Aortic valve replacement in isolated severe aortic stenosis with left ventricular dysfunction: long-term survival and ventricular recovery

Sol ventrikül disfonksiyonunun eşlik ettiği izole ileri aort darlığına aort kapağı replasmanı: Uzun dönem sağkalım ve ventriküler düzelse

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ABSTRACT

Objective: The aim of this study was to assess the effects of aortic valve replacement (AVR) on the recovery of left ventricular function and the predictors for long-term survival in patients suffering from isolated severe aortic stenosis (AS) with a significant left ventricular dysfunction (LVD).

Methods: This retrospective study was conducted on 46 patients with isolated severe AS and LVD (left ventricular ejection fraction (LVEF) ≤ 40%) who underwent AVR in our clinic between January 1993 and March 2006. Patients with coronary artery disease, with more than moderate aortic regurgitation (>2), with previous valve replacement or repair, and with other valve pathologies were excluded. The mean aortic valve area was 0.7±0.09 cm². The following fourteen variables were analyzed: etiology, age (≥70 years), sex, preoperative New York Heart Association (NYHA) functional class, chronic obstructive pulmonary disease, hypertension, diabetes, peripheral arterial disease, chronic renal insufficiency, need for concomitant procedures for the ascending aorta, cardiopulmonary bypass time ≥120 min, aortic cross-clamp time ≥90 min, intraaortic balloon pump support and inotropic support. Statistical analysis for comparison of pre- and postoperative changes in clinical and functional variables was performed using Wilcoxon rank test. The predictors of early mortality after AVR were analyzed using logistic regression analysis and late survival was studied using Cox proportional regression and Kaplan Meier survival analyses.

Results: Operative mortality was 8.6% with four patients. As the result of univariate logistic regression analysis, preoperative NYHA functional class ≥3 was found to be predictive of early mortality. Patients with NYHA class ≥3 had 12.6 times (OR: 12.6; 95%CI: 1.2-131.3; p=0.035) higher probability of early mortality than those with a lower NYHA class. However, multivariate logistic regression analysis demonstrated no predictor for early mortality. A positive change was observed in the LVEF in 79.3% of survivors and the mean LVEF increased from 34.5±3.9% to 44.7±10.4% (p<0.001). There were eight (19%) late deaths. Actuarial survival was 83.1±5.9% at 5 years and 59.6±10.9% at 10 years. Cox proportional hazards regression analysis demonstrated diabetes mellitus (HR: 6.6; 95% CI: 1.19-36.9, p=0.031) and intraaortic balloon pump use (HR: 10.7; 95% CI: 2.9-39.7, p<0.001) as significant predictors for late mortality.

Conclusion: Left ventricular ejection fraction and symptoms improve after AVR in patients with isolated severe AS and LVD with an acceptable operative mortality and satisfactory long-term survival. (Anadolu Kardiyo Derg 2009; 9: 41-6)

Key words: Aortic stenosis, left ventricular dysfunction, aortic valve replacement, survival, predictive models

ÖZET

Amaç: Bu çalışmada belirgin sol ventrikül disfonksiyonunun eşlik ettiği izole ileri aort darlığı hastalarında aort kapak replasmanının uzun dönem sağ kalm ve sol ventrikül fonksiyonu üzerine etkilerinin araştırılması amaçlanmıştır.

Yöntemler: Bu retrospektif çalışma, Ocak 1993-Mart 2006 tarihleri arasında merkezimizde aort kapağı replasmanı uygulanan 46 hastada yürütmüştür. Koroner arter hastalığı, orta dereceden daha ileri (≥2) aort yetmezliği, daha önceden geçirilmiş kapak replasmanı veya onarımı ve diğer kapak patolojileri öyküleri bulunan hastalar çalışmaya dahil edilmemiştir. Ortalama LVEF %34.5±3.9 idi ve ortalama aort kapak alani 0.7±0.09 cm² idi. Analiz toplam 14 deşğen dahil edildi: Etyoloji, yaş (≥70 yıl), cinsiyet, preoperatif New York Kalp Cemiyeti (NYHA) sınıfı, kronik obstrüktif akciğer hastalığı, hipertansiyon, diyabet, periferik arter yetersizliği, assandan aorta girişimleri için ihtiyaç, kardiopulmoner bypass süresi ≥120 dk, aortik kros-klemp süresi ≥90 dk, intraaortik balon pompa desteği ve inotrop desteği. İstatistiksel analizde, ameliat
measurements were performed by an experienced cardiologist in Preoperative patient characteristics are listed in Table 1. angiography was performed in 40 patients (86.9%) preoperatively. excluded from the study. Cardiac catheterization and coronary replacement or repair and with other valve pathologies were moderate aortic regurgitation (>2), with previous valve Committee of the hospital. All patients with CAD, with more than hospital records. This study was approved by the Research in a retrospective manner and all data were collected from between January 1993 and March 2006. The study was designed LVD (LVEF ≤40%) underwent isolated primary AVR in our clinic severe AS and LVD. As we aimed to evaluate the isolated effect of asystolic AS has poor prognosis compared to asymptomatic AVR is the only effective treatment modality in patients with AS and LVD, sympotms of left ventricular dysfunction in patients with isolated severe AS and LVD.

