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CLINICAL STUDIES

Predictors of Outcome for Aortic Valve Replacement in Patients With Aortic Regurgitation and Left Ventricular Dysfunction: A Change in the Measuring Stick

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Although left ventricular function is generally regarded as a key determinant of prognosis in aortic regurgitation, predictors of outcome of aortic valve replacement based on this factor have recently been questioned. This study was performed to examine the role of indexes of left ventricular function in predicting the outcome of surgery in patients with aortic regurgitation and left ventricular dysfunction.

Fourteen patients with aortic regurgitation with a preoperative ejection fraction of <0.55 (average 0.45 ± 0.02) who underwent aortic valve replacement were studied. The patients had 82 (58%) of a possible 140 predictors of negative outcome preoperatively, but 12 of the 14 patients had a decrease in symptoms and an increase in ejection fraction into the normal range after operation (average postoperative ejection fraction 0.59 ± 0.04).

Although improvement occurred despite the presence of many negative predictors of outcome, there was a significant correlation between postoperative ejection fraction and eight of the tested preoperative predictors. Preoperative end-systolic dimension correlated best ($r = -0.91$) with postoperative ejection fraction. An end-systolic dimension of 60 mm correlated with a postoperative ejection fraction of 0.55.

The results indicate that preoperative ventricular function is still an important determinant of outcome of aortic valve replacement for aortic regurgitation. However, current medical and surgical techniques permit a better prognosis in the presence of reduced ventricular function than was previously considered possible.

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The timing of aortic valve replacement for isolated aortic regurgitation remains controversial; yet there is general agreement that, to result in optimal clinical improvement, valve replacement must be performed before the development of an irreversible decrease in left ventricular function. Therefore, indexes of left ventricular function have been examined as predictors of outcome of aortic valve replacement (1–13). Recently, some of these predictors have been called into question by studies (14,15) that reported a good outcome for valve replacement in aortic regurgitation despite the prediction of a negative outcome. If, as seems likely, improved preoperative care and operative techniques have improved the prognosis for patients undergoing aortic valve replacement, then the limits for various indexes of left ventricular performance beyond which there is a poor prognosis may have changed without invalidating the concept that preoperative left ventricular function is a major predictor of outcome. For instance, previously an end-systolic dimension >55 mm indicated a level of left ventricular dysfunction for which the likelihood of a poor outcome was increased (3). However, if improved medical and surgical therapies have now increased the tolerable level of preoperative left ventricular dysfunction, the "55" rule might no longer be useful, but the concept of preoperative left ventricular dysfunction as an indicator of outcome could still be valid.

We noted that most of our patients with aortic regurgitation and left ventricular dysfunction did well at surgery despite exceeding the negative limits of various predictors of outcome previously reported. We hypothesized that, al-

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though our patients exceeded these limits, preoperative predictors of outcome based on ventricular function would still correlate with the results of surgery and postoperative cardiac performance. Our study was undertaken to test this hypothesis.

Methods

Study design. Preoperative predictors of outcome for valve replacement in aortic regurgitation were chosen from published data and determined retrospectively for our patients with aortic regurgitation and left ventricular dysfunction who underwent aortic valve replacement. The predictors were then compared with the patients' outcome as assessed by prospectively gathered data.

Selection of patients. Catheterization and echocardiographic data from all patients undergoing aortic valve replacement for aortic insufficiency from 1980 to 1987 at the Medical University of South Carolina were reviewed. Eighty-two such patients were identified. Patients were chosen for study if they met the following criteria:

1) They had severe aortic regurgitation (+3 or +4 angiographic grade).
2) They had an angiographic ejection fraction <55%. This value was chosen because it is generally recognized as the lowest limit of normal for ventriculographically determined ejection fraction.
3) No coronary artery had a significant stenosis (>40% reduction of luminal diameter).
4) The aortic valve gradient was ≤5 mm Hg.
5) There was no mitral stenosis or regurgitation.
6) Angiographic quality was such that left ventricular end-diastolic, end-systolic and wall thickness silhouettes could be determined easily.
7) Technically adequate echocardiograms were available for review.

