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# Aortic Valve Replacement in True Severe Aortic Stenosis with Low Gradient and Low Ejection Fraction

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## ABSTRACT

**Objective.** The results of aortic valve replacement are uncertain among patients with severe aortic stenosis, reduced left ventricular ejection fraction, and low mean transvalvular gradient. The aim of the present study was to report on 27 patients who underwent surgery for aortic stenosis with left ventricular ejection fraction ≤30% and mean transvalvular gradient <30 mmHg.

**Methods.** The study was performed between January 2000 and December 2005. Twenty-seven patients with aortic stenosis with a calculated valve area <1.0 $cm^2$, aortic mean transvalvular gradient <30 mmHg, and ejection fraction ≤30% were studied. Exclusion criteria were coronary artery disease, concomitant valvular operation, previous aortic valve replacement, or more than moderate aortic valve regurgitation. Preoperative clinical, echocardiography and dobutamine echocardiography, cardiac catheterization and coronary angiography, and operative data were recorded in all patients. Patients who were diagnosed with true aortic stenosis were divided into 2 groups according to left ventricular ejection fraction changes during dobutamine echocardiography, 16 with recruitable myocardium (group 1) versus 11 without (group 2).

**Results.** One patient from group 2 died. The functional capacities of all of the patients in group 1 significantly improved in the postoperative period ($P$ = .001). All of the patients except for 1 in group 1 had improved left ventricular ejection fraction after the operation ($P$ <.001). The comparison of the preoperative and postoperative functional status of these patients in group 2 was also statistically significant ($P$ = .001). The 10 of the 11 patients in group 2 who were alive had left ventricular ejection fraction value changes that were not significant statistically ($P$ = .096). The comparison of the improvement of functional capacities of the groups revealed a significant difference; that is, the improvement was higher in group 1 ($P$ = .039).

**Conclusion.** Left ventricular ejection fraction and functional capacity improved after aortic valve replacement in patients with left ventricular dysfunction, low mean transvalvular gradient, and aortic valve replacement in these patients has acceptable mortality rates with significantly improved functional status.

## INTRODUCTION

Aortic stenosis (AS) is a common valvular heart disease associated with life-threatening complications and a mortality rate up to 90% in a 2-year natural history of symptomatic patients. Left ventricular (LV) hypertrophy and heart failure are independent risk factors for overall mortality as well as for sudden cardiac death [Gradman 1981; Aronow 1993; Aronow 1994; Sharma 2004]. For patients with severe AS in the presence of severe LV dysfunction and a mean transvalvular gradient (mTVG) <30 mmHg, the benefits of aortic valve replacement (AVR) remain controversial [Pereira 2002]. AVR is the only effective treatment, but the operative risk increases with the development of LV systolic dysfunction [Connolly 2000].

The results of AVR are uncertain among patients with severe AS, reduced LV ejection fraction (LVEF), and low mTVG. Although these patients represent 5% of the patients with AS, increased perioperative risk and reduced late outcome compared with controls have been reported in patients with reduced LVEF [Connolly 1991]. LV dysfunction may be secondary to longstanding severe AS with superimposed myocardial fibrosis, extensive coronary artery disease, or prior myocardial infarction, and in this situation, the LV dysfunction is not likely to improve after AVR. Some have therefore suggested that AVR should not be considered in this subgroup of patients [Carabello 1991]. Few data are available on the clinical outcome of patients with AS, decreased LVEF, and low mTVG who undergo AVR.

In patients with anatomically severe AS and a low LVEF, AVR will relieve symptoms and improve survival. However, a subset of patients who present with low-output, low-gradient AS and a small calculated valve area may not have true severe, fixed AS but rather a concomitant cardiomyopathy and only mild AS. In such patients, the calculated effective valve area

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may be small because of inaccuracy of the standard valve area formula at low flow states or because of a lack of contractile force to fully open the aortic valve area (AVA) [Nishimura 2002]. The pressure gradient and the calculated AVA are flow-dependent; they may be disproportionately reduced in patients with LV dysfunction and may reflect the presence of low transvalvular flow rather than significant valvular disease [Schwammenthal 2001].

In the present study, we aimed to report the surgical outcomes of 27 patients whom we operated on for AS with LVEF ≤30% and mTVG ≤30 mmHg.

