Survival and functional results after valve replacement for aortic regurgitation from 1976 to 1983: impact of preoperative left ventricular function

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ABSTRACT Recent studies suggest that preoperative left ventricular function may no longer be an important determinant of survival or functional results after operation for aortic regurgitation because of improved operative techniques. To assess the effect of left ventricular function on prognosis in the current surgical era, we performed echocardiographic and radionuclide angiographic studies in 80 consecutive patients undergoing valve replacement from 1976 to 1983. No patient had associated coronary artery disease. For all patients, 5 year survival was 83 ± 5%, significantly better than the 62 ± 9% 5 year survival in our patients operated on from 1972 to 1976. Preoperative resting left ventricular ejection fraction (p < .001), fractional shortening (p < .001), and end-systolic dimension (p < .01) were the most significant predictors of survival (univariate life-table analysis). Five year survival was 63 ± 12% in patients with subnormal ejection fraction (n = 50) compared with 96 ± 3% in those with normal ejection fraction (n = 30). Patients with subnormal left ventricular ejection fraction and poor exercise tolerance or prolonged duration of left ventricular dysfunction (>18 months) comprised the high-risk subgroup (5 year survival 52 ± 11%). Patients in this subgroup also had persistent left ventricular dysfunction after operation, with greater left ventricular end-diastolic dimensions and reduced ejection fraction (both p < .001) compared with patients with normal preoperative left ventricular ejection fraction or a brief duration of left ventricular dysfunction (<14 months). Cold hyperkalemic cardioplegia was used for myocardial preservation in 46 patients. Survival was not influenced by cardioplegia, nor did cardioplegia alter the influence of left ventricular function on postoperative prognosis. Hence, despite improved operative techniques and better long-term survival compared with earlier results, preoperative resting left ventricular dysfunction continues to identify patients with aortic regurgitation at risk of death or persistent left ventricular dysfunction after aortic valve replacement. Early operation in such patients may result in further improvement in survival and functional results.

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LEFT VENTRICULAR systolic function is an important determinant of prognosis in patients with chronic aortic regurgitation. Numerous hemodynamic, angiographic, and echocardiographic studies indicate that indexes of preoperative left ventricular function identify patients at low risk and at high risk of death or persistent left ventricular dysfunction after aortic valve replacement.1-8 However, a few recent reports suggest that survival after valve replacement for aortic regurgitation is no longer influenced by preoperative left ventricular function.9-11 These studies suggest that improved operative techniques in the current surgical era have negated the influence of preoperative left ventricular function on postoperative prognosis.

To address this issue and to assess the continued importance of preoperative left ventricular function in aortic regurgitation, we evaluated the results of aortic valve replacement over a 7 year period (from 1976 to 1983) at the National Heart, Lung, and Blood Institute. Our results indicate that preoperative left ventricular systolic function continues to influence postoperative prognosis and suggest that the discordant conclusions of previous studies probably resulted from interpretive differences and differences in patient selection.
Methods

Patient selection. We evaluated the results of aortic valve replacement in 96 consecutive patients with chronic aortic regurgitation undergoing operation between August 1976 and September 1983. Sixteen patients had associated coronary artery disease (>50% reduction in luminal diameter of at least one major coronary artery) and were excluded from the current analysis because of the potential impact of coexistent coronary artery stenosis on both survival and left ventricular function after operation. Thus the 80 consecutive patients with chronic aortic regurgitation and no coronary artery disease form the basis of the current study. There were 63 men and 15 women, ranging in age from 15 to 74 years (mean 44). Data analysis was performed in March 1984, resulting in potential follow-up periods ranging from 6 to 90 months (mean 45).

During the course of this study, our indications for valve replacement were the development of moderate to severe cardiac symptoms. Since 1979 we added as an indication for surgery in the absence of symptoms the documentation of consistent and reproducible evidence of depressed left ventricular contractile function at rest by echocardiography and radionuclide angiography. The current operative series represents a consecutive series of patients who fulfilled these criteria for operation, except for one patient with symptoms of congestive heart failure who refused operation, and one asymptomatic patient with a subnormal ejection fraction who had severe kyphoscoliosis. Specifically, no patient was excluded from operation because of extreme symptoms, severely depressed ejection fraction, severely dilated left ventricular chamber, or a combination of these disorders.

Sixty-eight patients underwent aortic valve replacement because of moderate to severe cardiac symptoms (New York Heart Association functional class III to IV). The other 12 patients were either asymptomatic or mildly symptomatic (functional class I to II), and valve replacement was recommended because of consistent evidence of left ventricular dysfunction, based on serial echocardiographic and radionuclide angiographic studies. Nine of these patients were completely asymptomatic. All patients were evaluated preoperatively by echocardiography, radionuclide angiography, graded treadmill exercise testing, and cardiac catheterization, except for one patient in whom echocardiographic studies were of suboptimal quality and one patient who did not undergo radionuclide angiography. All preoperative studies were performed while patients were taking no cardiac medications.

Cardiac catheterization was performed in all patients; coronary arteriography was performed in all patients over 35 years of age as well as all patients under 35 with angina pectoris. Catheterization data confirmed the diagnosis of isolated aortic regurgitation in 76 patients. Four patients had associated small ventricular septal defects with left-to-right shunt ratios less than 1.5:1, which were closed at the time of aortic valve replacement. No patient had associated mitral valve disease or disease of the ascending aorta requiring repair at the time of aortic valve replacement.