Methods

Patients
A total of 46 consecutive patients with isolated severe AS and LVD (LVEF ≤40%) underwent isolated primary AVR in our clinic between January 1993 and March 2006. The study was designed in a retrospective manner and all data were collected from hospital records. This study was approved by the Research Committee of the hospital. All patients with CAD, with more than moderate aortic regurgitation (>2), with previous valve replacement or repair and with other valve pathologies were excluded from the study. Cardiac catherization and coronary angiography was performed in 40 patients (86.9%) preoperatively. Preoperative patient characteristics are listed in Table 1.

Echocardiographic measurements
Complete pre-operative transthoracic echocardiographic measurements were performed by an experienced cardiologist in all patients. Measurements of left ventricular dimensions were made from 2- dimensional echocardiographic images in the parasternal long-axis view and M-mode. Echocardiographic left ventricular volumes and LVEF were calculated by modification of Simpson’s method with two apical views. Mean and peak aortic gradients were determined by Doppler measurements, and native aortic valve orifice area was calculated by the continuity equation. Left ventricular mass was calculated using Devereux-modified American Society of Echocardiography (ASE) equation considering the diastolic measurements of left

Table 1. Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Age, years</th>
<th>55.02±13.3 (18-73)</th>
</tr>
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<tbody>
<tr>
<td>Gender (male/female), n(%)</td>
<td>37/9 (80.4/19.6)</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.74±0.19 (1.4-2.3)</td>
</tr>
<tr>
<td>Etiology, n(%)</td>
<td></td>
</tr>
<tr>
<td>Congenital</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Rheumatic</td>
<td>24 (52.2)</td>
</tr>
<tr>
<td>Degenerative</td>
<td>19 (41.3)</td>
</tr>
<tr>
<td>Comorbidities, n(%)</td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Preoperative symptoms, n(%)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>35 (76)</td>
</tr>
<tr>
<td>Angina</td>
<td>20 (43.4)</td>
</tr>
<tr>
<td>Syncope</td>
<td>10 (21.7)</td>
</tr>
<tr>
<td>New York Heart Association functional class, n(%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>7 (15)</td>
</tr>
<tr>
<td>III</td>
<td>29 (63)</td>
</tr>
<tr>
<td>IV</td>
<td>10 (22)</td>
</tr>
<tr>
<td>Rhythm, n(%)</td>
<td></td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>40 (88.9)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6 (13.1)</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation (range) for continuous variables and n (%) for categorical variables.
ventricular internal diameter, interventricular septal thickness and posterior wall thickness (8). Left ventricular mass index (LVMI) was calculated by dividing left ventricular mass by body surface area (derived from the height and weight). Stress echocardiography with dobutamine in presence of low transvalvular gradients was performed in 14 patients to distinguish severe LV dysfunction and real low transvalvular gradients.

Surgical data
An aortic valve replacement using a mechanical prosthesis was performed under moderate hypothermia and concomitant isothermic retrograde hyperkalemic blood cardioplegia was used for the myocardial protection. The aortic root was enlarged in two patients and the ascending aorta was replaced in four patients. The mean cardiopulmonary bypass (CPB) time was 100.6±34.4 minutes (ranged from 60 to 220 min) and the mean cross-clamp (ACC) time was 77.4±18.9 minutes (ranged from 39 to 150 min).

