Survival in elderly patients with severe aortic stenosis is dramatically improved by aortic valve replacement: results from a cohort of 277 patients aged ≥80 years

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Received 20 April 2006; received in revised form 24 July 2006; accepted 25 July 2006; Available online 6 September 2006

Abstract

Background: Calcific aortic stenosis (AS) is a disease of the elderly. However, there is reluctance to offer aortic valve replacement (AVR) for elderly patients with severe AS. We investigated if AVR confers a survival benefit in elderly patients with severe AS.

Methods: We screened our echocardiographic database from 1993 to 2003 for patients with severe AS (AV area < 0.8 cm²) and age ≥80 years. Two hundred and seventy seven patients were identified. Complete chart reviews were performed for clinical data. Mortality data were obtained from National Death Index. Survival curves of patients who underwent AVR during the follow-up period were compared with those managed nonsurgically.

Results: Patient characteristics were as follows: age 85 ± 4 years, 53% male, AV area 0.68 ± 0.16 cm², EF 52 ± 20%, CAD 47%, diabetes 17%. Over a mean follow-up of 2.5 years, 55 (20%) had AVR and there were 175 deaths. One-year, 2-year and 5-year survival rates among patients with AVR were 87, 78 and 68%, respectively, compared with 52, 40 and 22%, respectively, in those who had no AVR (p < 0.0001). Hazard ratio for death with AVR adjusted for 19 covariates including age, EF, gender, comorbidities and pharmacotherapy was 0.38 (95% CI 0.26–0.66, p < 0.0001).

Conclusion: Prognosis of medically managed severe calcific AS in the elderly patients is dismal. AVR appears to improve survival of these patients and should be strongly considered in the absence of other major comorbidities.

Keywords: Aortic stenosis; Aortic valve replacement; Survival; Echocardiography; Prognosis

1. Introduction

Aortic stenosis (AS) is the most frequent valvular lesion in the elderly in western countries [1]. The prevalence of AS (<1.2 cm²) in the general population increases with age from 2.5% at 75 years to 8.1% at 85 years [1,2]. With the proportion of elderly patients rising, AS is becoming a serious clinical issue. Indications for aortic valve replacement (AVR) are well defined in guidelines, and there is a consensus for AVR in patients with severe symptomatic AS [3]. Decisions to operate the elderly patients have specific problems related to increase in operative morbidity and mortality [4–14]. AVR is the only effective therapy for symptomatic aortic stenosis. Age alone is not a contraindication; several studies have, in fact, shown that AVR can be performed in the elderly with acceptable mortality and morbidity and postoperative quality of life. However, there is still a reluctance to offer AVR for patients aged 80 years and more. We investigated the survival patterns of octogenarians with severe AS managed with AVR in comparison with those treated medically.

2. Methods

2.1. Patient population

This is a retrospective cohort study from a large university medical center. Our echocardiographic database was searched for patients with severe aortic stenosis defined as Doppler-derived valve area <0.8 cm². This yielded a total of 740 patients. Of these, 277 patients were ≥80 years forming the study cohort. Detailed chart reviews were then performed on these patients (both alive and dead) by senior medical residents.

2.2. Clinical variables

Hypertension (HTN) was defined as blood pressure greater than 130/90 mmHg or a history of hypertension or being on medications. Diabetes was defined as having a history of or being treated with medications. Renal insufficiency was...
defined as serum creatinine \( \geq 2 \) mg/dl, and coronary artery disease was defined as having a history, electrocardiographic presence of Q-waves or being on anti-anginal medications.

2.3. Pharmacological data

Pharmacotherapy at the time of echocardiography was recorded. This was broadly categorized into beta blockers, calcium channel blockers, diuretics, angiotensin-converting enzyme inhibitors, digoxin and statins.

2.4. Echocardiographic data

All patients had standard two-dimensional echocardiographic examinations. LV ejection fraction was assessed by a level-3 trained echocardiographer and entered into a database at the time of the examination. Anatomic and Doppler measurements were performed according to the recommendations of the American society of Echocardiography [15]. Aortic valve area was obtained by continuity equation.