Patient stratification. The patients were divided into two subgroups on the basis of preoperative left ventricular ejection fraction at rest as measured by radionuclide angiography. Twenty-nine patients with left ventricular ejection fraction greater than 45% (the lower limit of normal by our technique) were included in the subgroup with normal ejection fraction, while those with ejection fraction of 45% or less were placed in the subgroup with left ventricular dysfunction. In all patients in the left ventricular dysfunction subgroup, impaired contractile function was confirmed by subnormal fractional shortening by echocardiography (<29%). The one patient in whom preoperative radionuclide angiography was not performed was included in the normal left ventricular function subgroup on the basis of echocardiographic demonstration of only moderate left ventricular dilatation (end-diastolic dimension 68 mm, end-systolic dimension 44 mm) with normal fractional shortening (35%).

The 50 patients with left ventricular dysfunction were subdivided further on the basis of exercise tolerance; 17 patients had impaired exercise tolerance, defined as inability to complete the 22.5 min of the first stage of the NIH exercise protocol because of limiting symptoms, while 33 patients manifested preserved exercise tolerance, completing the first stage of exercise without symptoms. These latter 33 patients were stratified again on the basis of duration of preoperative left ventricular dysfunction. In six patients, the duration of left ventricular dysfunction was prolonged, documented by subnormal fractional shortening on previous echocardiographic studies (when all were asymptomatic) performed 18 to 57 months (mean 33 ± 14) before operation and confirmed in four of these six patients by serial radionuclide angiographic studies demonstrating subnormal ejection fraction at rest. In 10 patients the duration of preoperative left ventricular dysfunction was brief, with previous echocardiographic studies performed 1.5 to 14 months before operation (when all were asymptomatic), demonstrating normal fractional shortening and confirmed by serial ejection fraction by radionuclide angiography in seven of these patients; the onset of left ventricular dysfunction occurred within this short time period. In the remaining 17 patients with left ventricular dysfunction and preserved exercise tolerance, the duration of depressed left ventricular systolic function was unknown, since impaired left ventricular systolic function was evident at the time of the initial preoperative evaluation and serial data were not available. In this fashion, the 80 patients were subdivided into five groups on the basis of preoperative left ventricular function, exercise tolerance, and duration of left ventricular dysfunction.

Echocardiography. M mode echocardiograms were obtained with a 2.25 MHz, 1.25 cm diameter unfocused Aerotech transducer and an Ekoline 20A or Hoffrel 201 ultrasound receiver interfaced with a Honeywell 1856 strip-chart recorder, or an Irex System II ultrasound unit with a 2.25 MHz, 1.3 cm diameter transducer. Echocardiographic 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.5, 15 The end-diastolic left ventricular dimension was measured at the R wave of the electrocardiogram. 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 dimension and systolic dimension to the left ventricular diastolic dimension.6 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. The left ventricular radius-to-wall thickness ratio (an index of the volume-to-mass ratio and a measure of the degree to which left ventricular muscle mass is appropriate for a given chamber volume8, 17–19) was computed as one-half the left ventricular end-diastolic dimension divided by the posterior wall thickness. The muscle cross-sectional area, an index of left ventricular myocardial mass, 8, 20, 21 was also computed: cross-sectional area = π[(diastolic dimension/2) + wall thickness]² – π(diastolic dimension/2)².

Gated blood pool cardiac scintigraphy. Radionuclide cineangiography was performed with patients in the supine position at rest and during maximum symptom-limited exercise. Left ventricular ejection fraction was computed from the scintigraphic data as previously described.12 Exercise studies were performed with a bicycle ergometer and a restraining harness to minimize patient motion under the camera. Exercise loads were increased by 25 W increments.
every 2 min until the development of angina or limiting fatigue or dyspnea. Heart rate and blood pressure (by cuff sphygmo-
manometry) were monitored during exercise. Imaging was be-
gun shortly after the onset of exercise, but only that portion of
the data series that occurred during maximal exercise, encom-
passing approximately the last 2 to 2.5 min of exercise, was
selected for analysis. Exercise data were not obtained in four
patients because they were severely symptomatic. Two other
patients did not speak English and could not cooperate satis-
factorily to obtain adequate exercise images. Hence, exercise ra-
dionuclide angiographic data were obtained in 74 of the 80
patients.

**Graded treadmill exercise testing.** Preoperative exercise
capacity was evaluated using the NIH treadmill protocol.13, 14 In
the first stage of the protocol, the treadmill is driven at a con-
stant speed of 2.2 mph at inclination of 0%. Every 2.5 min the
inclination is increased by 2.5% until a maximum of 22.5 min
elapse. The maximum workload at this final stage is 2.5 mph at
20% incline or approximately 8 mets. Fifty-four of the 80 pa-
tients (68%) were able to complete this workload without limit-
ing symptoms, including 33 of 50 patients (66%) in whom the
ejection fraction at rest was subnormal. Two patients with se-
vere symptoms at rest (New York Heart Association functional
class IV) were not exercised and are included in the subgroup
with poor exercise tolerance.