Follow-up
All survivors were retrospectively assessed. The patients were invited to ambulatory controls after telephone interviews. Of these, 34 patients were examined during a follow-up period of 72.3 ± 41.5 months (range 8-158 months). The data records of four patients who died during follow-up were retrospectively reviewed from the latest ambulatory examinations of these patients. The eight patients who died during follow-up were under clinical control either at our department or at peripheral hospitals. Follow-up including an echocardiographic control was completed for all survivors.

Definitions
Severe aortic stenosis was defined as an aortic valve area less than 1.0 cm², the mean gradient greater than 40 mmHg, or jet velocity greater than 4.0 m per second (9). Left ventricular dysfunction was defined as LVEF ≤40%. Chronic obstructive pulmonary disease was defined as the need for pharmacologic therapy for chronic pulmonary compromise or as a preoperative spirometry with a severe obstruction. Chronic renal insufficiency was defined as serum creatinine ≥2 mg/dL. Inotropic support was considered as the use of postoperative inotropic agents for >24 hours. Early mortality was defined as death occurring within 30 days of operation, and late mortality as death occurring after that time. Long-term survival was defined as a life period after hospital discharge.

Statistical Analysis
Statistical analysis was performed using the statistical software SPSS 12.0 for Windows (SPSS Inc, Chicago, IL). Data are expressed as mean ± standard deviation for continuous variables and as numbers with percentages for categorical variables. Logistic regression analysis was used to assess the predictors for early mortality, and Cox proportional hazard regression analysis was used to study survival after AVR. All multivariate analyses were performed with p <0.05 as the limit on univariate analysis for entering or removing variables. Wilcoxon rank-sum test was used as appropriate for comparison of continuous variables (between preoperative and postoperative stages). Survival curve was plotted using the Kaplan-Meier method. A p value <0.05 was considered statistically significant.

Results

Early mortality
Early mortality was 8.6% with four patients. They required high dose inotropic support while weaning from the cardiopulmonary bypass (CPB) and died due to low cardiac output syndrome: two patients on postoperative third day, one on postoperative fourth day and one on postoperative tenth day.

Predictors of early mortality
Predictors of early mortality were analyzed using logistic regression analysis. The following fourteen variables were analyzed: etiology, age (≥70 years), sex, preoperative New York Heart Association (NYHA) functional class, chronic obstructive pulmonary disease, hypertension, diabetes, peripheral arterial disease, chronic renal insufficiency, need for concomitant procedures for the ascending aorta, CPB time ≥120 min, aortic cross-clamp (ACC) time ≥90 min, intraaortic balloon pump (IABP) support, inotropic support. As the result of univariate logistic regression analysis, preoperative NYHA functional class ≥3 was found to be predictive of early mortality. Patients with NYHA class ≥3 had 12.6 times (OR: 12.6; 95% CI: 1.2-131.3; p=0.035) higher probability of early mortality than those with a lower NYHA class. However, multivariate logistic regression analysis failed to identify any independent predictor of early mortality. Advanced age, presence of comorbidities such as diabetes and hypertension, prolonged CPB and ACC times and concomitant procedures involving ascending aorta were not found to be predictors of early mortality (p>0.05).

Postoperative outcomes
During the postoperative period, 24 patients required an inotropic support, and three of them required IABP. Univariate analysis revealed that the ACC time ≥90 minutes (p=0.006) and CPB time ≥120 minutes (p=0.001) were associated with the increased requirement of inotropic use. Mechanical ventilation longer than 24 hours was necessary in six patients (13%), but four of them died during the early postoperative period. One patient required a permanent pacemaker implantation. The mean duration of stay in the intensive care unit was 5.05±2.01 days (ranged from 2 to 37 days) and in the hospital was 14.38±7.56 days (ranged from 5 to 113 days).

Late outcomes

Late mortality
There were eight (19%) late deaths. The late deaths were cardiac in six patients and non-cardiac in two patients (carcinoma and stroke). Three of them required IABP support during the early postoperative period.

Survival
Kaplan-Meier survival analysis revealed that the overall 5-year survival rate was 83.1%±5.9% and 10-year survival rate was 59.6%±10.9% (Fig. 1).

Determinants of long-term survival
Cox proportional hazards regression analysis demonstrated diabetes mellitus (HR: 6.6; 95% CI: 1.19-36.9, p=0.031) and
intraaortic balloon pump use (HR: 10.7; 95% CI: 2.9-39.7, p<0.001) to be significant predictors for late mortality.