Twenty-one of the 82 patients had a preoperative ejection fraction <0.55. Of these patients, four were excluded because they had coronary artery disease and three were excluded because of inadequate ventriculograms. The other 14 patients met the study criteria and constituted the study group. No patient who met the criteria was excluded. In no case did the investigator (B.A.C.) who selected the patients have knowledge of their surgical outcome. Eight patients had no gradient detectable at pullback of the left heart catheter from the left ventricle to the aorta. Six patients had a trivial gradient, varying from 2 to 5 mm Hg. The origin of the aortic regurgitation was thought to be rheumatic in four patients, annuloaortic ectasia in two, previous valve endocarditis in two and unknown in six. No patient had active endocarditis or Marfan's syndrome.

Additional preoperative evaluation. All patients underwent a history and physical examination before cardiac catheterization. The New York Heart Association functional classification was determined from the report of the attending cardiologist before catheterization. Eight patients were in functional class II and six were in class III.

Preoperative indexes of ventricular function. Table 1 displays the indexes chosen for study and the appropriate published source. We did not attempt to choose all indexes proposed, but selected those representative of echocardiographic, hemodynamic, ejection phase and geometric descriptors of the left ventricle in aortic regurgitation. Unfortunately, only two patients underwent exercise stress radionuclide ventriculography; thus, we could not evaluate exercise-induced changes in ejection fraction, which is another index proposed in the evaluation of such patients. Although not previously reported, we suspected that right ventricular failure might also be of prognostic importance. Therefore, we examined elevated right atrial pressure (an indicator of right ventricular failure) as a predictor of outcome.

Echocardiography. Echocardiograms were recorded using standard techniques on commercially available ultrasound equipment with the patient in the supine or slight left lateral decubitus position. The left ventricular measurements were obtained according to standards recommended by the American Society of Echocardiography using the leading edge method (16). The left ventricular end-diastolic dimen-

Table 1. Previously Reported Risk Factors Evaluated

Risk Factor	Value Predictive of a Poor Outcome	Reference No.
Pulmonary capillary wedge pressure	>12 mm Hg	1
Cardiac index	<2.2 liters/min per m^2	1
Ejection fraction	<0.50	2
Shortening fraction	<0.27	3
End-systolic dimension	>55 mm	3
End-systolic dimension index	>2.6 mm/m^2	4
End-diastolic dimension index	>3.8 mm/m^2	4
End-systolic volume index	>90 mm/m^2	5,6
Ratio of diastolic radius to thickness	>3.8	4
Ratio of regurgitant to end-diastolic volume	<0.25	7

sion (EDD) was defined as the distance between the left-sided endocardial surface of the interventricular septum and that of the posterior wall at the beginning of the QRS complex on the electrocardiogram. The left ventricular end-systolic dimension (ESD) was measured as the smallest left ventricular diameter. Percent fractional shortening (% FS) was defined as:

$$\% \text{ FS} = \frac{\text{EDD-ESD}}{\text{EDD}} \times 100.$$

Ventriculography. Pressures were obtained from fluid-filled catheters immediately before left ventriculography. Cardiac volumes were calculated from cineangiograms obtained in the single plane right anterior oblique position filmed at 60 frames/s. Volumes were calculated by the area-length method using the regression equation of Wynne et al. (17). End-systolic wall stress was obtained from catheterization data using Mirsky's formula (18):

$$\text{Stress} = \frac{P \cdot b}{h}\left[1 - \frac{b}{2h} - \frac{b^2}{2a^2}\right] \times 1{,}332 \text{ dynes/cm}^2 \text{ per mm Hg},$$

where P = end-systolic pressure, b = end-systolic semiminor axis (D + h)/2, a = end-systolic semimajor axis (L + h)/2, and h = end-systolic wall thickness. End-systolic wall thickness was calculated from end-diastolic thickness using the assumption that cardiac mass remains constant throughout the cardiac cycle (19).