**Aortic valve replacement.** At operation, 37 patients re-
ceived Starr-Edwards prostheses (1260 series in 24, 2320 series
in four, and 2400 series in nine), 38 received Hancock porcine
bioprosthesis model 242, three received Bjork-Shiley pro-
theses, and two received Ionescu-Shiley prostheses. Cardiopul-
monary bypass was performed with disc or bubble oxygenator
with a flow rate of 2.2 liters/min/m². Cardiopulmonary bypass
times ranged from 55 to 158 min (mean 86 ± 21), and aortic
cross-clamp times ranged from 33 to 97 min (mean 55 ± 15).
In addition to systemic hypothermia to 25° to 30°C in all pa-
tients, myocardial preservation techniques included topical 4°
aicd saline with coronary perfusion in 34 patients and hyperka-
lemic cold cardioplegia and topical hypothermia in 46. Myocardial
preservation techniques, cardiopulmonary bypass and aortic
cross-clamp times, and the type of prosthetic valve implanted
were not different among the five subgroups of patients.

**Postoperative studies.** Seventy-three of the 75 patients
who survived 6 months returned within 4 to 8 months after operation
for repeat echocardiographic and radionuclide angiographic
studies. Repeat cardiac catheterization was performed in 69 of
the 73 patients. These studies were performed after patients
were withdrawn from all cardiac medications, except for an-
tiarhythmic drugs in 11 patients (procainamide in six, quini-
dine in three, and disopyramide in two patients). Left heart
catheterization was performed with either the transseptal or the
left ventricular puncture technique. Echocardiographic left ven-
tricular end-systolic dimension and fractional shortening were
not analyzed for the group because of the frequent occurrence of
abnormal septal motion after operation.5, 22

Postoperative hemodynamic data demonstrated peak systolic
gradients across the prosthetic valve of less than 10 mm Hg in 50
patients, between 10 and 20 mm Hg in 13 patients, and 20 mm
Hg or greater in six patients. No patient had a prosthetic valve
gradient greater than 40 mm Hg. One patient with left ventricu-
lar dysfunction of unknown duration had persistent severe (4 +
out of 4 +) aortic regurgitation 7 months after operation because
of a perivalvular leak. He underwent a second operation 8
months after the initial valve replacement and was asymptot-
ic 32 months after repair of the perivalvular leak. For compari-
son with other patients, the 6 month data in this patient were
derived from the studies obtained 6 months after the second
operation.

**Statistical methods.** Comparison of preoperative or postop-
erative data among the five subgroups was performed by analy-
sis of variance. Changes in echocardiographic and radionuclide
angiographic data from before to after operation within sub-
groups were analyzed by the paired t test. The association be-
tween preoperative echocardiographic, radionuclide angiogra-
phic, and hemodynamic variables and subsequent postoperative
survival was tested by the Cox method of life-table analysis.23
Life-table curves were plotted by modification of the method of
Kaplan and Meier,24 and differences between subgroups were
analyzed by the method of Mantel and Haenszel.25

**Results**

**Preoperative data.** Preoperative hemodynamic, echo-
cardiographic, and radionuclide angiographic data are
presented in table 1 for the five subgroups of patients. Patients
with normal preoperative left ventricular ejection
fraction by radionuclide angiography had significantly
higher fractional shortening and smaller end-
systolic dimensions by echocardiography compared
with patients with subnormal ejection fraction (p < .001). However, hemodynamic measurements of left
ventricular function and echocardiographic indexes of
left ventricular diastolic size and myocardial mass
were not different between patients with normal or
subnormal ejection fraction. Among the four patient
subgroups with depressed preoperative ejection frac-
tions, patients with impaired exercise tolerance were
older, had greater systolic dysfunction, and had higher
pulmonary wedge pressures than patients with good
exercise tolerance, but there were no differences in
degree of left ventricular dilatation or hypertrophy.

**Postoperative survival.** The postoperative survival
curve for the 80 patients derived by life-table analysis
is shown in figure 1. There were no intraoperative
deaths, but three patients died within 35 days, yielding
an early postoperative mortality rate of 4%. In two of
these patients, in whom death occurred in hospital,
there was evidence of heart failure and reduced cardiac
output; the third patient died suddenly shortly before
hospital discharge. A total of 11 patients died after
operation. The preoperative data obtained in these 11
patients are presented in table 2. Two of the postopera-
tive deaths were related to the prosthetic valve: pros-
thetic valve endocarditis and severe regurgitation of a
porcine bioprosthesis. The other nine deaths were car-
diac in origin and not apparently related to the pro-
sthetic valve: three patients died suddenly and six pa-
tients died from congestive heart failure. These latter
six patients all had postoperative symptoms of pulmo-
nary congestion and low cardiac output as well as
objective evidence of left ventricular dysfunction after
operation. The 5 year postoperative survival rate was
83 ± 5% (± SE), yielding an annual postoperative
TABLE 1

