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Circulation. 2002;106:2687-2693

doi: 10.1161/01.CIR.0000038498.59829.38

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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Outcomes After Aortic Valve Replacement in Patients With Severe Aortic Regurgitation and Markedly Reduced Left Ventricular Function

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Background—Left ventricular dysfunction is an indication for aortic valve replacement (AVR) in patients with severe aortic regurgitation (AR). However, the postoperative outcome of patients with severe AR and a markedly low ejection fraction (EF) is not known.

Methods and Results—The study group consisted of a total of 450 patients who had AVR for isolated AR between 1980 and 1995. Patients with markedly reduced left ventricular function (EF <35%, LoEF, n=43) were compared with those with moderate reduction in left ventricular function (EF 35% to 50%, MedEF, n=134) and those with normal left ventricular function (EF ≥50%, NI EF, n=273). The operative mortality rate was higher with LoEF (14%) than with MedEF and NI EF (6.7% and 3.7%, respectively, $P=0.02$). At 10 years, 41%±9% of LoEF patients had survived compared with 56%±5% and 70%±3% of MedEF and NI EF patients, respectively ($P<0.0001$). Congestive heart failure occurred at 10 years in 25%±9% with LoEF compared with 17%±4% and 9%±2% with MedEF and NI EF, respectively ($P<0.003$). Postoperative EF improved by 4.9%±13.8% in the LoEF group and by 4%±11.9% in the MedEF group compared with -2.3%±10.9% in the NI EF group ($P<0.002$ and $P<0.0001$, respectively).

Conclusions—Patients with severe AR and markedly low EF incur excess operative mortality rates, postoperative mortality rates, and congestive heart failure after AVR. However, postoperative EF improves markedly, and most patients enjoy a long postoperative survival without recurrence of heart failure after AVR; thus they should not be denied the benefits of AVR. (*Circulation*. 2002;106:2687-2693.)

Key Words: aorta ■ regurgitation ■ surgery ■ survival ■ valves

Natural history studies have demonstrated the poor outcome of patients who have a low ejection fraction (EF) and chronic aortic regurgitation (AR) treated conservatively.¹⁻⁴ Although preoperative EF is a determinant of the postoperative prognosis after aortic valve replacement (AVR),⁵ AVR for patients with severe AR currently is recommended when the EF is depressed, even to a mild degree.⁶

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However, the clinical question remains whether it is too late to operate when the EF is severely depressed. The most recent and authoritative guidelines underscore the gaps in our knowledge when recommending AVR for patients with a markedly low EF.⁶ The very definition of thresholds for defining a marked reduction of left ventricular (LV) function in patients with severe AR is unknown, and little is known

about the outcome of patients with such severe reduction because previous studies included few patients with markedly reduced EF.^{5,7,8}

It is unclear how to identify a high-risk group in the setting of severe AR, thus making the treatment and outcome of such patients unclear. For these patients, uncertainty remains regarding treatment options and whether to recommend vasodilator therapy or cardiac transplantation rather than AVR and recent guidelines underscore the need for new data on long-term outcome.⁶

We hypothesized that patients operated on for severe AR and markedly reduced EF incur excessive operative and postoperative risk in comparison with patients with milder LV function reduction. We also hypothesized that rates of postoperative cardiovascular morbidity and mortality are not prohibitive and that AVR improves the clinical status of most of these patients.

Received June 25, 2002; revision received September 4, 2002; accepted September 4, 2002.

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000038498.59829.38

Methods

All patients whose EF was measured before surgery and who had surgery for isolated severe AR at the Mayo Clinic between 1980 and 1995 were eligible. Patients with concomitant procedures such as CABG or ascending aortic surgery associated with AVR were not excluded. One patient had tricuspid valve repair. Exclusion criteria were aortic stenosis, aortic dissection, previous aortic valve surgery, previous or associated mitral valve replacement or repair, tricuspid valve replacement, and congenital disease unrelated to AR. Among 500 patients operated for AR, the 450 with preoperative EF measurement constituted the study group. Patients with markedly reduced LV function (EF<35%, LoEF, n=43) were compared with those with moderate reduction in LV function (EF 35% to 50%, MedEF, n=134) and those with normal LV function (EF≥50%, NI EF, n=273). Baseline symptoms were those occurring within 1 month before AVR. Death occurring within 30 days after AVR or during the same hospital stay was classified as operative death. Thromboembolic events were either transient or permanent neurological deficits identified by the attending physician or neurologist. The median duration of follow-up was 8.1 years. Follow-up was complete up to 2000 or death for 97% of patients.