## PATIENTS AND METHODS

The study was approved by the local ethics committee. Between January 2000 and December 2005, 27 patients who met the inclusion criteria were included in the study. Inclusion criteria were diagnosis of AS with a calculated valve area of <1.0 $cm^2$ by the continuity equation, aortic mTVG <30 mm Hg, and LVEF ≤30%. The patients were prospectively sent to dobutamine echocardiography so that a clinical decision for aortic valve operation could be made [Nishimura 2002].

Patients were excluded if they had coronary artery disease, concomitant valvular operation other than AVR, previous AVR, or more than moderate aortic valve regurgitation [Connolly 2000]. Preoperative clinical, echocardiography and dobutamine echocardiography, cardiac catheterization and coronary angiography, and operative data were recorded in all patients.

### *Dobutamine Echocardiography Protocol*

The American College of Cardiology/American Heart Association guidelines for the management of valvular heart disease recommend the use of dobutamine challenge to differentiate between patients with true severe AS and those with a low cardiac output and only mild AS by examining the response of the aortic valve gradient, stroke volume, and valve area [Task Force on Practice Guidelines 1998].

Dobutamine infusion was started at 5 μg/kg per minute and was increased by increments of 5 μg/kg per minute every 5 minutes. The predetermined end points were a maximal dose of 30 μg/kg per minute, mean gradient >40 mmHg, 50% increase in the cardiac output, heart rate >140 beats per minute, or intolerable symptoms or side effects [Nishimura 2002]. Hemodynamic assessment of AS was performed by 2-D/Doppler methodology, and AVA was calculated by the continuity equation [Connolly 2000].

### *Definitions*

*AS Severity*. AS was defined as severe when the augmentation of systolic flow caused by the dobutamine infusion was paralleled by an increase in the maximal orifice velocity on the continuous-wave Doppler signal, so that the calculated AVA did not increase by >0.29 $cm^2$ and remained <1.0 $cm^2$. AS was defined as nonsevere when systolic flow increased more than the maximal orifice velocity, because the effective AVA had increased by at least 0.3 $cm^2$ to at least 1.0 $cm^2$ [Schwammenthal 2001]. These patients were excluded from the study.

*Contractile Reserve*. Contractile reserve was defined as being preserved when the systolic flow could be increased by >20% of the baseline values (requiring at least the preservation of stroke volume) as the ejection time decreases during dobutamine infusion [Schwammenthal 2001].

### *Preoperative Findings*

Patients who were diagnosed with true AS were divided into 2 groups according to LVEF changes during dobutamine echocardiography, 16 with recruitable myocardium (group 1) versus 11 without (group 2). LVEF ratios measured by echocardiography and New York Heart Association (NYHA) functional status of patients are seen in Table 1 and Table 2. The mean age of the patients was 59.3 ± 10.9 years (range, 39-79 years) and 55.4 ± 13.6 years (range, 36-76 years) for groups 1 and 2, respectively. There was only 1 female patient in each group. There was 1 diabetic patient in group 2 and no one had diabetes in group 1. The clinical data of the patients are seen in Table 1.

### *Surgical Technique*

Under general anesthesia, median sternotomy was performed. All operations were performed under moderate degree hypothermia with a nasopharyngeal temperature of 28°C. After cross clamping the ascending aorta, we accomplished cardiac arrest with antegrade infusion of isothermic hyperkalemic blood cardioplegia. Arrest was maintained by a continuous retrograde infusion of maintenance cardioplegia [Yilik 2004]. All AVRs were done by bileaflet mechanical heart valve prosthesis.