<table>
<thead>
<tr>
<th>Preoperative data</th>
<th>Patients with normal LV EF at rest (n = 30)</th>
<th>Patients with subnormal LV EF at rest</th>
<th>Good exercise tolerance</th>
<th>Patients with poor exercise tolerance (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>41 ± 15 NS</td>
<td>46 ± 14</td>
<td>44 ± 14</td>
<td>42 ± 15</td>
</tr>
<tr>
<td>Echocardiographic data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV diastolic dimension (mm)</td>
<td>74 ± 6 NS</td>
<td>75 ± 7</td>
<td>75 ± 4</td>
<td>76 ± 6</td>
</tr>
<tr>
<td>LV systolic dimension (mm)</td>
<td>51 ± 6 &lt;.001</td>
<td>58 ± 7</td>
<td>55 ± 3</td>
<td>58 ± 6 E</td>
</tr>
<tr>
<td>LV fractional shortening (%)</td>
<td>31 ± 4 &lt;.001</td>
<td>24 ± 4</td>
<td>26 ± 2 E</td>
<td>24 ± 3 E</td>
</tr>
<tr>
<td>R/Th ratio</td>
<td>2.9 ± 0.5 NS</td>
<td>3.0 ± 0.4</td>
<td>3.1 ± 0.5</td>
<td>3.3 ± 0.4</td>
</tr>
<tr>
<td>Cross-sectional area (cm²)</td>
<td>35 ± 6 NS</td>
<td>35 ± 7</td>
<td>34 ± 5</td>
<td>36 ± 5</td>
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<tr>
<td>Radionuclide angiographic data</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LV EF at rest (%)</td>
<td>52 ± 7 c</td>
<td>37 ± 7</td>
<td>40 ± 6</td>
<td>38 ± 5</td>
</tr>
<tr>
<td>LV EF during exercise (%)</td>
<td>45 ± 8 c</td>
<td>30 ± 7</td>
<td>30 ± 9</td>
<td>31 ± 6</td>
</tr>
<tr>
<td>LV EF exercise response (%)</td>
<td>-7 ± 7 NS</td>
<td>-8 ± 5</td>
<td>-10 ± 7</td>
<td>-7 ± 4</td>
</tr>
<tr>
<td>Hemodynamic data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary wedge pressure (mm Hg)</td>
<td>13 ± 8 NS</td>
<td>15 ± 7</td>
<td>11 ± 4</td>
<td>16 ± 6</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>14 ± 8 NS</td>
<td>17 ± 9</td>
<td>16 ± 8</td>
<td>16 ± 7</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.8 ± 0.5 NS</td>
<td>2.6 ± 0.7</td>
<td>2.7 ± 0.7</td>
<td>2.9 ± 0.7</td>
</tr>
</tbody>
</table>

Data are mean ± SD; statistical significance by analysis of variance.
EF = ejection fraction; LV = left ventricular; R/Th = radius-to-wall thickness ratio.
*Comparison between patients with normal ejection fraction and all patients with subnormal ejection fraction.
**Exercise LV ejection fraction minus resting ejection fraction.
Comparison not made since patient subgroups were defined on basis of ejection fraction.
*p < .05 compared with all other subgroups with subnormal ejection fraction at rest.
*p < .05 compared with patients with normal ejection fraction.

mortality rate (including the three in-hospital deaths) of less than 4% per year.

By the Cox univariate life-table analysis, several preoperative echocardiographic and radionuclide angio-

FIGURE 1. Life table depicting postoperative survival in the 80 patients undergoing operation from 1976 to 1983. Brackets indicate standard error. Two patients with death related to the aortic valve prosthesis are indicated by open symbols.

PATHOPHYSIOLOGY AND NATURAL HISTORY—AORTIC VALVE REPLACEMENT
TABLE 2
Preoperative data in 11 patients who died after aortic valve replacement

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Postoperative survival (mo)</th>
<th>Cause of death</th>
<th>LVDD (mm)</th>
<th>LVSD (mm)</th>
<th>LVFS (%)</th>
<th>CSA (cm²)</th>
<th>Rest EF (%)</th>
<th>Exercise EF (%)</th>
<th>Exercise response (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>M</td>
<td>1</td>
<td>LV dysfunction</td>
<td>76</td>
<td>64</td>
<td>16</td>
<td>30</td>
<td>30</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>M</td>
<td>1</td>
<td>LV dysfunction</td>
<td>75</td>
<td>60</td>
<td>20</td>
<td>36</td>
<td>26</td>
<td>20</td>
<td>—9</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>M</td>
<td>1</td>
<td>Sudden</td>
<td>90</td>
<td>75</td>
<td>17</td>
<td>38</td>
<td>23</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>M</td>
<td>2</td>
<td>Sudden</td>
<td>84</td>
<td>72</td>
<td>14</td>
<td>40</td>
<td>13</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>M</td>
<td>5</td>
<td>Valvea</td>
<td>65</td>
<td>48</td>
<td>26</td>
<td>35</td>
<td>45</td>
<td>41</td>
<td>—4</td>
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<td>6</td>
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<td>—7</td>
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<tr>
<td>7</td>
<td>62</td>
<td>F</td>
<td>26</td>
<td>Sudden</td>
<td>62</td>
<td>41</td>
<td>34</td>
<td>25</td>
<td>50</td>
<td>46</td>
<td>—4</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>M</td>
<td>36</td>
<td>Valveb</td>
<td>85</td>
<td>70</td>
<td>18</td>
<td>40</td>
<td>36</td>
<td>24</td>
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<td>9</td>
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<td>26</td>
<td>59</td>
<td>40</td>
<td>27</td>
<td>—13</td>
</tr>
</tbody>
</table>