Patient follow-up. All 14 patients were available for follow-up study. At 6 to 72 months (average 23 ± 8) after surgery, each patient underwent a history, physical examination and radionuclide ventriculogram to ascertain clinical class and cardiac performance. Synchronized gated cardiac blood pool scans were performed in the 45° left anterior oblique and anterior projections acquiring 4 million counts in each projection utilizing 22 frames. These were performed on a Picker mobile camera equipped with an Elscint computer. Wall motion analysis was performed in the anterior and left anterior oblique projections, and the ejection fraction was calculated by the standard technique in the left anterior oblique projection. Although we recognize that ejection fraction is load dependent, we used it to judge left ventricular function postoperatively after valve replacement had lessened the abnormal loading conditions.

Medications. Digoxin was received by 13 of the 14 patients preoperatively and was discontinued postoperatively in 6 patients. All six subsequently demonstrated an increase in ejection fraction despite discontinuation of the drug. Eight patients received a vasodilator preoperatively, but only two (those with persistent left ventricular dysfunction) received a vasodilator postoperatively.

Normal subjects. Ten patients who underwent catheterization for chest pain atypical of myocardial ischemia and were subsequently proved to be free of coronary disease formed the group of normal subjects. None had abnormal ejection performance, elevated left ventricular end-diastolic pressure or mitral valve prolapse. None was receiving drugs known to affect cardiac function other than sublingual nitroglycerin. The average age of the normal subjects (46 ± 7 years) was similar to that of the patients with aortic regurgitation (49 ± 6 years).

Valve surgery. Surgery was performed during the administration of cold hyperkalemic cardioplegia in all patients. In no case was there electrocardiographic or serum enzyme evidence of intra- or postoperative myocardial infarction. All patients received a mechanical prosthetic valve.

Statistics. Comparisons between variables in normal subjects and patients with aortic regurgitation were made using an unpaired Student's *t* test. When preoperative ejection fraction in patients with aortic regurgitation was compared with postoperative ejection fraction, a paired *t* test was performed. Correlation of preoperative predictive indexes and postoperative ejection fraction was made using least-square linear regression. Dispersion from the mean is reported as the standard error of the mean.

Results

Outcome of surgery. All patients survived surgery and were available for follow-up. No patient had evidence by physical examination (14 patients) or Doppler echocardiographic examination (8 patients) of prosthetic valve dysfunction. Ten patients returned to functional class I, two patients had improvement from class III to class II and two patients remained in class III. Ejection fraction in 12 of the 14 patients (who also returned to functional class I or II) returned to normal (≥55%) postoperatively. Thus, 12 of the 14 patients had a return to functional class I or II and normal ejection performance defined by us as a good outcome.

Preoperative risk factors. Tables 2 and 3 show the comparisons of echocardiographic and angiographic data between normal subjects and the patients with aortic regurgitation. Patients with aortic regurgitation had significantly increased cardiac dimensions, volumes and end-systolic stress, but decreased percent shortening fraction and ejection fraction (as defined by study design) compared with values in normal subjects.

Table 4 demonstrates the risk factors investigated and the patients having each risk factor. Our patients had a total of 82 of a possible 140 predictors of a negative outcome (58% of the possible total, an average of 6 risk factors per patient), and all patients had at least 4 negative predictors. One could argue that ejection fraction and shortening fraction, end-systolic dimension and dimension index and end-systolic volume index all depend on similar ventricular characteristics and, thus, are redundant. However, elimination of ejection fraction, end-systolic dimension and end-systolic

Table 2. Selected Echocardiographic Variables: Normal Subjects Versus Patients With Aortic Regurgitation

	EDDI (mm/m^2)	ESD (ml)	ESDI (ml/m^2)	SF	r/h	h
NL	30 ± 1	35 ± 1.2	19 ± 1.0	0.36 ± 0.02	3.43 ± 0.2	0.82 ± 0.05
AR	39 ± 2.1	57 ± 2.5	30 ± 1.5	0.23 ± 0.01	3.44 ± 0.02	1.15 ± 0.04
p Value	<0.01	<0.001	<0.001	<0.001	NS	<0.001

AR = aortic regurgitation; EDDI = end-diastolic dimension index; ESD = end-systolic dimension; ESDI = end-systolic dimension index; h = end-diastolic wall thickness; NL = normal subjects; NS = not significant; r/h = ratio of end-diastolic radius to thickness; SF = shortening fraction.

volume index from consideration still yielded a group of patients with 52 (53%) of a possible 98 negative predictors.