2.5. Mortality data

The endpoint of the study was all-cause mortality. Mortality data were obtained from the National Death Index using social security numbers.

2.6. Statistical analysis

Analysis was performed using Stat View 5.01 (SAS Institute Inc., Cary, NC, USA). Characteristics of patients with and without AVR were compared using the Student’s t-test for continuous variables and Chi-squared test for categorical variables. Statistical tools used for survival analysis included the Kaplan—Meier method, Cox regression model, propensity score analysis and sensitivity analysis as described later.

A \( p \)-value of \( \leq 0.05 \) was considered significant.

### Table 1

Characteristics of patients with and without AVR

<table>
<thead>
<tr>
<th></th>
<th>No AVR (n = 197)</th>
<th>AVR (n = 80)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>85.3 ± 4.1</td>
<td>83.0 ± 2.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Males</td>
<td>42%</td>
<td>57%</td>
<td>0.02</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>50 ± 21%</td>
<td>56 ± 18%</td>
<td>0.04</td>
</tr>
<tr>
<td>Aortic valve area (cm(^2))</td>
<td>0.68 ± 16</td>
<td>0.68 ± 15</td>
<td>ns</td>
</tr>
<tr>
<td>Mean aortic gradient (mmHg)</td>
<td>39 ± 15</td>
<td>44 ± 16</td>
<td>0.02</td>
</tr>
<tr>
<td>LV end diastolic dimension (cm)</td>
<td>4.8 ± 0.8</td>
<td>4.8 ± 0.8</td>
<td>ns</td>
</tr>
<tr>
<td>LV end systolic dimension (cm)</td>
<td>3.4 ± 1.0</td>
<td>3.2 ± 0.9</td>
<td>ns</td>
</tr>
<tr>
<td>Interventricular septum (cm)</td>
<td>1.4 ± 0.2</td>
<td>1.4 ± 0.2</td>
<td>ns</td>
</tr>
<tr>
<td>Posterior wall (cm)</td>
<td>1.2 ± 0.2</td>
<td>1.2 ± 0.1</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40%</td>
<td>60%</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16%</td>
<td>17%</td>
<td>ns</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>41%</td>
<td>62%</td>
<td>0.001</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>13%</td>
<td>7%</td>
<td>ns</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>51%</td>
<td>45%</td>
<td>ns</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>11%</td>
<td>12%</td>
<td>ns</td>
</tr>
<tr>
<td>Aspirin</td>
<td>31%</td>
<td>62%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>18%</td>
<td>44%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>30%</td>
<td>30%</td>
<td>ns</td>
</tr>
<tr>
<td>Statin</td>
<td>15%</td>
<td>27%</td>
<td>0.01</td>
</tr>
<tr>
<td>Digoxin</td>
<td>20%</td>
<td>31%</td>
<td>0.06</td>
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</table>

### 3. Results

3.1. Patient characteristics

Patients characteristics were as follows: mean age 85 ± 4 years, 53% male, mean AV area 0.68 ± 0.16 cm\(^2\), mean aortic gradient 40 ± 15 mmHg, EF 52 ± 20%, CAD 47%, diabetes 17%, HTN 46%. Over a mean follow-up of 2.5 years, there were 175 deaths. All the 80 patients underwent aortic valve replacement with a bioprosthetic valve. The concomitant surgical procedures included the following: three (4%) had aortic root enlargement, 37 (46%) coronary artery bypass surgery and eight (10%) had mitral valve repairs.

Table 1 summarizes characteristics of elderly patients with severe AS with and without AVR. AVR group had a greater preponderance of males (57% vs 42%, \( p = 0.02 \), higher EF (56 ± 18% vs 50 ± 21%, \( p = 0.04 \)), higher prevalence of hypertension (60% vs 40%, \( p = 0.002 \)), higher prevalence of coronary artery disease (CAD) (62% vs 41%, \( p = 0.001 \)), and greater use of cardiac medications such as

![Fig. 1. Survival of patients with severe AS with and without AVR.](image-url)
aspirin (62% vs 31%, \( p < 0.0001 \)) and beta blockers (44% vs 18%, \( p < 0.0001 \)).