Echocardiographic and Angiographic Methods

The degree of AR (grade 3 or 4) was determined by composite analysis of either angiography⁹ or color flow Doppler.¹⁰ Echocardiographic measurements obtained during routine clinical studies within 1 month before surgery were prospectively collected and electronically transferred without alteration. Heart diameters were measured by 2-dimensional echocardiography-guided M-mode as previously described.¹¹ LVEF¹¹⁻¹³ and end-systolic wall stress¹⁴ were calculated. LVEF was measured by left ventriculography and echocardiography in 156 patients, echocardiography alone in 250 patients, and left ventriculography alone in 44. When both modalities were used, the average of the 2 values was taken for the EF. The mean difference in EF between modalities was 1% ($P=0.4$). All postoperative studies (n=341) were performed with echocardiography. Median time from surgery to postoperative echocardiography was 11.3 months.

Statistical Analysis

Continuous variables were expressed as mean±SD. Baseline continuous variables were compared among the 3 EF groups (LoEF versus MedEF versus NI EF) by means of ANOVA, whereas categorical variables were compared by means of the χ^2 test. Multivariate logistic models were fit to identify variables associated with operative mortality rates. Overall survival and freedom from events (congestive heart failure and thromboembolism) after AVR were estimated by use of the Kaplan-Meier method. Multivariate Cox proportional hazards models were fit to identify variables associated with long-term outcome. Odds ratios, hazard ratios, and 95% CIs, were reported. EF was used as a continuous and discrete variable (LoEF versus MedEF versus NI EF). Comparisons of outcome were also stratified by association of concomitant surgical procedures (CABG or ascending aorta repair). Comparison of preoperative and postoperative echocardiographic values used paired *t* tests, and that of categorical variables used the Wilcoxon signed rank test. A value of $P<0.05$ was considered significant.

Results

Baseline Characteristics

The cause of AR was bicuspid in 118 patients (26%), rheumatic disease in 62 (14%), endocarditis in 41 (9%), degenerative lesions in 133 (30%), aortic root dilatation in 76 (17%), and miscellaneous causes in 20 (4%). Twenty-two patients (19%) with bicuspid valve required concomitant ascending aortic surgery. Of the 450 patients, 43 had markedly low EF (EF<35%; LoEF group; median 29%; range, 15% to 34%). These patients were compared with 134

patients who had a milder EF reduction (EF 35% to 50%; MedEF group; median 44%; range, 35% to 49%) and 273 patients who had normal EF (EF≥50%; NI EF group; median 59%; range, 50% to 79%). Clinical and echocardiographic variables are summarized in Table 1. Differences in age, sex, and concomitant procedures (40% versus 47% and 47%, respectively, $P=0.65$) among groups was not significant. As expected, LV was larger in LoEF patients than in MedEF and NI EF patients. Patients had severe symptoms (class 3 or 4) more frequently in the LoEF group (58%) than in the MedEF group (49%) and the NI EF group (29%, $P<0.0003$). Conversely, a large proportion of patients had no symptoms in the LoEF group (28%) similar to the MedEF (30%, $P=0.85$) or NI EF group (37%, $P=0.31$).

Operative Mortality

Operative mortality rate overall was 5.5%. Baseline EF, age, associated procedure, and symptoms (New York Heart Association class) were univariately associated with operative mortality rate, but in multivariate analysis, EF and associated procedure were independent determinants of operative mortality rate (both $P=0.02$). Operative mortality rate in each subgroup is indicated in Table 2. Compared with the NI EF group, operative risk was higher with LoEF (adjusted OR, 4.3; 95% CI, 1.4 to 13.9; $P=0.01$). Operative mortality rate in the LoEF group was 14% (versus 3.7% with NI EF) in the overall population but was lower in the subset without associated procedure (7.7% versus 2.1% with NI EF). Operative mortality rate was not significantly different ($P=0.1$) before 1990 versus after 1990, after adjusting for EF.