Preoperative risk factors and postoperative left ventricular function. Although our patients had multiple preoperative indicators suggesting a bad surgical result, 85% had a good surgical result. Figure 1 further substantiates our patients' improvement and demonstrates the increase in ejection fraction that occurred in most patients after surgery. Despite the fact that our patients had many predictors of a negative outcome, Table 5 shows a significant correlation between many of the risk factors and postoperative ejection fraction. The value for the predictor ± the standard error of the estimate likely to yield a postoperative ejection fraction of 0.55 is also shown. Figure 2 demonstrates an especially good correlation ($r = -0.91$) between echocardiographic end-systolic dimension and postoperative ejection fraction.

Discussion

An important finding of this study is that patients with aortic regurgitation and moderate left ventricular dysfunction have an excellent prognosis after valve replacement. Such patients usually experience a postoperative decrease in symptoms and increase in ejection fraction despite the presence of many predictors previously thought to indicate a poor outcome. Thus, we believe that similar patients should not be denied surgery despite the presence of these negative predictors.

Relation to other studies. Our study is consistent with other recent studies (14,15,20–23) that show an improvement in postoperative left ventricular performance in patients with aortic insufficiency. Ejection fraction returned to normal in 85% of our patients after surgery. Average preoperative functional class (2.4) was similar to that (2.6) of an earlier report (24) that examined postoperative change in ejection fraction. Although no statistical comparison can be made, our results seem better than those from that study (24) involving patients examined 10 years ago and in which <50% of similar patients showed a return to normal ejection performance. Improved surgical techniques and possible earlier referral for surgery causing left ventricular dysfunction to be present for a shorter period of time are likely explanations for the improved results (9). Earlier referral for surgery is suggested by the fact that no patients in functional class IV were present for inclusion into our study.

The mechanism by which left ventricular function improved in most of our patients could not be elucidated by our study design. However, the improved ejection performance seen postoperatively almost surely resulted from a decrease in afterload (25) (known to be elevated in patients with aortic regurgitation with reduced left ventricular function [26]), or an increase in muscle function, or both.

Preoperative ventricular function and surgical outcome. A second major finding in our study was that there were significant correlations between postoperative left ventricular performance and various predictors of outcome based on preoperative left ventricular function. Thus, there is an

Table 3. Angiographically Derived Variables: Normal Subjects Versus Patients With Aortic Regurgitation

	EDVI (cc/m^2)	ESVI (cc/m^2)	EF	ESS ($kdynes/cm^2$)
NL	72 ± 4	25 ± 2	0.65 ± 0.02	134 ± 12
AR	198 ± 25	111 ± 18	0.45 ± 0.02	194 ± 6
p Value	<0.001	<0.001	<0.001	<0.001

EDVI = end-diastolic volume index; EF = ejection fraction; ESS = end-systolic stress; ESVI = end-systolic volume index; other abbreviations as in Table 2.

Table 4. Preoperative Risk Factor and Outcome in 14 Patients With Aortic Regurgitation

Patient No.	PCW >12 mm Hg	CI <2.2 liters/min per m²	SF <0.27	EF <0.50	ESD >55 mm	ESDI >26 mm/m²	EDDI >38 mm/m²	ESVI >90 cc/mm²	r/h >3.8	RV/EDV <0.25	Total	Outcome: NYHA Class	Outcome: EF_p
1	X	O	X	X	O	O	O	O	O	X	4	I	0.76
2	X	O	X	X	X	X	X	X	X	X	9	III	0.35
3	O	O	X	O	X	X	X	O	X	O	5	I	0.62
4	O	X	X	X	O	X	O	X	O	O	5	I	0.62
5	X	O	X	X	X	X	O	O	O	X	6	II	0.55
6	O	O	X	O	O	X	X	O	O	X	4	I	0.73
7	X	X	X	X	X	X	X	X	X	X	10	III	0.33
8	O	X	X	X	O	O	O	O	O	X	4	I	0.56
9	O	X	O	O	O	X	X	X	O	O	4	I	0.69
10	X	X	X	X	X	X	X	X	O	O	8	II	0.55
11	O	O	O	X	O	X	X	X	X	O	5	I	0.71
12	O	O	X	X	X	X	O	O	O	O	4	I	0.55
13	X	X	X	X	O	O	O	X	O	X	6	I	0.73
14	X	X	X	X	X	X	X	X	O	O	8	I	0.58
Total	7	7	12	11	7	11	8	8	4	7	82		