In patients who had aortic valve replacement, 13% had cerebrovascular accident compared with 12% in those who did not undergo valve replacement during the entire follow-up period.

### 3.2. Survival with AVR

Of the 277 patients, 80 underwent AVR during follow-up. Survival in patients who underwent AVR was significantly better than those managed medically using Kaplan–Meier analysis with log-rank statistic (Fig. 1). One-year, 2-year and 5-year survival rates among patients with AVR were 87, 78 and 68%, respectively, compared to 52, 40 and 22%, respectively in those who had no AVR (\( p < 0.0001 \)).

### 3.3. Survival adjusted for confounding variables

Hazard ratio for death with AVR adjusted for 19 covariates including age, EF, gender, comorbidities and pharmacotherapy was 0.38 (95% CI 0.26–0.66, \( p < 0.0001 \)). Table 2 shows the independent predictors of mortality by Cox regression analysis.

### 3.4. Propensity score analysis (PSA)

In addition to Cox regression, PSA was used to address the effect of covariate imbalance between the treatment and control groups. Probability of receiving AVR (propensity score) for each patient was modeled by using logistic regression conditioned on covariate values for that individual. Effect of AVR on survival in each of the four strata of equal size was analyzed on the basis of propensity score. Fig. 2a–d shows the Kaplan–Meier survival curves in the four individual strata. Patients who underwent AVR had a significant survival benefit in all four strata.

### 3.5. Sensitivity analysis (SA)

Sensitivity analysis was carried out by serially eliminating observations within 30 days, 90 days, 1 year and 2 years, respectively, to minimize the effect of unmeasured and unmeasurable variables on mortality and the nonproportional early mortality hazard in the nonsurgical arm. Fig. 3a–d shows the Kaplan–Meier survival curves for observations eliminated before 31 days, 91 days, 1 year and 2 years, respectively. Survival with AVR was superior compared to the non-AVR group in each of the strata. These analyses strongly suggest that AVR conferred survival benefit.

### 3.6. Survival benefit with AVR in subsets

Fig. 4a shows the Kaplan–Meier survival curves in patients with ejection fraction ≤30% (\( n = 60 \)). Five-year survival rate was 10% in patients who did not undergo AVR compared with 52% who underwent AVR (\( p = 0.003 \)). In patients with EF ≤30% and a mean aortic gradient ≤30 mmHg (\( n = 25 \)), only two patients had underwent AVR (Fig. 4b). Survival benefit with

<table>
<thead>
<tr>
<th>Table 2: Cox regression model showing independent predictors of survival</th>
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<tr>
<td>Relative risk</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Age (per year)</td>
</tr>
<tr>
<td>Ejection fraction (per 1%)</td>
</tr>
<tr>
<td>AVA (per cm(^2))</td>
</tr>
<tr>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>AVR</td>
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Fig. 2. (a–d): Survival with and without AVR based on propensity score analysis. Stratum 1 least likely to receive AVR and stratum 4 most likely to receive AVR.
AVR could not be assessed because of low number of patients with AVR in this subgroup, but in those patients with no AVR in this subgroup with severe AS, 1-year survival rate was dismal at 18%. Analysis of patients with CRI (n = 32) shows that only six patients had AVR, 5-year survival rate was 12% in those who did not undergo AVR compared with 42% in those who underwent AVR ($p = 0.13$) (Fig. 4c).

4. Discussion

The elderly population of 65 years and more is the fastest growing segment of population in western countries [16]. AVR has been shown to be safe in the elderly population [4—14]. In a study conducted by Lung et al. [2] in the Euro Heart Survey, it was found that 33% of elderly patients with severe symptomatic AS were denied surgery. Old age and LV dysfunction were the most striking reasons for denial of surgery. In our patients, nonsurgical management was associated with older age, female gender and lower ejection fraction. Presence of CAD was a trigger for AVR in many of these patients.