Postoperative Survival

For all patients, overall survival rate was 82%±2% at 5 years, 63%±3% at 10 years, and 48%±3% at 15 years. Preoperative EF, NYHA class, and age were independent predictors of overall survival (all $P<0.001$).

At 10 years, survival of LoEF patients was 41±9% compared with 56±5% and 70±3% for MedEF and NI EF patients, respectively, and at 15 years, it was 11±9% compared with 41±5% and 56±4%, respectively ($P<0.0001$) (Figure 1). The adjusted hazard ratio for LoEF versus NI EF was 2.4 (95% CI, 1.5 to 3.7, $P<0.001$) and 1.9 (95% CI, 1.2 to 3.1, $P=0.005$) for LoEF versus MedEF. Even after excluding patients with coronary disease, adjusted hazard ratios for LoEF were 2.7 (95% CI, 1.5 to 4.7, $P=0.001$) versus NI EF and 2.1 (95% CI, 1.1 to 3.7, $P=0.01$) versus MedEF. Similarly, after excluding diabetic patients, adjusted hazard ratios were respectively 2.6 and 2.1. Separation of patients with EF≤25% or EF 25% to 35% was not justified as 10-year survival (46±14% versus 39±10%, $P=0.52$) was similar.

Late survival rates (excluding operative mortality rates) for each patient group compared with expected survival are shown in Figure 2. In the LoEF group, late survival rate at 10 years was 48%, or 62% of expected, whereas at 14 years, it was 25%, or only 38% of expected (Figure 2, $P<0.001$). In contrast, 10-year late survival rates were 77% of expected for MedEF and 94% of expected for NI EF. In these two groups, there was also a trend toward late excess mortality rates

TABLE 1. Baseline Characteristics of 450 Patients Who Underwent AVR for AR With Baseline EF Measurement

	LoEF EF <35%	MedE EF 35%–50%	NI EF EF ≥50%	<i>P</i>
No.	43	134	273	...
Female sex, %	19	23	22	0.82
Age, y	58±14	58±15	56±16	0.22
Associated CABG, %	21	25	21	0.63
CAD, %	22	31	23	0.12
CCS class III–IV, %	16	6	9	0.60
Atrial fibrillation, %	23	16	14	0.28
Hypertension, %	35	31	34	0.78
Creatinine, %	1.16±0.26	1.17±0.37	1.24±0.64	0.43
Diabetes, %	16	6	2	0.0002
NYHA class III–IV, %	58	49	29	<0.0001
Echocardiographic variables				
LVD, mm	74±8	70±8	65±9	<0.0001
LVS, mm	61±8	53±7	42±8	<0.0001
EF, %	28±5	43±5	59±6	<0.0001
LVD/WT	6.8±1.4	6.7±1.5	6.1±1.4	0.004
LVS/WT	4.4±1.2	3.4±0.7	2.5±0.6	0.0001
SWST (10 ⁵ · dyne · s ⁻¹)	159±49	122±34	82±30	0.0001

Continuous data presented are mean±SD.

CAD indicates known coronary artery disease; CCS, Canadian Cardiovascular class of angina; NYHA, New York Heart Association functional class; LVD, left ventricular end-diastolic dimension; LVS, left ventricular end systolic dimension; EF, ejection fraction; LVD/WT and LVS/WT, ratio of LV diameter to wall thickness (end-diastolic and end-systolic); and SWST, systolic wall stress.

inasmuch as late survival rates at 14 years were only 71% and 90% of expected, respectively. The hazard ratio compared with expected was 3.2 (95% CI, 2.0 to 5.0, $P<0.001$) for LoEF, 1.7 (95% CI, 1.3 to 2.2, $P<0.001$) for MedEF, and 1.4 (95% CI, 1.1 to 1.7, $P=0.002$) for NI EF.