Table 1. Clinical Data of the Groups

| | Group 1 (n = 16) | Group 2 (n = 11) | *P* |
|---|---|---|---|
| Age | 59.3 ± 10.9 | 55.4 ± 13.6 | .443 |
| Male:Female | 15:1 | 10:1 | 1.000 |
| Hypertension | — | — | — |
| Diabetes | — | 1 | .407 |
| Peripheral arterial disease | — | — | — |
| Chronic obstructive pulmonary disease | 1 | — | 1.000 |
| Smoking | 4 | 2 | 1.000 |
| Cerebrovascular disease | — | — | — |
| Carotid artery disease | — | — | — |
| Ventilator support | 10.0 ± 3.3 | 13.3 ± 7.5 | .171 |
| Transfusion | 1.5 ± 0.6 | 1.72 ± 1.0 | .559 |
| Revision | — | — | — |
| Reintubation | 1 | — | 1.000 |
| Intra-aortic balloon pump support | 1 | 1 | 1.000 |
| Intensive care unit follow-up | 2.4 ± 0.9 | 2.5 ± 0.9 | .386 |
| Length of postoperative hospital stay | 6.5 ± 2.4 | 6.9 ± 1.4 | .202 |
| Mortality | — | 1 | .407 |
| Implanted valve size | 22.5 ± 1.7 | 22.5 ± 1.6 | .854 |
| Body surface area | 1.78 ± 0.08 | 1.80 ± 0.07 | .656 |

Table 2. Left Ventricular Ejection Fraction Ratios Measured by Echocardiography and New York Heart Association Functional Status of Patients

| | Group 1 Preoperative | Group 2 Preoperative | Group 1 Postoperative | Group 2 Postoperative |
|---|---|---|---|---|
| Mean base line LVEF, % | 26.5 ± 2.8 | 26.1 ± 3.2 | 32.8 ± 4.8 | 28.9 ± 5.0 |
| Mean max LVEF elevation by dobutamine, % | 32.6 ± 3.6 | 26.6 ± 3.1 | Not performed | Not performed |
| NYHA I | — | — | 9 patients | — |
| NYHA II | — | — | 7 patients | 6 patients |
| NYHA III | 12 patients | 6 patients | — | 3 patients |
| NYHA IV | 4 patients | 5 patients | — | 1 patient |

*LVEF indicates left ventricular ejection fraction; NYHA, New York Heart Association.

### *Statistical Analysis*

Statistical analysis was done with a SPSS 10.0 statistical software program (SPSS, Chicago, IL, USA). Continuous variables were expressed as the mean ± 1 standard deviation. The preoperative and postoperative LVEF differences of the groups were compared by Wilcoxon signed rank test. The preoperative and postoperative NHYA functional capacities of the groups were compared by chi-square test. The preoperative and postoperative LVEF values of the groups were compared by the Mann-Whitney *U* test. *P* values less than .05 were considered to be statistically significant.

## RESULTS

One patient in group 2 died in the early postoperative period due to low cardiac output. Other patients were discharged an average of 10 days after the operation. All patients were examined on the first postoperative month. On the sixth postoperative month, the patients were evaluated with echocardiography. The data of the patients are seen in Table 2.

The functional capacities of all of the patients in group 1 significantly improved in the postoperative period ($P = .001$). All of the patients except for 1 in group 1 had improved LVEF after the operation. This improvement was statistically significant when the preoperative and postoperative LVEF values were compared ($P < .001$).

Of the 10 surviving patients in Group 2, 8 had functional status improvement in the postoperative period. The improvement of the functional status of these 8 patients was also statistically significant ($P = .001$). However, when we compared the LVEF improvement of all 10 patients in group 2 the LVEF value changes were not statistically significant ($P = .096$).

The comparison of the improvement of functional capacities of the groups revealed a significant difference; that is, the improvement was higher in group 1 ($P = .039$).

## DISCUSSION

Perioperative mortality and morbidity rates are high in patients with AS and LV dysfunction who also have relatively low transvalvular pressure gradients [Schwammenthal 2001]. In severe AS, the LV compensates for chronic pressure overload by hypertrophy in an attempt to normalize the wall stress. Initially, LVEF and cardiac output are maintained. When the wall stress exceeds the compensating mechanisms, LV systolic function declines secondary to afterload mismatch, and the mean pressure gradient generated by the LV may be low despite the presence of severe AS. LV function and mean aortic valve gradient are prognostic indicators of outcome among patients undergoing AVR for AS [Morris 1993; Connolly 1997]. However, the outcome of AVR among patients with LV dysfunction and low transvalvular mean gradient has not been well characterized [Connolly 2000].

AVR decreases the ventricular afterload, consequently leading to myocardial adaptation and regression of hypertrophy [Pantely 1978]. Most of the reports are in clear agreement on the improvement of EF after surgery. However, some studies have shown the opposite effects and thus denied the concept of AVR before the onset of symptoms [Henry 1980]. AS has the highest prevalence in the elderly population and is often associated with secondary cardiac diseases. It is conceivable that the rate of change of LVEF is influenced by multiple factors. The study by Connolly and associates showed 21% perioperative mortality in the patients with low preoperative LVEF and low systolic gradient [Connolly 1997]. We excluded the patients with coronary artery disease from the study because coronary artery disease directly affects the LVEF of the patients.