Echocardiographic recovery

Echocardiographic evaluation was obtained in all surviving patients at 6-month follow-up (Table 2). A positive change in LVEF was observed in 79.3% of patients and LVEF significantly improved from 34.5±3.9% preoperatively to 44.7±10.4% after AVR (p < 0.001).

NYHA functional class

Significant improvement was observed in most of the survivors. Preoperatively, 79% of patients were classified as NYHA functional class III or IV, compared with 15% after AVR (p < 0.001 Fig. 2).

Discussion

Left ventricular dysfunction is a major prognostic indicator of the outcome in patients undergoing AVR for AS (3,10,11). This group of patients constitutes the most controversial and clinically challenging patients with AS. In this study conducted on patients suffering from isolated severe AS with significant LVD, aortic valve replacement was found to be beneficial. A positive change was observed in the LVEF in 79.3% of survivors and the mean LVEF increased from 34.5% to 44.7% (p<0.001). Operative mortality was 8.6% and late mortality was 19%. Multivariate logistic regression analysis failed to demonstrate any predictor for early mortality, where Cox proportional hazards regression analysis demonstrated diabetes mellitus (p=0.031) and IABP use (p<0.001) as significant predictors for late mortality.

The early mortality rate observed in our study correlates with the majority of previous reports demonstrating mortality rates between 8% and 18% (3,12-16). Fuster et al (16) showed that LVMI had the worst effect on the poor prognosis, whereas the other preoperative risk factors such as chronic renal failure and

![Figure 1. Kaplan-Meier survival curve](chart.png)

**Table 2. Pre- and postoperative echocardiographic data of patients**

<table>
<thead>
<tr>
<th>Echocardiographic variables</th>
<th>Preoperative (n=46)</th>
<th>Postoperative (n=34)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>34.5±3.9 (25-40)</td>
<td>44.7±10.4 (25-64)</td>
<td>0.005</td>
</tr>
<tr>
<td>Aortic valve area, cm²</td>
<td>0.77±0.09 (0.6-0.95)</td>
<td>1.64±0.45 (1.1-3.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean transvalvular gradient, mmHg</td>
<td>58.4±11.6 (28-78)</td>
<td>29.68±9.38 (15-45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular end-systolic diameter, cm</td>
<td>5.15±0.81 (3.6-7.2)</td>
<td>4.56±0.84 (3.4-6.2)</td>
<td>0.1</td>
</tr>
<tr>
<td>End-diastolic diameter, cm</td>
<td>6.43±0.98 (5-9.5)</td>
<td>5.97±0.86 (4.8-7.6)</td>
<td>0.4</td>
</tr>
<tr>
<td>Septal diastolic wall thickness, cm</td>
<td>1.29±0.19 (1-1.9)</td>
<td>1.21±0.26 (0.8-1.8)</td>
<td>0.8</td>
</tr>
<tr>
<td>Posterior wall thickness, cm</td>
<td>1.2±0.19 (1-1.7)</td>
<td>1.19±0.16 (1-1.6)</td>
<td>0.7</td>
</tr>
<tr>
<td>Mass index, gr/m²</td>
<td>235.79±78.76 (118.78-507.61)</td>
<td>186.04±42.48 (112.13-295.75)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation (range) for continuous variables and n (%) for categorical variables. *p values of Wilcoxon rank-sum test; statistical significance is expressed as p<0.05.
Operative mortality rate is higher in certain patient groups such as those undergoing concomitant coronary artery bypass grafting (2, 17). Therefore, it is suggested that patients with severe AS and accompanying LVD should have coronary angiography and early AVR in the earliest phase of LVD even if they are asymptomatic (5, 18). Unlike most other studies in the literature which included patients with CAD, we excluded those patients with CAD to evaluate the isolated effect of AVR on ventricular function, mortality and morbidity in isolated AS. Left ventricular dysfunction may occur due to afterload mismatch in patients with severe AS, and AVR results in an improvement of LVEF in these patients. Development of fibrosis leads to irreversible myocardial dysfunction and reduces potential benefits of AVR in patients with aortic stenosis. However, in patients with concomitant CAD, previous myocardial infarctions and the presence of hibernation may cause LVD and these patients should be evaluated carefully before operation. We believe that it is difficult to interpret the effect of AVR on the recovery of LVD in the presence of preoperative myocardial hibernation. Therefore, in order to prevent such confusion and assess the effect of surgery on the recovery of the left ventricular function in patients with isolated severe AS and LVD, we excluded patients with CAD.