CI = cardiac index; EF_p = postoperative ejection fraction; NYHA Class = New York Heart Association functional class; O = absent; PCW = pulmonary capillary wedge pressure; RV/EDV = regurgitant volume divided by end-diastolic volume; X = present; other abbreviations as before.

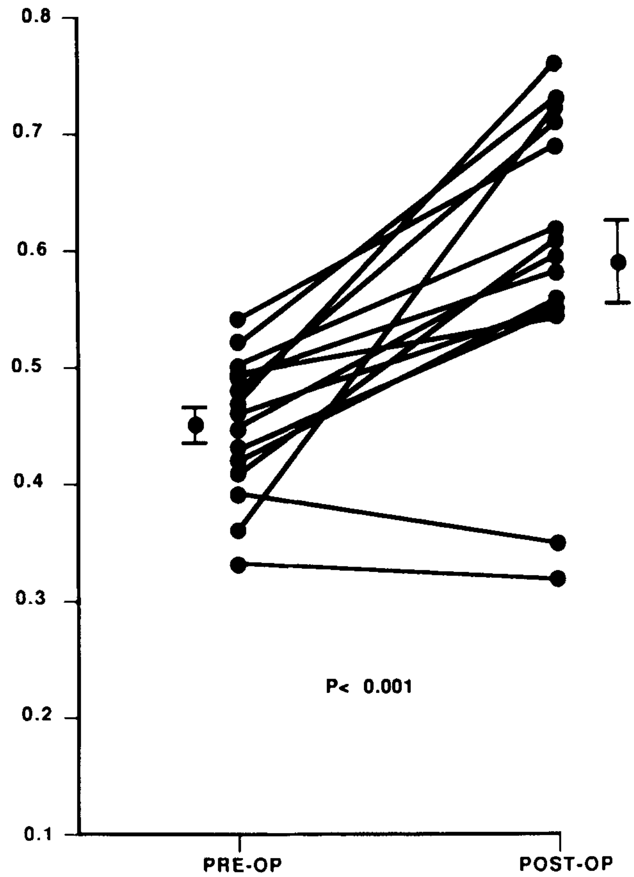


Figure 1. Preoperative (PRE-OP) and postoperative (POST-OP) ejection fraction for 14 patients with aortic regurgitation.

apparent paradox: our patients did well despite the presence of many negative predictors, yet postoperative performance correlated with these predictors. A likely explanation for this paradox is that left ventricular function is a key determinant of surgical outcome, but that improved medical and surgical care have changed the measuring stick—that more left ventricular dysfunction is tolerable before a negative outcome is likely. Thus, our patients were able to exceed the limits of various predictors, but still do well at surgery. Our study confirms the findings of Bonow et al. (23), who also found that preoperative indexes of left ventricular function were still predictive of outcome for aortic valve replacement in the current surgical era. Our study extends their findings and suggests that the preoperative levels for various current predictive indexes are consistent with a normal postoperative ejection fraction. Thus, for example, our regression equation suggests that a preoperative shortening fraction of 0.21 ± 0.04 or a preoperative end-systolic dimension of 60 ± 4 mm are now consistent with a normal postoperative ejection fraction. These new limits must be tested in a prospective manner to be validated.