CI = cardiac index; CSA = cross-sectional area; DD = diastolic dimension; EDP = end-diastolic pressure; EF = ejection fraction; FS = fractional shortening; LV = left ventricular; PAW = pulmonary arterial wedge pressure; SD = systolic dimension.

aProsthetic valve endocarditis.

bSevere regurgitation of aortic porcine bioprostheses; died after second valve replacement operation.

namic variable was significantly associated with subsequent mortality (table 3). The method of myocardial preservation used at operation also did not influence outcome. At 5.5 years after operation, the survival rate in patients treated with hyperkalemic cardioplegia was 81 ± 8%, compared with 82 ± 8% in patients who did not receive hyperkalemic cardioplegia (preoperative hemodynamic, echocardiographic, and radionuclide angiographic data were similar between these two groups). No relationship was evident between the type of prosthetic valve used and postoperative survival.

TABLE 3
Association between preoperative variables and subsequent postoperative mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>p value</th>
<th>All deaths (n = 11)</th>
<th>Deaths not related to prostatic valve (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiographic data</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>LV fractional shortening</td>
<td>&lt; .001A</td>
<td>&lt; .005A</td>
<td></td>
</tr>
<tr>
<td>LV systolic dimension</td>
<td>&lt; .01A</td>
<td>&lt; .01A</td>
<td></td>
</tr>
<tr>
<td>LV diastolic dimension</td>
<td>.25</td>
<td>.21</td>
<td></td>
</tr>
<tr>
<td>LV R/Th ratio</td>
<td>.42</td>
<td>.38</td>
<td></td>
</tr>
<tr>
<td>LV myocardial cross-sectional area</td>
<td>.47</td>
<td>.52</td>
<td></td>
</tr>
<tr>
<td>Radionuclide angiographic data</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LV EF at rest</td>
<td>&lt; .001A</td>
<td>&lt; .001A</td>
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<tr>
<td>LV EF during exercise</td>
<td>&lt; .02A</td>
<td>&lt; .02A</td>
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<tr>
<td>LV EF response to exerciseb</td>
<td>.81</td>
<td>.76</td>
<td></td>
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<tr>
<td>Hemodynamic data</td>
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<tr>
<td>Pulmonary wedge pressure</td>
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<td>.07</td>
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<tr>
<td>LV end-diastolic pressure</td>
<td>.18</td>
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<td>Cardiac index</td>
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<tr>
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<td>.26</td>
<td>.047A</td>
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<tr>
<td>Sex</td>
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<td>.43</td>
<td></td>
</tr>
<tr>
<td>Hyperkalemic cardioplegia</td>
<td>.29</td>
<td>.74</td>
<td></td>
</tr>
</tbody>
</table>

EF = ejection fraction; LV = left ventricular; R/Th = diastolic radius-to-wall thickness ratio.

A Significant value by Cox univariate analysis.

bLV EF response to exercise = exercise EF minus rest EF.
paralleled by changes in left ventricular function after operation. In patients with preoperative left ventricular dysfunction, the ejection fraction at rest did not change significantly 6 months after operation in either the sub-group with poor exercise tolerance or the subgroup with good exercise tolerance but prolonged duration of dysfunction (table 4, figure 5). In contrast, patients with good exercise tolerance and only a brief duration of left ventricular dysfunction manifested a significantly greater increase in ejection fraction after operation, and the postoperative ejection fraction in this group was identical to that observed in patients in whom the preoperative ejection fraction was normal. Nearly identical results were obtained when the postoperative changes in the ejection fraction during exer-
cise were analyzed (table 4, figure 6). Patients with a brief duration of preoperative left ventricular dysfunction manifested a significant increase in exercise ejection fraction after operation to a value comparable to that observed in patients in whom the preoperative ejection fraction at rest was normal. However, the exercise ejection fraction did not change significantly after operation in those patients with preoperative left ventricular dysfunction at rest who either manifested poor preoperative exercise tolerance or a prolonged