Although AS patients with preoperative low LVEF and secondary cardiac diseases constitute a small subset and seem to have relatively higher surgical mortality, these patients should not be denied AVR only on the basis of low LVEF. The LV mass regression is an independent (of age, sex, or types of valve substitutes) and the most consistent effect of valve replacement [Sharma 2004].

In patients with documented severe valvular AS and LV dysfunction, aortic valve operations can be performed with low mortality and excellent results [Ross 1976]. Patients with true fixed AS must be differentiated from those with a primary myocardial process and only mild AS [Nishimura 2002]. There is a subset of patients with AS and LV systolic dysfunction who present with a low mean aortic valve gradient and have a poor outcome after an aortic valve operation [Carabello 1997]. The poor outcome in this subset may have been due to the inclusion of patients who had a primary contractile dysfunction that is responsible for the low ejection fraction and low cardiac output. In these patients, there may be only a mild degree of AS, which results in a small calculated valve area for several reasons. The low output reduces the valve-opening forces, and so a mildly stenotic valve may have limited mobility [Nishimura 2002].

Connolly and colleagues reported that AVR for AS decreased ventricular afterload. LVEF was expected to improve after AVR among patients with severe AS and decreased preoperative LVEF [Connolly 2000]. Those who did not improve probably had permanent myocardial fibrosis. Previous studies have shown that decreased preoperative LVEF and low preoperative aortic valve gradient were associated with decreased postoperative LVEF [Carabello 1997; Connolly 2000]. The present study suggests similar results. The LVEF values of the patients significantly increased in the patients who had increased LVEF and decreased relative AVA in the preoperative dobutamine echocardiography. Similarly, there was a significant improvement in the functional capacities.

Smith et al reported 19 patients with severe AS and severely reduced LVEF [1978]. They found an operative mortality rate of 21% with a 3-year survival rate of 74 ± 10%, with 13 of the survivors changing NYHA classes from III–IV to I–II and based upon these results, they recommended AVR in this patient group [Smith 1978]. A subsequent study by Carabello et al confirmed these findings in 14 patients by finding an operative mortality rate of 21%, with 10 of the 11 surviving patients undergoing functional NYHA class improvement from NYHA class III–IV to I–II [Carabello 1980]. Subsequently, Connolly et al in their study of 154 patients found an operative mortality rate of 9% with the majority of patients improving their functional NYHA class after surgery, thereby supporting earlier studies [Connolly 1997]. In another study of 112 patients with critical AVR and NYHA class III and IV failure, Obadia et al found only a 7% operative mortality rate and a 5-year survival rate of 77% [Obadia 1995].

AVR should be undertaken in patients with AS and depressed function despite the high perioperative mortality rate around 20% at most centers, because patients who survive have substantial symptomatic improvement. In 2 studies, the survival rate at 5 years has been shown to be approximately 70%, which was better than the 2-year life expectancy in medically treated patients [Paul 2004].

A more controversial subset of patients with severe AS is those who also have LV dysfunction (EF ≤35%), as well as a low transvalvular gradient (valve gradient ≤30 mm Hg). In this subset of patients, LV dysfunction may be secondary to superimposed myocardial fibrosis from longstanding AS or prior ischemic cardiac disease and hence irreversible and not rectifiable by AVR. In the initial study by Carabello et al, of the 4 patients in their study who met these criteria, 3 died in the perioperative period and the other did not improve symptomatically [Carabello 1980]. Hence, AVR was not recommended for this patient population. A recent study by Connolly et al examined the results of AVR in this most controversial group of patients [Connolly 2000]. In their series of 52 patients, the operative mortality rate was 21%, with 3- and 5-year survival rates of 71% each for those without coronary disease, and 58% and 29%, respectively, for those with coronary disease. Most patients in the study also had symptomatic improvement, with 77% of surviving patients at follow-up improving by greater than 1 functional NYHA class. AVR was recommended in this subset despite the high operative mortality as the majority of surviving patients had symptomatic improvement.