Morbidity After AVR

Postoperative heart failure rates at 5, 10, and 15 years were 7±1%, 12±2%, and 17±3%, respectively. Preoperative EF was the sole independent predictor of heart failure ($P=0.003$). The 10- and 15-year heart failure rates were 25%

and 50% in LoEF versus 17% and 25% in MedEF and 9% and 10% in NI EF patients ($P<0.003$, Figure 3). The adjusted hazard ratios for LoEF versus NI EF were 3.2 (95% CI, 1.4 to 7.3, $P=0.01$) and 1.7 (95% CI, 0.7 to 3.8, $P=0.2$) for LoEF versus MedEF. In all groups, postoperative NYHA functional class improved after AVR. NYHA class I or II in LoEF, MedEF, and NI EF groups was noted before surgery in 41%, 52%, and 72%, respectively, whereas after surgery it was 80%, 83%, and 87% ($P<0.001$).

Thromboembolism at 5, 10, and 15 years was 10%±2%, 18%±2%, and 23%±3%, respectively. Thromboembolism was not different among groups (at 10 years 23±9%, 24±4%, and 14±3% in LoEF, MedEF, and NI EF groups, respectively, $P=0.13$).

TABLE 2. Operative Mortality Rates for AVR for Severe AR by EF Group and by Associated Procedure Performed

	Overall Population*	No Associated Procedure	Associated Procedure†
No.	450	242	208
Overall population, %*	5.5	3.3	8.8
NI EF, %	3.7	2.1	5.5
MedEF, %	6.7	4.2	9.5
LoEF, %	14	7.7	23.5

LoEF indicates low EF group; MedEF, moderate EF group; and NI EF, normal EF group.

*Both EF and associated procedure performance are independent predictors of operative mortality rates (both $P=0.02$).

†Associated procedure indicates procedure performed simultaneously with AVR for severe AR, either CABG or ascending aortic repair or both.

Postoperative Echocardiography

Postoperative EF showed a trend toward improvement in LoEF patients ($P=0.06$) and significantly improved in MedEF patients ($P=0.002$). A small decrease in EF was observed in NI EF patients ($P=0.005$) (Figure 4). Postoperative end-diastolic and end-systolic dimensions decreased significantly in all groups (Table 3).

Discussion

The present long-term study, spanning almost 20 years, shows that patients with severe AR and markedly low EF (representing ≈10% of AVR for AR) usually have severe

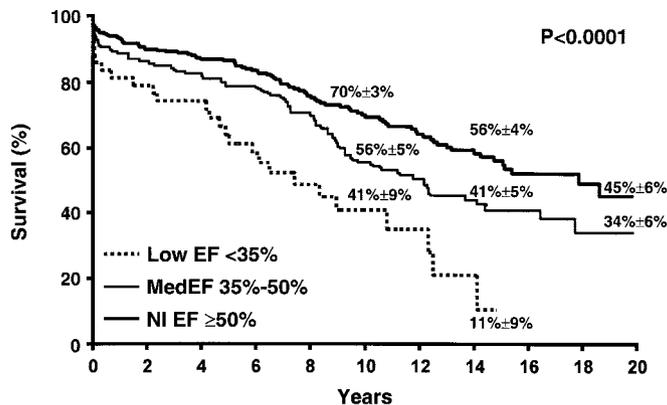


Figure 1. Survival after AVR for the entire study population, with significant AR stratified according to EF. Patients with markedly low EF had significantly lower survival rates than those with normal EF and moderately reduced EF before AVR.

LoEF (EF <35%)	43	35	31	21	15	8	6	3		
MedEF (EF 35%-50%)	134	115	108	95	78	50	34	30	19	9
NI EF (EF ≥50%)	273	245	231	184	141	112	83	60	32	17

symptoms but may also be asymptomatic. These patients have higher operative and postoperative long-term mortality rates and heart failure risk than patients with milder or no decrease in EF. However, in patients with a low EF, operative mortality rate, although increased, is not overwhelming (14% overall and 7.7% without associated procedure), and late survival, although reduced, represents 62% of expected survival. Patients with markedly low EF have higher long-term likelihood of postoperative heart failure, but at 10 years only a minority of patients (25%) had this complication. Also, there is no excessive risk of thromboembolism. A mechanistic explanation for the relatively low rate of heart failure is the postoperative EF improvement, which is greater in these patients than in those with better preoperative EF. Thus, although a markedly decreased preoperative EF is a predictor of worse postoperative outcome, surgery should not be contraindicated for most patients who have severe AR and markedly low EF because the majority can enjoy years of survival and symptomatic improvement.