Table 5. Correlation of Preoperative Risk Factors With Postoperative Ejection Fraction

Risk Factor	r	p Value	V
Pulmonary capillary wedge pressure	−0.29	NS	
Cardiac index	0.23	NS	
RV/EDV	0.43	NS	
End-diastolic dimension index	−0.47	<0.05	39 ± 7
Preoperative ejection fraction	0.55	<0.05	0.45 ± 0.05
r/h	−0.56	<0.05	3.6 ± 0.66
End-systolic volume index	−0.62	<0.05	124 ± 54 cc/m^2
Right atrial pressure	−0.62	<0.05	8 ± 3 mm
End-systolic dimension index	−0.70	<0.01	31 ± 4 mm/m^2
Shortening fraction	0.71	<0.01	0.21 ± 0.04
End-systolic dimension	−0.91	<0.001	60 ± 4 mm

V = value from regression equation (± standard error of the estimate) that predicts a postoperative ejection fraction of 0.55; other abbreviations as before.

Implication of increased right atrial pressure. Additionally, our study found that the objective evidence of right ventricular failure as indicated by an elevated right atrial pressure also correlates negatively with postoperative left ventricular performance. It is likely that elevated right atrial pressure is reflective of severe left ventricular dysfunction leading to right ventricular overload. An alternative explanation for increased right atrial pressure in our patients is that the enlarged left ventricle in aortic regurgitation increased right ventricular stiffness through septal and pericardial interactions. Our study was not designed to resolve this issue.

Limitations. Our study is a small retrospective one and may suffer from the potential biases inherent in such a study. To minimize these biases, the investigator acquiring the preoperative data was blinded to the postoperative results.

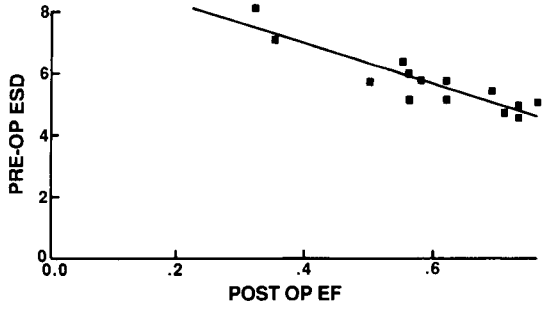
We used postoperative ejection fraction to assess left ventricular function. Although we are aware that ejection fraction is altered not only by contractile function, but also by loading conditions, we used ejection fraction to indicate ventricular performance once aortic valve replacement had lessened the abnormal loading conditions imposed by the aortic insufficiency.

Some problems inherent in our angiographic techniques must be addressed. We used single plane angiography to calculate left ventricular volumes. Although single plane angiography may overestimate cardiac size, especially in the large left ventricle present in aortic regurgitation (27), the appropriate regression equations were used to correct for this problem. Furthermore, our study is comparable with that of Borow et al. (5), who used single plane angiography and who reported end-systolic volume to be a predictive indicator of outcome. Additionally, our pressure and volume data were not recorded simultaneously, but rather pressures were recorded just before ventriculography. This may have resulted in minor discrepancies in the stress calculation, as we have noted previously (26).

Conclusions. Patients with moderate left ventricular dysfunction secondary to aortic insufficiency who have previously noted predictors of a poor outcome have a good prognosis after aortic valve replacement. Despite the apparent improved outcome compared with that in previously reported studies, there is a correlation between preoperative indicators of left ventricular dysfunction and postoperative performance. Thus, we believe that preoperative left ventricular function is still a major determinant of outcome in aortic insufficiency but that the amount of preoperative left ventricular dysfunction that is tolerable has increased.

Although improved medical and surgical care may have increased the level of left ventricular dysfunction consistent with a good result, we are not advocating delay in aortic valve replacement for aortic regurgitation. However, it seems that some patients once thought to be inoperable or operable only with a poor outcome now have a better prognosis.

Figure 2. Preoperative echocardiographic end-systolic dimension (PRE-OP ESD) demonstrated a good negative correlation with postoperative ejection fraction (POST-OP EF). A preoperative end-systolic dimension of 6.0 ± 0.4 cm (60 ± 4 mm, Table 5) predicts a postoperative ejection fraction of 0.55.



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