>0 ± 5</td>
</tr>
<tr>
<td>LVIDd (cm^3/m^2)</td>
<td>49</td>
<td>3.5 ± 0.6</td>
</tr>
<tr>
<td>LVIDsl (cm^3/m^2)</td>
<td>48</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td>FS%</td>
<td>48</td>
<td>35 ± 9</td>
</tr>
<tr>
<td>LAI (cm^2/m^2)</td>
<td>49</td>
<td>2.7 ± 0.6</td>
</tr>
<tr>
<td>LVMi (g/m^2)</td>
<td>48</td>
<td>138 ± 38</td>
</tr>
<tr>
<td>ETT (min)</td>
<td>40</td>
<td>9 ± 5</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>49</td>
<td>50 ± 12</td>
</tr>
<tr>
<td>Symptomatic (%)</td>
<td>49</td>
<td>58% (11/19)</td>
</tr>
</tbody>
</table>

ETT = exercise treadmill test; other abbreviations as in table 2.

*p < .05.
Life table analysis confirmed the strikingly poor survival in patients with depressed right and/or left ventricular function (figure 4). The presence of ventricular tachycardia also defined a subgroup of patients with poor survival. However, a Cox model analysis of survival found that no covariable (including resting left ventricular ejection fraction, left ventricular systolic dimensions, or fractional shortening) added significantly to resting right ventricular ejection fraction as a prognostic factor related to survival. Furthermore, when either left ventricular ejection fraction or the presence or absence of ventricular tachycardia were "forced" into the analysis first, additional predictive value was provided by adding right ventricular ejection fraction to the model.

Follow-up of surgically treated patients. Among the 21 patients who underwent mitral valve replacement, there were three late postoperative deaths (figure 3, B). One death occurred 5 months after operation in a patient who had suffered a perioperative cerebrovascular
accident. The second death occurred 19 months after surgery in a patient who had undergone coronary artery bypass grafting and placement of a permanent pacemaker. In this second patient, despite a marked fall in left ventricular ejection fraction after surgery (ascribed to pacemaker-induced contraction pattern abnormalities and/or a perioperative infarction), preoperative symptoms were improved and stable after surgery until the time of his sudden and unexpected death. A third death occurred 9 months after surgery, secondary to progressive congestive heart failure in the setting of 2+/4+ prosthetic mitral regurgitation. Thus, over an average 32 ± 19 month of postoperative follow-up, the survival in the surgically treated group was 86%. Cox model analysis revealed that only age was a significant predictor of survival in this group.

Survival in high-risk patients receiving medical vs surgical treatment (figure 5). Treatment was not randomized in our patients, and comparison of results in groups treated differently therefore must be approached with caution. However, as noted above, in the nonoperated group, high risk was predicted by objective descriptors of ventricular performance, permitting comparison of nonoperated and operated patients with these descriptors. High risk in our nonoperated patients was effectively predicted by a right ventricular ejection fraction of 30% or less, which was present in six medically treated patients. Similarly, six patients with this find-
survival was improved in the patients who underwent valve replacement (figure 5, C).

Discussion

Our data suggest that assessment of right ventricular performance, like assessment of left ventricular performance, is of significant prognostic value in patients with chronic mitral regurgitation. Among patients who did not undergo operation, right ventricular ejection fraction was a highly specific predictor of survival. This finding, while not previously reported, is not unexpected. Mitral regurgitation is inherently a biventricular disease that can cause marked chronic right ventricular pressure loading. Consistent with this thesis, an early study suggested that preoperative pulmonary arterial pressure was an important predictor of postoperative outcome in patients with mitral valve disease. However, the prognostic power of this variable in nonoperative patients with mitral regurgitation has not been evaluated. Moreover, assessment of the clinical value of the earlier observation has been limited because of the practical difficulty associated with serial measurement of pulmonary arterial pressure during the slow and protracted development of this chronic disease.

Our findings suggest that the prognostic value of right ventricular ejection fraction in nonoperated patients is, at least in part, due to the relationship between this parameter and pulmonary arterial pressure. In extending our earlier preliminary report, our present data indicate an inverse relationship between pulmonary pressure and right ventricular ejection fraction, a finding also recently reported by other investigators studying patients with valvular heart disease and patients with pulmonary hypertension due to other causes. Because pulmonary venous congestion, with resultant elevation of pulmonary arterial pressure, is one of the pathophysiologic bases of exercise intolerance in patients with mitral regurgitation, the relationship between right ventricular ejection fraction and pulmonary pressure also helps to explain our finding that both symptom status and treadmill exercise tolerance are strongly related to right ventricular ejection fraction. Furthermore, this observation is consistent with earlier reports relating symptoms to right ventricular ejection fraction in mixed valvular disease and chronic congestive heart failure.