Characteristics of AR and Markedly Low EF

Patients with a markedly low EF represent a minority (10%) of patients with severe AR. In previous studies, small sample sizes prevented this specific subgroup from being defined. Importantly, our data show that the severe LV function

reduction cannot be ascribed to advanced age or excessive coronary disease, atrial fibrillation, or hypertension. A higher prevalence of diabetes mellitus in the LoEF group suggests that it may have a role in the reduction of LV function, albeit in a small number of patients. Another important observation is the markedly increased LV wall stress with LoEF. This excessive afterload emphasizes the combination of volume and pressure overload in AR and explains in part the LV function improvement after the overload has been relieved by AVR. Another important observation is that patients with LoEF often remain asymptomatic, emphasizing the insidious development of LV dysfunction in AR and the need for frequent LV function assessment to detect deterioration before a marked reduction occurs, which has severe consequences even after successful AVR.

AR and Markedly Reduced EF: Outcome Implications

The risks attached to a markedly low EF in patients operated on for severe AR have not been well described. The most recent guidelines have underscored⁶ the relative consensus that a low EF generally appears to affect outcome.⁷ However, these guidelines also emphasized gaps in knowledge regarding patients with markedly reduced LV function and the difficulty in making recommendations because of this lack of

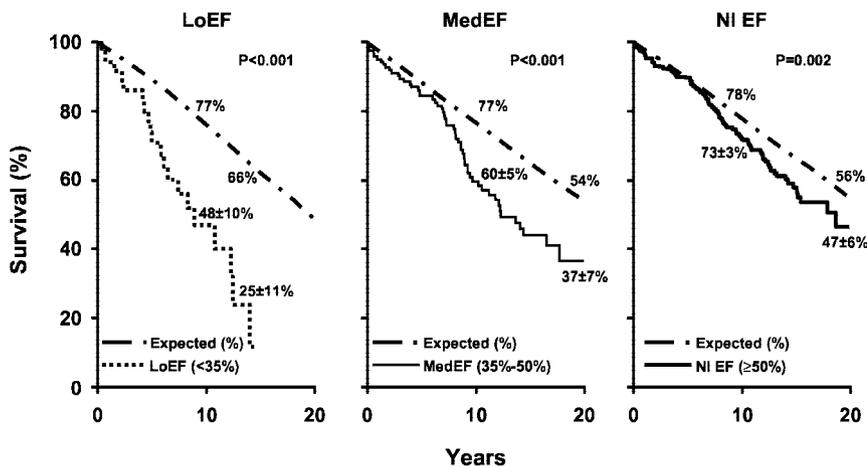


Figure 2. Late survival after AVR for each group (low ejection fraction [LoEF], moderate EF [MedEF], and normal EF [NI EF]), based on preoperative EF compared with expected survival of an age- and sex-matched 1990 US white population.

TABLE 3. Comparison of Preoperative and Postoperative Echocardiographic Variables

	LoEF EF <35% (n=43)			MedEF EF 35%–50% (n=134)			NI EF EF ≥50% (n=273)		
	Preop	Postop	Change	Preop	Postop	Change	Preop	Postop	Change
EF, %	29±6	34±14*	4.9±13.8†	43±6	47±12‡	4±11.9§	58±7	56±10‡	−2.3±10.9
LVD, mm	74±8.3	63±10‡	−10.3±10.4	70±8.3	57±9.2¶	−14.4±9.5	65±8.7	53±7.4¶	−13.1±8.4
LVS, mm	61±8	51±13‡	−8.5±12.3	53±7	41±10¶	−12.4±9.6†	42±8	35±7.9¶	−8.3±7.9
LVD/WT	6.8±1.4	5.1±1.5‡	−1.2±1.1	6.7±1.5	4.8±1.1¶	−1.9±1.3	6.1±1.4	4.6±1¶	−1.6±1.5
LVS/WT	4.4±1.2	3.2±1.2‡	−1.3±1.2#	3.4±0.7	2.4±0.6¶	−1.1±0.8†	2.5±0.6	2±0.6¶	−0.6±0.7
SWST, 10 ⁵ · dyne · s ^{−1}	159±49	105±49.3‡	−53.7±52.8#	122±34	74.2±25.7¶	−47.6±36.5†	82±30	61±24¶	−27±32