4.1. Benefit of AVR

Our study shows that in octogenarians with severe AS, survival is dramatically improved with AVR. AVR had significant survival benefit with 1-year, 2-year and 5-year survival rates of 87, 78 and 68%, respectively, compared with 52, 40 and 22%, respectively, in those who had no AVR ($p < 0.0001$). On multivariate analysis, lower ejection fraction and, renal insufficiency were predictors of increased mortality. Old age and smaller aortic valve area showed a trend towards increased mortality, which was not statistically significant. AVR was a strong independent predictor of improved survival. There is a paucity of studies in the literature comparing survival with and without AVR for severe aortic stenosis in those aged ≥80 years. Gilbert et al. [11] reported that 103 patients from a single center in the UK with severe AS underwent AVR. Median age in this study was 82 years. The 50% actuarial survival in this study was 62 months. Early postoperative mortality was related to increasing age, renal impairment and peripheral vascular disease. Patients who survived the surgery had good long-term prognosis. One-year, 2-year and 5-year survival rates were 78, 75 and 58%, respectively, in all patients undergoing AVR (by examining the published Kaplan—Meier survival curves). Bouma et al. [14] evaluated the decision-making process leading to medical or surgical treatment for aortic stenosis in elderly patients. There were 67 patients aged ≥80 years. This study showed 3-year survival rates of 80% in the surgical group compared with 49% in the non-AVR group. Our study is the largest study evaluating the survival pattern with and without AVR in patients aged 80 and more with severe AS and shows similar survival patterns.

4.2. Outcomes after AVR in patients aged 80 and more

There are studies reporting good outcomes after AVR in the elderly. Gehlot et al. [8] studied 322 patients with a mean age of 82.2 years who underwent AVR. On multivariate analysis, the most important independent predictors
of mortality included female gender, renal impairment, EF < 35%, bypass grafting and chronic obstructive pulmonary disease. Age and year of operation did not influence mortality. Five-year survival rates for all patients and for operative survivors were 60.2 ± 3.2% and 70.3 ± 3.4%. Asimakopoulos et al. [10] reported on data collected from 1100 patients >80 years undergoing AVR from the UK Heart Valve Registry. Actuarial survival rates were 89, 79, 69% and 46% at 1, 3, 5 and 8 years, respectively. Survival in the operated patients in our series was practically identical to this. Sundt et al. [17] retrospectively evaluated 133 patients between the age of 80 and 91 years undergoing AVR. Actuarial survival rates at 1 and 5 years were 80 and 55%, respectively. Urgent or emergent surgery, aortic insufficiency, perioperative stroke or renal dysfunction were significant risk factors for operative death by multivariate analysis.

4.3. Strengths of our study

Ours is the largest study addressing this issue, and our patients are well characterized in terms of clinical, pharmacologic and echocardiographic data. We used robust statistical tools like propensity score analysis and sensitivity analysis in addition to the standard Kaplan–Meier analysis. Propensity score analysis was used to correct covariate imbalances. Modeling based on propensity scores is estimated to remove up to 90% of inherent bias of a retrospective study [18]. Propensity score analysis reveals strong survival benefit with AVR in octogenarians with severe AS. As there is a nonproportionate mortality hazard during the first 30 days, sensitivity analysis was carried out to serially eliminate these initial observations and determine the survival benefit of AVR. By serial elimination of observations before 30 days, 90 days, 1 year and 2 years, AVR continues to show a very strong survival benefit.

4.4. Limitations

This is a retrospective, observational study and hence is prone to inherent bias of a retrospective study. Though various statistical tools were used to attempt to remove effect of selection of bias on survival, a prospective randomized study is the only way to answer this clinical question in unequivocal terms.

4.5. Conclusions

Our study shows that medically managed octogenarians with severe aortic stenosis have a dismal prognosis, and AVR improves survival. Hence, strong consideration should be given for aortic valve replacement in octogenarians in the absence of serious comorbidities.
Acknowledgement

The authors acknowledge the statistical expertise of Dr Daniel O. Stram PhD, Professor, Department of Preventive Medicine and Biostatistics, University of Southern California, Los Angeles, CA.

References