Clinical Profile and Natural History of 453 Nonsurgically Managed Patients With Severe Aortic Stenosis

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Background. Severe aortic stenosis (AS) is a surgically correctable condition. However, aortic valve replacement (AVR) is not offered to many patients with severe AS for various reasons. We investigated the profile and survival patterns of patients with severe AS who did not have AVR.

Methods. Our echocardiographic database was screened for patients with severe AS, defined as a Doppler estimated aortic valve area of 0.8 cm² or less between 1993 and 2003. Seven hundred and forty patients with severe AS were identified, of whom 453 patients had no AVR through the follow-up period, forming the study cohort. These patients were comprehensively characterized by obtaining clinical, pharmacologic, and surgical data through a comprehensive chart review and extracting survival data from the National Death Index.

Results. Patient characteristics were as follows: age 75 ± 13 years, 48% male, left ventricular (LV) ejection fraction 52 ± 21%, coronary artery disease in 34%, hypertension in 35%, serum creatinine level greater than 2 mg/dL in 11%, and diabetes mellitus in 14%. The survival at 1 year, 5 years, and 10 years was 62%, 32%, and 18%, respectively. The univariate predictors of reduced survival were advanced age, low LV ejection fraction, heart failure, elevated serum creatinine level, severe mitral regurgitation, and pulmonary hypertension; and the independent predictors were advanced age, low LV ejection fraction, heart failure, elevated serum creatinine level, and systemic hypertension. Concomitant pharmacotherapy had no impact on survival.

Conclusions. Conservatively treated patients with severe AS have a grave prognosis, and it is worse in the presence of advanced age, LV dysfunction, heart failure, and renal failure.

(Am J Cardiol 2006;82:2111–5) © 2006 by The Society of Thoracic Surgeons
with the patients and not by the investigators. Mean duration of follow-up for patients with AVR was 3.8 years, and for those without AVR it was 1.5 years; the short duration of follow-up for the no AVR group principally is due to a high short-term mortality rate. Of the 453 patients who did not undergo AVR, 102 patients had follow-up echocardiograms after a mean of 1.6 years.

**Clinical Variables**

Hypertension was defined as blood pressure greater than 130/90 mm Hg or a history of hypertension and being on antihypertensive medications. Diabetes mellitus was defined as fasting blood sugar greater than 125 mg/dL or being on a regimen of antidiabetic agents. Renal insufficiency was defined as serum creatinine of 2 mg/dL or greater. Coronary artery disease was deemed to be present if any of the following were present: a history of angina pectoris, myocardial infarction, a positive stress test, angiographic evidence of coronary artery disease, coronary intervention, coronary artery bypass surgery, or presence of significant Q waves on the surface electrocardiogram. In the absence of angiographic data on all patients, it is likely that the prevalence of coronary artery disease could be underestimated.

**Pharmacologic Data**

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

**Echocardiographic Data**

All patients had standard two-dimensional echocardiographic examinations. Left ventricular (LV) ejection fraction was assessed visually by a level 3 trained echocardiographer and entered into a database at the time of the examination. That has been proved to be reliable and has been validated against contrast and radionuclide LV angiography [6, 7]. Anatomic and Doppler examinations and measurements were performed according to the recommendations of the American Society of Echocardiography [8]. Severe pulmonary hypertension was defined as a pulmonary artery systolic pressure of 60 mm Hg or greater.

**Mortality Data**

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

**Statistical Analysis**

All the data were initially entered into Microsoft Excel program. The data were then imported into Stat View 5.01 (SAS Institute, Cary, North Carolina) program for statistical analysis. Kaplan-Meier survival curves were computed for patients with and without AVR and were compared using the log-rank statistic. Characteristics of patients with and without AVR were compared using the Student t test for continuous variables and the χ² test for categorical variables. A logistic regression model was used to adjust for the effect of group difference on survival. A p value of 0.05 or less was considered significant.