Data presented are mean±SD. Abbreviations as in Table 1.
 Postoperative values compared with preoperative values: **P*<0.06; †*P*<0.05; ‡*P*<0.001.
 Compared with NI EF group: ||*P*=NS; #*P*<0.05; †*P*<0.01; §*P*<0.0001

data.⁶ A major finding of our study is that patients with markedly low EF (<35%) and severe AR constitute a high-risk group even after successful surgery. These patients with LoEF compared with NI EF have excessive operative mortality rates (OR, 4.3) and long-term mortality rates (risk ratio, 2.3). Even excluding operative mortality rates, the risk ratio to expected mortality rate is 3.2 versus 1.4 in NI EF. For late morbidity after AVR, earlier studies have provided either no^{4,7,15} or limited information.^{8,16} Even in studies with data on morbidity, specific information is not available about patients with markedly reduced EF.^{8,16} In our study, long-term morbidity after AVR is dissociated in the subgroup with LoEF, increased for heart failure, but similar for thromboembolism. Therefore, our study establishes for the first time that patients with markedly reduced EF and severe AR represent a high-risk group even after successful AVR. In view of this high risk, AVR ideally should be performed before such a severe decrease in EF occurs. However, for patients who have AR and already have severe LV dysfunction, an important issue to consider is whether AVR represents too high a risk and conservative treatment is preferable.

Natural history studies have focused mainly on asymptomatic patients with normal function, but recent data show that

the outcome with conservative treatment of patients with even mild LV dysfunction is poor. Indeed, patients with either EF <55% or LV systolic dimension ≥25 mm/m², even if asymptomatic at presentation, have excessive long-term mortality rates if treated conservatively.⁴ Although patients with severe LV dysfunction could not be analyzed specifically, the uniform risk increase with decreasing EF under conservative treatment^{1–4} suggests that such patients are at very high risk if not operated on and that an aggressive approach is justified.

The balance of benefits and risks of AVR versus alternative treatment strategies in this subgroup is unknown. Vasodilators are effective in patients with asymptomatic AR and normal LV function.¹⁷ However, the value of this treatment is unclear in patients with LV dysfunction and severe AR because vasodilators have not been tested in this subset. Hence, this treatment is not considered an alternative to surgery.⁶ The value of a short course of vasodilator treatment preceding surgery is unknown, but this approach may be considered.⁶ Cardiac transplantation is an option, as results have improved considerably.¹⁸ However, delay caused by

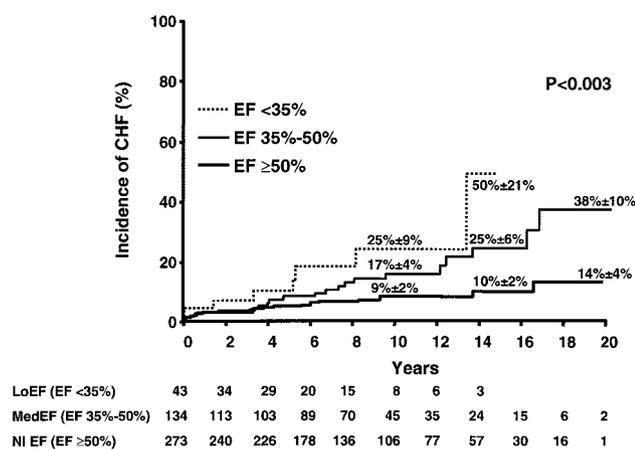


Figure 3. Congestive heart failure (CHF) after AVR in the entire study population with significant AR, stratified according to EF. Patients with markedly low EF had a higher rate of CHF than patients who had moderately reduced or normal EF before AVR.