TABLE 4
Postoperative data

<table>
<thead>
<tr>
<th>Echocardiographic data</th>
<th>Patients with subnormal preoperative EF at rest</th>
<th>Patients with normal preoperative EF at rest</th>
<th>Good preoperative exercise tolerance</th>
<th>Patients with poor preoperative exercise tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV diastolic dimension (mm)</td>
<td>53 ± 7 &lt;.01 58 ± 9 49 ± 3³ 58 ± 8³ 60 ± 10³ 64 ± 8³</td>
<td>49 ± 3³ 58 ± 8³ 60 ± 10³ 64 ± 8³</td>
<td>49 ± 3³ 58 ± 8³ 60 ± 10³ 64 ± 8³</td>
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<tr>
<td>Change in LV diastolic dimension (mm)³</td>
<td>−21 ± 8 NS −18 ± 9 −26 ± 5³ −19 ± 10 −16 ± 7 −11 ± 7³</td>
<td>−21 ± 8 NS −18 ± 9 −26 ± 5³ −19 ± 10 −16 ± 7 −11 ± 7³</td>
<td>−21 ± 8 NS −18 ± 9 −26 ± 5³ −19 ± 10 −16 ± 7 −11 ± 7³</td>
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<tr>
<td>Radionuclide angiographic data</td>
<td></td>
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<tr>
<td>LV EF at rest (%)</td>
<td>57 ± 16 &lt;.001 45 ± 15 65 ± 7³ 47 ± 10³ 37 ± 12³ 34 ± 15³</td>
<td>57 ± 16 &lt;.001 45 ± 15 65 ± 7³ 47 ± 10³ 37 ± 12³ 34 ± 15³</td>
<td>57 ± 16 &lt;.001 45 ± 15 65 ± 7³ 47 ± 10³ 37 ± 12³ 34 ± 15³</td>
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<tr>
<td>Change in LV EF at rest (%)³</td>
<td>9 ± 10 NS 7 ± 14 25 ± 9³ 8 ± 11 2 ± 9³ 2 ± 11³</td>
<td>9 ± 10 NS 7 ± 14 25 ± 9³ 8 ± 11 2 ± 9³ 2 ± 11³</td>
<td>9 ± 10 NS 7 ± 14 25 ± 9³ 8 ± 11 2 ± 9³ 2 ± 11³</td>
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<tr>
<td>LV EF during exercise (%)³</td>
<td>61 ± 14 &lt;.001 45 ± 16 62 ± 9³ 46 ± 12³ 36 ± 13³ 33 ± 11³</td>
<td>61 ± 14 &lt;.001 45 ± 16 62 ± 9³ 46 ± 12³ 36 ± 13³ 33 ± 11³</td>
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<td></td>
</tr>
<tr>
<td>Change in LV EF during exercise (%)³</td>
<td>15 ± 10 NS 15 ± 15 32 ± 13³ 15 ± 12 6 ± 10 4 ± 9³</td>
<td>15 ± 10 NS 15 ± 15 32 ± 13³ 15 ± 12 6 ± 10 4 ± 9³</td>
<td>15 ± 10 NS 15 ± 15 32 ± 13³ 15 ± 12 6 ± 10 4 ± 9³</td>
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<tr>
<td>Hemodynamic data</td>
<td></td>
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<tr>
<td>Prosthetic valve gradient</td>
<td>9 ± 9 NS 7 ± 9 11 ± 13 8 ± 8 5 ± 6 5 ± 5</td>
<td>9 ± 9 NS 7 ± 9 11 ± 13 8 ± 8 5 ± 6 5 ± 5</td>
<td>9 ± 9 NS 7 ± 9 11 ± 13 8 ± 8 5 ± 6 5 ± 5</td>
<td></td>
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<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>9 ± 4 NS 10 ± 4 11 ± 13 8 ± 8 5 ± 6 5 ± 5</td>
<td>9 ± 4 NS 10 ± 4 11 ± 13 8 ± 8 5 ± 6 5 ± 5</td>
<td>9 ± 4 NS 10 ± 4 11 ± 13 8 ± 8 5 ± 6 5 ± 5</td>
<td></td>
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<tr>
<td>Cardiac index (l/min/m²)</td>
<td>3.1 ± 0.8 NS 3.0 ± 0.9 2.8 ± 0.7 2.9 ± 0.8 3.3 ± 0.4</td>
<td>3.1 ± 0.8 NS 3.0 ± 0.9 2.8 ± 0.7 2.9 ± 0.8 3.3 ± 0.4</td>
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</tr>
</tbody>
</table>

See table 1 for abbreviations.

¹Comparison between patients with normal preoperative ejection fraction and all patients with subnormal ejection fraction.

²Comparison with preoperative value.

³p < .01 compared with all other subgroups with subnormal preoperative ejection fraction at rest.

⁴p < .05 compared with patients with normal preoperative ejection fraction at rest.

⁵p < .01 compared with patients with normal preoperative ejection fraction at rest.
FIGURE 5. Change in radionuclide angiographic ejection fraction at rest from before (Preop) to 6 months after (Postop) operation in patients with normal preoperative left ventricular (LV) ejection fraction at rest and the four subgroups with subnormal preoperative ejection fraction. Open symbols, patients who died before the 6 month repeat evaluation; asterisks, cardiac deaths after 6 month study; cross, valve-related death after 6 month study. Significance values by analysis by variance.

FIGURE 6. Change in ejection fraction during exercise from before to 6 months after operation in the five patient subgroups. Symbols are defined in legend to figure 5.
duration of left ventricular dysfunction. In any individual patient, the value of the preoperative ejection fraction during exercise per se did not indicate whether or not a patient was likely to manifest a substantial improvement in left ventricular ejection fraction after operation, either at rest or during exercise (figure 6).

The changes in left ventricular ejection fraction after operation were paralleled closely by the magnitude of reduction in left ventricular diastolic dimension after operation (table 4, figure 7). Preoperative left ventricular diastolic dimension was not different among the five subgroups of patients but was reduced to a greater extent after operation in those patients with normal preoperative ejection fraction or preoperative left ventricular dysfunction of only brief duration, compared with that in patients with preoperative left ventricular dysfunction and poor exercise tolerance or a prolonged duration of left ventricular dysfunction.