While our data suggest an important and previously unappreciated role for assessment of right ventricular function in clinical decision making in patients with mitral regurgitation, our findings also support earlier reports suggesting that determination of left ventricu-
lar function is of value in prognostication. Thus, among our nonoperated patients, determination of left ventricular ejection fraction or fractional shortening also permitted segregation of high- and low-risk subgroups. While similar data for nonoperated patients have not been reported previously, our findings are consistent with several reports indicating the value of preoperative left ventricular ejection fraction in predicting survival after mitral valve replacement. Thus, in a retrospective study of 105 operated patients, Phillips et al.\textsuperscript{2} found that a preoperative left ventricular ejection fraction of less than 40\% at contrast angiography was associated with a very poor (38\%) 5 year survival that was significantly lower than survival among patients in higher left ventricular ejection fraction subgroups. In fact, patients with left ventricular ejection fractions of greater than 50\% before operation had a far better (89\%) 5 year survival. Preoperative left ventricular ejection fraction has also had prognostic value in other surgical series.\textsuperscript{6, 34} The results of which have tended to discourage mitral valve replacement in patients with severely depressed left ventricular ejection fractions.\textsuperscript{2, 35}

Our studies do not permit clear definition of the relative value of the assessment of right and left ventricular function in prognostication. In fact, the strength of the association of survival with depression of ejection fractions of the right and left ventricles was not statistically distinguishable, and all patients in the medical group who died during follow-up manifested both right and left ventricular dysfunction. Provisionally, therefore, it seems appropriate to suggest that assessment of performance of both ventricles should be used in efforts at prognostication and management decision making. Nonetheless, multiple regression analysis indicated that left ventricular ejection fraction did not add independent prognostic information to that available from right ventricular ejection fraction, although the opposite was true. This finding suggests that optimal weighting of left and right ventricular performance descriptors in prognostication will require further observations involving larger numbers of patients.

In theory, the relative predictive weakness of left ventricular ejection fraction is not unexpected in patients with mitral regurgitation since this ejection phase index is potentially importantly influenced by the existence of a low impedance outflow path into the left atrium. The magnitude of impedance to regurgitation into the left atrium is variable and unpredictable. Thus, a particularly wide range of ejection phase measurements (and of pulmonary vascular engorgement) might be expected among patients with relatively similar intrinsic myocardial damage, confounding the predictive value of left ventricular ejection phase indexes.

As we have previously reported,\textsuperscript{25} complex ventricular arrhythmias, including ventricular tachycardia, were present on ambulatory electrocardiographic examination of many of our patients with mitral regurgitation. Ventricular tachycardia was most prominent among patients with depressed ventricular performance. Although the association of complex ventricular arrhythmias with nonischemic left ventricular dysfunction is widely appreciated,\textsuperscript{24} the present findings demonstrate a parallel association with right ventricular dysfunction in patients with mitral regurgitation. Recognition of ventricular tachycardia by ambulatory electrocardiography permitted segregation of high- and low-risk groups among our nonoperated patients, but ventricular tachycardia was less potent as a predictor of death than was ventricular performance. Ventricular tachycardia was, however, associated with sudden death in our high-risk patients.

Our data permit definition of a group at particularly high mortality risk in the absence of valve replacement. However, a protective effect of valve replacement in this group, while suggested by our results, is not clearly proven. Within the small group of operated patients whose objective measurements were comparable to those of the nonoperated high-risk group, survival has been excellent, and significantly better than in the nonoperated patients. However, our series was not randomized, and comparability of groups treated differently cannot be inferred with certainty. The apparent preponderance of ventricular tachycardia among the nonoperated patients, and the trend toward lower left ventricular ejection fraction in this subgroup, precludes firm conclusions. Nonetheless, the fact that long-term survival has been achieved in several patients with markedly depressed right or left ventricular ejection fractions and in a smaller group of patients with marked biventricular dysfunction argues against automatic rejection of surgery in this group because of the presumption of poor outcome. This conclusion is consistent with that of Hammermeister et al.,\textsuperscript{1} who also suggested that surgical therapy may offer survival benefit in a high-risk subset of patients with poor left ventricular performance and mitral valve disease. Moreover, our severely symptomatic patients with poor ventricular performance, like our patients with less severely damaged ventricles, experienced at least some degree of symptom relief after operation. Clearly, however, firm conclusions regarding the impact of valve replacement on our high-risk subgroup will
require additional observations among high-risk patients.

In summary, our data suggest the importance of assessment of right ventricular performance, as well as that of left ventricular performance, in prognostication in patients with chronic mitral regurgitation, and suggest a potential role for such assessment in selection of patients for operation, irrespective of symptom status. Nonetheless, recommendations for management strategy based on these data must be considered provisional. Many of our nonoperated patients did not undergo catheterization, and the severity of mitral regurgitation, or of any clinically inapparent associated lesions, cannot be known with certainty. In addition, the number of patients who died and the number of patients who went to operation both are relatively small, and while several of our findings achieve striking statistical significance and therefore are unlikely to be attributable to chance alone, the magnitude of group differences may not be accurately reflected in data from relatively small numbers of subjects. Moreover, therapy was not randomly assigned. Finally, although a high-risk subset of nonoperated patients has been defined, optimal timing of valve replacement for survival as well as symptom relief may require that patients undergo operation before reaching this very high-risk status. Our data do not as yet provide information regarding the rate of progression of objective abnormalities or of predictors of imminent development of the high-risk state we have defined. Nonetheless, these data provide potentially important directions for planning further observation and study.

We gratefully acknowledge the assistance of David Pazer, B.A., Roseanne Del George, M.A., and John Clement, M.A., in the performance of these studies and preparation of this manuscript.

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Vol. 73, No. 5, May 1986


Mitral regurgitation: relationship of noninvasive descriptors of right and left ventricular performance to clinical and hemodynamic findings and to prognosis in medically and surgically treated patients.

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Circulation. 1986;73:900-912
doi: 10.1161/01.CIR.73.5.900

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