Monin et al used dobutamine echocardiography to differentiate between those patients with severe AS, LV dysfunction, and a low transvalvular gradient with irreversible myocardial damage versus those with "afterload mismatch" and hence reversible myocardial dysfunction from the pressure-overloaded state of AS [Monin 2001]. Dobutamine echocardiography allows the determination of AVA in 2 different flow states (baseline and dobutamine), so that severe AS that is fixed can be distinguished from AS that is flow dependent. Those patients with flow-dependent AS will demonstrate a decrease in valve area with the increased flows caused by the enhanced inotropic-mediated contractile state. In these patients, AVR is more likely to be beneficial as the depressed contractility is due to increased afterload [Monin 2001; Paul 2004]. The operative mortality rate was 8% in those patients with contractile reserve and 50% in those without. In comparison to medical therapy, at a median follow-up of 24 months, AVR patients had improved long-term survival. In contrast, those patients with no contractile reserve had a poorer prognosis when compared with medical therapy. This study, along with that of Pereira et al [2002], clearly demonstrates a survival benefit with AVR in comparison to medical therapy in this high-risk patient population.

Nishimura et al identified 32 patients with NYHA class III–IV heart failure, "critical" AS, and low LVEF (<40%) [Nishimura 2002]. Twenty-one of these patients underwent surgery at the discretion of the treating physicians. Patients with preserved systolic function (n = 15), which was defined as >20% increase in stroke volume, were found to have better outcomes than those who did not. The operative mortality rate was 7% in patients with contractile reserve (n = 15), compared to 33% in patients without reserve (n = 6). At follow-up, all of the survivors in the group with preserved systolic function had improved symptoms and were NYHA class I–II, while 2 more patients in the other group had died because of progressive heart failure. We operated on the 11 patients who did not have contractile reserves. The postoperative LVEF of these patients did not improve. Postoperative values remained the same as the preoperative values. However, the functional capacities of these patients significantly improved except for one. Although differentiation of no severe AS in patients with low LVEF and low mTVG but recruitable myocardium is possible with dobutamine echocardiography, this is impossible in patients with nonrecruitable myocardium. Whether the cusps are flexible or not, the AVA does not increase because the stroke volume does not increase. It should be kept in mind that correction of AS would decrease the afterload and the wall stress even in these patients. The reports suggest that the perioperative mortality decreased in the patients with low LVEF and low transvalvular gradient. This can be related to advances in surgical techniques, improvements in valve prostheses and related hemodynamic variables, anesthetic monitoring, and the use of new inotropes, such as phosphodiesterase inhibitors [Pereira 2002]. The perioperative mortality rate in our study population seems to be lower than the previously

reported studies. No mortality occurred even in the patients with recruitable myocardium.

Paul and coworkers reported that AVR could be performed safely in a patient population with low gradient, low LVEF [Paul 2004]. AVR in patients with contractile reserve led to symptomatic improvement and short- and long-term survival benefit in comparison to medical therapy. They discussed whether AVR should have been recommended in patients with AS and a valvular cardiomyopathy with LV function ≤35% or NYHA class III or IV symptoms as opposed to heart transplantation. Most patients in this subgroup were elderly and hence generally not candidates for heart transplantation. Thus, AVR should have been recommended for these elderly patients as long as dobutamine echocardiography showed evidence of contractile reserve. For those patients younger than 65 years of age, heart transplantation was typically associated with 1-year survival rates of 70% to 80% and 5-year survival rates of 60% to 70% for all patients. The transplantation survival rates, however, were similar to the survival rates reported by Monin [2001] and Pereira [2002] for AVR in a considerably more elderly population with a median age of 70 years for both studies. They reported that survival benefit from AVR was probably greater in patients less than 65 years old, as the survival data came from a considerably older set of patients who were likely to have more comorbidities. Furthermore, by having AVR as the first operation, transplantation would remain an option should symptoms progress. Our study population in both groups included patients who were advanced in age and were not candidates for transplantation.

In conclusion, LVEF and functional capacity improve after AVR in patients with LV dysfunction, low mTVG, and AS but with augmentable LV performance with dobutamine. On the other hand, AVR has acceptable mortality rates in patients with limited LV reserves, and among these patients, it is associated with significantly improved functional status.

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