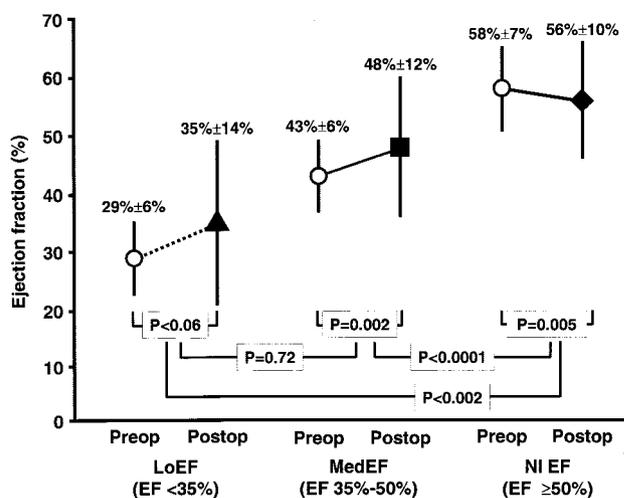


Figure 4. Ejection fraction improved significantly in patients who had lower preoperative EF (groups LoEF and MedEF). There was a slight decrease in EF in patients with normal EF (NI EF).

short organ supply may further aggravate the condition. Furthermore, the morbidity of transplantation limits its applicability in this context.

Conversely, although patients with a markedly low EF and severe AR are at high risk, their medium-term outcome is not uniformly ominous. The usual operative mortality rate reported for AVR ranges from 1% to 7%.^{4,7,8,15} Our study undeniably shows excessive operative mortality rates among patients with markedly low EF, but it is not overwhelming, particularly for patients not requiring associated procedures (7.7%). Most importantly, our data indicate that a majority of patients remain free of heart failure 10 years after AVR. Therefore, a notable period of event-free survival can be achieved in most patients after correction of AR despite their very low preoperative EF. The functional status of most patients improves after surgery, irrespective of preoperative EF. Thus, a markedly low EF (<35%) is not, in our judgment, a contraindication to AVR.

Cursory comparison of outcome after AVR for severe AR and low EF to that of patients with nonvalvular LV dysfunction treated medically¹⁹ suggests lower complication rates in patients with AR. A major reason for such a lower complication rate is that LV size and EF improve after AVR. This improvement is in stark contrast to the situation with mitral regurgitation,²⁰ in which EF usually decreases after surgery, even after valve repair.^{21,22} Conversely, with a similar volume overload, EF generally improves after AVR for AR, probably because of afterload reduction measured as systolic wall stress.²⁰ Therefore, patients with a low EF and markedly increased wall stress are likely to benefit from decrease in wall stress with notable EF increase (5 percentage points on average) after surgery.¹⁵ Improvement in EF is not uniformly distributed,²³ and patients with depressed EF before surgery improve the most after surgery.

Study Limitations

Preoperative EF measurement by echocardiography can be viewed as a limitation but is a powerful predictor of outcome.^{2,4,15,21} The thresholds selected can be debated but are similar to those used in previous studies of AR⁶ and to those used as criteria for markedly low EF in major clinical trials.^{19,24} Furthermore, the outcome of patients with EF 25% to 35% was not better than that of patients with EF <25%. Therefore, patients with EF <35% should be considered to have markedly low EF and to be at high risk. Not all patients underwent postoperative echocardiography. It is not possible to speculate on reasons for not performing postoperative echocardiography or for not returning for follow-up, but patients with and without postoperative echocardiography are similar in many aspects. They have similar preoperative EF (52±12 versus 51±12%, $P=0.56$) and similar distribution of coronary disease ($P=0.83$), sex ($P=0.79$), and age ($P=0.15$). Preoperative symptoms ($P=0.63$) and history of heart failure were similar ($P=0.29$). Remarkably, the distribution of patients without postoperative echocardiography was similar across preoperative EF groups ($P=0.81$) and does not appear to reveal a bias.

The role of better medical therapy in improving survival of patients with reduced EF cannot be addressed in our study. There was no difference in survival with and without vasodilators, but the present study is not a clinical trial, and their potential benefits should not be denied on the basis of our data.

Although there was no difference in age among groups, extension of our data to older patients should be done cautiously, and comorbid conditions should be assessed carefully before proceeding with AVR.

Conclusions

In patients with severe AR, those with markedly reduced EF represent a high-risk group, even after successful AVR, and should preferably be operated on before such an advanced LV dysfunction occurs. However, after AVR, mid-term symptom-free survival is obtained in most patients. Hence, a marked EF reduction should not be considered a contraindication to AVR for severe AR.

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