**Results**

**Baseline Patient Characteristics**

The baseline features of patients are summarized in Table 1. In brief, the age was 75 ± 13 years, 48% were males, LV ejection fraction was 52% ± 21%, coronary artery disease was present in 34%, hypertension in 35%, serum creatinine level greater than 2 mg/dL in 11%, and diabetes mellitus in 14%. The LV ejection fraction was 40% or less in 35%, 30% or less in 24%, and 20% or less in 12%. Forty-five percent of the patients were 80 years or older, 47% had symptoms in the form of chest pain (10%), 42% had dyspnea (42%), 11% had a prior stroke, and 18% had a pulmonary artery systolic pressure of 60 mm Hg or greater, indicating severe pulmonary hypertension.

![Figure 1](image-url)
univariate predictors of lower survival for this group were advanced age ($p < 0.0001$), lower LV ejection fraction ($p < 0.0001$), presence of congestive heart failure ($p < 0.0001$), presence of chronic obstructive pulmonary disease ($p = 0.0005$), presence of severe mitral regurgitation ($p = 0.0009$), and pulmonary hypertension ($p = 0.0002$). Use of any of the drug therapies had no effect on survival.

**Table 2. Univariate Predictors of Survival**

<table>
<thead>
<tr>
<th>Variables</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 75 years</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ejection fraction &lt; 41%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Presence of congestive heart failure</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Presence of chronic renal insufficiency</td>
<td>0.0005</td>
</tr>
<tr>
<td>Presence of severe mitral regurgitation</td>
<td>0.0009</td>
</tr>
<tr>
<td>Pulmonary hypertension ($\geq$60 mm Hg)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Survival of Patients Aged 80 Years and Older

As shown in Figure 1, the 5- and 10-year survival rates were 21% and 7%, respectively, for patients greater than 80 years compared with 48% and 30%, respectively, for those who were younger ($p = 0.0002$). The characteristics of the older patients who were alive were as follows: 40% males, mean ejection fraction 54% ± 19%, 51% had hypertension, 16% were diabetic, 40% had coronary artery disease, and 47% were symptomatic.

Cox Proportional Hazard

All variables significant on univariate analysis were entered into Cox proportional hazard model for the prediction of survival (Tables 3 and 4). Using this, age, presence of severe pulmonary hypertension, LV ejection fraction, and chronic obstructive pulmonary disease were independent predictors of survival. Only 315 patients had measurable tricuspid regurgitation velocities for estimation of pulmonary artery pressure. When all patients were included in the model (hence, excluding pulmonary artery pressure as a predictor
variable), age, LV ejection fraction, congestive heart failure, chronic obstructive pulmonary disease, and hypertension emerged as independent predictors of survival.

**Follow-Up Echocardiograms**

Follow-up echocardiograms were available in 102 patients at a mean follow-up of 1.6 years. During this period, the aortic valve area dropped by 0.13 cm² ($p = 0.01$), the mean transvalvular gradient increased by 5 mm Hg ($p = 0.007$), the mean LV ejection fraction decreased by 4% ($p = 0.05$), and the pulmonary artery systolic pressure increased by 7 mm Hg ($p = 0.001$). The low number of follow-up echocardiograms is due to the high attrition rate of patients with nonoperated severe AS.

**Comment**

Our study confirms that severe AS, left untreated surgically, carries a dismal prognosis. Our series is larger than all the other reported series and has additional comprehensive echocardiographic and pharmacologic data that have potential prognostic implications.