Eleven patients were receiving antiarrhythmic drugs at the time of the postoperative studies. Although seven of these patients had depressed preoperative ejection fractions, none was in the subgroup with poor exercise tolerance or prolonged duration of preoperative left ventricular dysfunction. Similarly, although six patients had prosthetic valve gradients of 20 mm Hg or greater at the postoperative study, none of these patients was in the subgroup with preoperative left ventricular dysfunction and either poor exercise tolerance or prolonged duration of dysfunction. Hence, postoperative data in subgroups at highest risk of persistent left ventricular dysfunction were not influenced by potential drug effects or prosthetic valve gradients.

On the basis of these functional changes after operation, the survival analysis was repeated to assess postoperative prognoses in subgroups with a high likelihood of normal postoperative left ventricular function compared with subgroups with a likelihood of persistent dysfunction (figure 8). Patients with either normal preoperative ejection fraction or a brief duration of left ventricular dysfunction with good exercise tolerance had an excellent postoperative survival rate (97 ± 3% at 5.5 years). In contrast, postoperative survival was significantly reduced in those patients with left ventricular dysfunction and poor exercise tolerance or prolonged duration of left ventricular dysfunction. The survival rate at 5.5 years was 52 ± 17% in this combined subgroup of patients. Hence, patients with left ventricular dysfunction and impaired exercise tolerance, and those with a prolonged duration of preoperative dysfunction, define the high-risk group.

![FIGURE 7](image-url) Change in echocardiographic left ventricular end-diastolic dimension from before to 6 months after operation in the five patient subgroups. Symbols are defined in legend to figure 5.
PATHOPHYSIOLOGY AND NATURAL HISTORY—AORTIC VALVE REPLACEMENT


Discussion

The impact of preoperative left ventricular dysfunction on postoperative survival in patients with aortic regurgitation remains a subject of controversy. Numerous studies demonstrate that patients who exhibit impaired preoperative left ventricular systolic function are at risk of manifesting irreversible myocardial dysfunction and of dying postoperatively from congestive heart failure despite technically successful valve replacement.\(^1\)\(^-\)\(^4\) Other reports emphasize, however, that impaired preoperative left ventricular function may improve dramatically, and even normalize, in many patients after operation.\(^5\)\(^-\)\(^8\)\(^,\)\(^9\)\(^-\)\(^11\)\(^,\)\(^13\)\(^-\)\(^14\)\(^,\)\(^17\)\(^-\)\(^20\)\(^,\)\(^21\)\(^,\)\(^26\)\(^-\)\(^28\) Some investigators have interpreted this potential for improvement as an indication that survival and functional results after valve replacement for aortic regurgitation may no longer be influenced by preoperative left ventricular function.\(^8\)\(^-\)\(^11\)

We believe the principal reason for the disparate conclusions of recent studies regarding survival and functional results of aortic valve replacement relate to patient selection factors and to interpretive differences. The influence of patient selection on the results is evident from the following analysis. In the current study, our in-hospital mortality rate was 4% and the annual postoperative mortality rate (including perioperative deaths) was less than 4% per year, yielding a 5 year survival rate of 83%. This represents a significant improvement in postoperative survival compared with our previous experience from 1972 to 1976 (figure 9), in which survival at 4 years was only 62%. Similar improvement in postoperative survival in the late 1970s compared with the early 1970s has been reported by Turina et al.\(^29\) These improved survival results in the recent era probably represent, in part, differences in selection of patients for operation. During the course of the current study, our strategy for patient management in aortic regurgitation was changed because of data implicating left ventricular function and severity of symptoms as important determinants of postoperative prognosis.\(^1\)\(^-\)\(^4\)\(^,\)\(^8\)\(^,\)\(^13\)\(^-\)\(^17\)\(^,\)\(^20\)\(^-\)\(^35\) Hence, many patients with left ventricular dysfunction in the current study underwent operation before the development of severe symptoms or impaired exercise capacity. Fifty-four of the 80 patients (68%) were able to complete stage I of our treadmill protocol, including 33 of 50 (67%) with subnormal ejection fractions. In contrast, from 1971 to 1976, our only indication for aortic valve replacement was moderate to severe cardiac symptoms (New York Heart Association functional class III to IV), and only 12% of patients were able to complete stage I. Turina et al.\(^29\) also suggested that improved late survival in their recent operative experience was the result of earlier operation before the onset of severe clinical and hemodynamic impairment.

The improved survival may also reflect advances in operative techniques. Our study was not designed to study the effects of different myocardial preservation techniques, and the two procedures used in this study were historically controlled rather than concurrently performed. Nonetheless, we could not demonstrate a beneficial effect of hyperkalemic cardioplegia in enhancing postoperative survival in our study. It is possible, however, that other subtle operative factors developed over the course of a decade may have important effects that would not be apparent simply by description of myocardial preservation techniques.

Despite the recent improvement in postoperative survival, our current results demonstrate that ejection phase indexes of left ventricular function remain significantly associated with subsequent postoperative cardiac mortality (table 3). In addition to the significant association between postoperative mortality and reduced preoperative left ventricular fractional shortening and increased systolic dimension by echocardiography, as in our previous experience, mortality in the current study was also highly associated with low values of resting left ventricular ejection fraction by an independent noninvasive technique, radionuclide angiography, which does not have the potential limitations of echocardiography in assessing left ventricular systolic performance in the volume-loaded left ventricle. Because of the ongoing controversy surrounding the use of echocardiography in the diagnosis of aortic regurgitation, we used resting ejection fraction by radionuclide angiography as the standard with which to subgroup patients in this study into those with normal vs subnormal systolic function. Patients with normal ejection fraction before operation had a significantly higher postoperative survival rate than patients with preoperative left ventricular dysfunction (figure 3).