The overall 5-year survival rate was 83.1±5.9% and 10-year survival rate was 59.6±10.9%. Five-year survival rate complies with the rates (range 49%-75%) reported in other studies (4, 12, 14, 15). These findings signify the importance of AVR for the improvement of late survival of this patient group and support the suggestion that severe AS rarely has clinical contraindications to surgery for cardiac reasons (9). We also observed that 50% of the late deaths showed no improvement of LVEF after the operation. This can be explained by the fixed myocardial damage instead of afterload mismatch, which results in the same mortality rate seen in non-operated patients. The proper use of dobutamine stress test may help to differentiate these patients who would benefit from surgery (7, 19). Diabetes mellitus was found to be a significant risk factor for late death in our study like others (1, 4, 6). Different from the other studies we found that IABP support was a significant risk factor for late death. We can explain that preoperatively severe LVD may cause low cardiac output syndrome after surgery and result in a need for excessive inotropic and IABP supports. Preoperative left ventricular function is accepted as a key determinant of surgical outcome in patients with severe AS, while the development of left ventricular hypertrophy in terms of an increase in LVMI is recognized as an independent cardiac risk factor (16, 20).

Patients with severe AS constitute a challenging group. Patients with low LVEF have two different reasons for LVD: afterload mismatch, which generally respond well to surgery and immediately normalizes left ventricular afterload; and advanced left ventricular systolic dysfunction, which causes a high operative risk group. Increased LVMI could be responsible of higher mortality by means of contractile impairment, diastolic dysfunction, abnormalities of coronary flow reserve or cardiac arrhythmias. A significant decrease in LVMI after operation shows better survival (16, 20). In our study, survivors had a significantly decrease in LVMI after operation. Serial

Aortic valve replacement and long-term survival

Figure 2. Comparison of preoperative (n=46) and postoperative (n=34) (follow-up) New York Heart Association functional class

N: number of patients; *: deaths

prolonged CPB (>120 minutes) were associated with early mortality. In this study, gender, advanced age, presence of atrial fibrillation and concomitant diseases such as diabetes mellitus and hypertension, prolonged CPB and ACC times, concomitant procedures for the ascending aorta were not found to be predictive of early mortality. Although ACC and CPB times were quite longer in patients who underwent concomitant ascending aorta replacement, they did not increase early mortality. This can be attributed to the improved surgical and myocardial preservation techniques. Only preoperative NYHA functional class ≥3 was identified as a predictor of early mortality on univariate logistic regression analysis (p=0.035); whereas multivariate analysis failed to identify any independent predictor of early mortality. Patients with NYHA class ≥3 had 12.6 times (OR: 12.6; 95%CI: 1.2-131.3; p=0.035) higher probability of early mortality than those with a lower NYHA class. It can be suggested that these patients would better be referred for assessment of surgical treatment before severe LVD with symptoms (NYHA functional capacity ≥3) develop. Although current guidelines for treating severe AS identify the onset of symptoms as the critical point, Cleveland Clinic (4) has showed recently that relying on symptoms alone in therapeutic decision making is inadequate and higher NYHA functional class is one of the most significant risk factors for late death. That means that AVR should be performed before severe LVD develops.
measurements of left ventricular mass may be helpful for assessing the efficacy of therapeutic intervention and in determining the timing of surgery for patients with chronic aortic valve disease.

**Limitations of the study**

This study is limited by its retrospective nature and sample size. Dobutamine stress echocardiography is not performed routinely in our unit, but only when other preexisting comorbidity indicates a need to demonstrate recoverable myocardium and we have only used to risk stratify patients and not to include or exclude surgical candidacy.

**Conclusion**

Left ventricular ejection fraction and symptoms improve after AVR in patients with severe isolated AS and LVD with acceptable operative mortality and satisfactory long-term survival. Particularly, patients with severe AS and LVD should undergo AVR in the earliest phase of LVD, because preoperative worsening of functional capacity can increase operative mortality. Likewise, impaired left ventricular function affects long-term survival, especially the need for IABP support is one of the important predictors for late death.

**References**