**Comparison With Other Studies**

Chizner and colleagues [3] reported poor survival in their study of 42 patients with severe or moderate stenosis (32 symptomatic), who underwent cardiac catheterization and did not undergo early valve surgery. Mortality rates from onset of symptoms were 26% at 1 year, 48% at 2 years, and 57% at 3 years. Fifty-six percent of deaths occurred suddenly, within hours of new symptoms. Horstkotte and colleagues [4] showed a dismal prognosis for patients with severe AS. In their study, 55 patients with severe AS who had refused aortic valve replacement had a mean average survival of 23 months, and the 5-year probability of survival was 18% [4]. All these patients had died within 12 years of observation. Livanainen and colleagues [5] showed severe AS (n = 13) predicted a fourfold to sixfold relative risk for death even after adjustment for age, sex, and LV measurements. The 4-year survival in this study in severe AS, medically treated, was 24%. The mortality rate in this study in patients with severe AS started to increase after 18 months of follow-up. The 5-year mortality rate in these studies in patients with severe AS ranged between 18% and 50% [3–5]. Our study, comprising a large number of well-characterized, conservatively managed severe AS patients, revealed a dismal 5-year survival of 32%, which is similar to the other studies. In addition, our study identifies subgroups who are at higher risk of intermediate term mortality.

**Reasons for Nonsurgical Management**

Reasons for nonsurgical management were difficult to establish in many of the patients in view of the retrospective study nature. Some of the prominent reasons included lack of symptoms, patient refusal, high surgical risk, and non-cardiac comorbidities such as stroke, dementia, and physical debility.

**Predictors of Survival in Nonsurgically Managed Patients**

Not surprisingly, advanced age, low ejection fraction, presence of heart failure, and renal failure were predictors of reduced survival. Although many of these patients had coronary artery disease, treatment with aspirin or statins did not improve survival, possibly indicating the overriding negative impact of severe AS on survival. Beta-blockers can potentially reduce the risk of atrial fibrillation or ventricular arrhythmias, but in this cohort did not affect survival. Although 35% of the patients had an ejection fraction less than 40%, neither the β-blockers nor the angiotensin-converting enzyme inhibitors improved survival, either in the whole cohort or in the subset with reduced ejection fraction.

In conclusion, patients with severe AS have a dismal prognosis when managed conservatively. The mortality rate is increased with age, heart failure, and renal insufficiency. Medical therapy with β-blockers, angiotensin-converting enzyme inhibitors, or statins does not seem to affect survival in the entire group of conservatively treated patients with severe AS.

**References**

INVITED COMMENTARY

It is very easy to forget the details of the natural course of surgical conditions we treat every day. Problems whose unaltered course we surgeons would claim to be aware of, only confessing under closer cross-examination to remembering that someone had described it but “can’t remember who and can’t remember when!” Aortic stenosis is one such condition. Most of us, if not all, are familiar with its presentation and its course through the operating room. Here Varadarajan and colleagues [1] have collected an impressive series of patients with severe aortic stenosis who for various reasons did not undergo surgery. This group is made up of a staggering 61% of 740 patients with severe aortic stenosis (echocardiographic valve area, ≤0.8 cms²) who presented to their hospital in Los Angeles during the 11 years between 1993 and 2003. Surgery was not considered appropriate through the patient’s lack of symptoms, estimated high risk, or refusal. To be fair this is an unusual group (ie, unusual in its size), reminding us surgeons that not all patients come forward for surgery, and with this group, ie, a minority at 39% of all who presented with severe aortic stenosis. This group is also unusual in its composition. Within it may sit patients who do not represent those who undergo aortic valve surgery. Whatever! It is all we are going to see of a group describing the current natural course of severe aortic stenosis; and rightly so. They do describe the dreadful outcome that untreated severe aortic stenosis achieves. This reminds us of the risks of not operating and of the impact that our surgery has on the immediate and late outcome of patients with this condition.

Death is basically the only outcome that is offered in this huge retrospective collection of patients. It would have been good to read in greater detail the maze of paths that patients with severe aortic stenosis take as they approach their often early and inevitable cardiac death. Without doubt, death is an unarguable endpoint. Sudden death of presumed arrhythmia, the slow worsening restriction of heart failure, ever more frequent dizzy spells and syncope, and the distressing death of sepsis from endocarditis could have been quantified for sepsis from endocarditis could have been quantified for quantification of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989;2:358–67.

REFERENCES

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