Importantly, within the group with depressed ejection fraction, we also identified patients who constituted subgroups at low and high risk (figures 4 and 8). Patients with subnormal ejection fraction but preserved exercise tolerance and only a brief duration left ventricular dysfunction had excellent postoperative survival (no patient died), whereas patients with either impaired exercise tolerance or good exercise tolerance but prolonged left ventricular dysfunction had survival rates less than 60% at 5 years. These survival results were paralleled by changes in left ventricular function after operation (table 4, figures 5 to 7). These data suggest that differences in patient selection might explain discordant results in previous studies regarding the frequency and magnitude of reversal of left ventricular dysfunction after valve replacement. These data also indicate that delaying operation in an asymptomatic or mildly symptomatic patient with impaired left ventricular function until the development of more severe symptoms places the patient at greater risk of death or irreversible ventricular dysfunction.

These findings relate to three recent studies in which discrepancies between preoperative left ventricular function and postoperative results were apparently identified, insofar as the authors concluded that echocardiographic evidence of preoperative left ventricular systolic dysfunction did not identify subgroups of patients at risk of death or persistent left ventricular dysfunction after operation. These investigators suggested that improved operative techniques and valve design have in effect negated the impact of left ventricular function on postoperative survival, so that indexes of left ventricular dilatation and function cannot be used in the timing of operation. We believe that the results of these studies and our current results are quite similar and that the disparate conclusions arise from interpretive differences.

The reason echocardiography was of no predictive value regarding survival in the studies by Fioretti et al. is readily apparent: there was only one postoperative death. Despite improved postoperative results, however, all other centers continue to report a more finite risk to life of aortic valve replacement as was our experience in the current study. Fioretti and associates excluded from study all patients who had “complicated” postoperative courses, an action that may have influenced their results importantly. Moreover, although Fioretti’s group did not demonstrate a relationship between left ventricular function and postoperative survival, 50% of their patients with preoperative left ventricular dysfunction by echocardiography had persistent left ventricular dilatation after operation.

Although Daniel et al. were also critical of the predictive value of echocardiographic indexes of left ventricular function in assessing postoperative prognosis, their data actually demonstrate poor postoperative survival in patients with preoperative left ventricular dysfunction. Survival curves were not presented in that study; however, only 79% of patients with left ventricular dysfunction (assessed echocardiographically) were alive at a mean follow-up of 29.5 months. This translates into an average mortality rate in such patients of 8.6% per year. In contrast, 91% of patients without left ventricular dysfunction were alive during the same postoperative period, representing an annual mortality rate of 3.7%. All but four of the deaths in that series were related to the prosthetic valve. Such complications must be considered chance events and would not be predicted by preoperative left ventricular function. In the four patients with cardiac deaths, however, all four had subnormal preoperative left ventricular fractional shortening (less than 29%); three of the four had end-systolic dimensions greater than 60 mm, and the fourth had an end-systolic dimension of 53 mm. Patients with preoperative left ventricular dysfunction also had a greater prevalence of persistent severe postoperative left ventricular dilatation.

The prognostic value of the resting ejection fraction
in our study was not enhanced further by analysis of the ejection fraction response to exercise (table 3). The majority of patients with normal ejection fraction at rest manifested an abnormal exercise response (that is, a decrease in ejection fraction compared to the value at rest). However, since survival in these patients was excellent, the abnormal ejection fraction response did not identify patients with normal ejection fractions in whom survival after operation was reduced. In addition, neither the value of the exercise ejection fraction nor the magnitude of the ejection fraction response to exercise predicted which patients with subnormal ejection fraction at rest were at risk of death or persistent left ventricular dysfunction after operation (tables 1 and 3, figure 7). Thus, despite the good correlation between the decrease in ejection fraction during exercise and increased left ventricular dimensions, 28, 45 increased left ventricular wall stress, 35-47 and perhaps abnormal exercise hemodynamic data, 48, 49 the ejection fraction response to exercise does not appear to provide meaningful information regarding postoperative prognosis over the initial 5 to 7 years after aortic valve replacement.

Our data demonstrate improved long-term postoperative survival in the current operative series compared with our earlier results. Despite this improvement, preoperative left ventricular systolic dysfunction continues to identify patients with aortic regurgitation at risk of death or persistent left ventricular dysfunction after aortic valve replacement. Indexes of left ventricular systolic size and systolic function are the most important determinants of prognosis. Patients with left ventricular dysfunction and impaired exercise tolerance, or those with a prolonged duration of preoperative left ventricular dysfunction, define the high-risk subgroup. We emphasize, however, that operation is not contraindicated in such patients; many will do well after operation, although the probability of survival and normalization of left ventricular function is considerably less than in patients in the low-risk group. Our data indicate that early operation in such patients should result in further improvement in long-term survival.

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