Low-Gradient Aortic Stenosis
Operative Risk Stratification and Predictors for Long-Term Outcome: A Multicenter Study Using Dobutamine Stress Hemodynamics

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Background—The prognostic value of dobutamine stress hemodynamic data in the setting of low-gradient aortic stenosis has been addressed in small, single-center studies. Larger studies are needed to define the criteria for selecting the patients who will benefit from valve replacement.

Methods and Results—Six centers prospectively enrolled 136 patients with aortic stenosis (96 men; median age, 72 years [range, 65 to 77 years]; median aortic valve area, 0.7 cm² [range, 0.6 to 0.8]; mean transaortic gradient, 29 mm Hg [range, 23 to 34 mm Hg]; cardiac index, 2.11 L·min⁻¹·m⁻² [range, 1.75 to 2.55 L·min⁻¹·m⁻²]). Left ventricular contractile reserve on the dobutamine stress Doppler study was present in 92 patients (group I) and absent in 44 patients (group II). Operative mortality was 5% (3 of 64 patients) in group I compared with 32% (10 of 31 patients) in group II (P=0.0002). Predictors for operative mortality were the lack of contractile reserve (odds ratio, 10.9; 95% confidence interval [CI], 2.6 to 43.4; P=0.001) and a mean transaortic gradient ≤20 mm Hg (odds ratio, 4.7; 95% CI, 1.1 to 21.0; P=0.04). Predictors for long-term survival were valve replacement (hazard ratio, 0.30; 95% CI, 0.17 to 0.53; P=0.001) and left ventricular contractile reserve (hazard ratio, 0.40; 95% CI, 0.23 to 0.69; P=0.001).

Conclusions—In the setting of low-gradient aortic stenosis, surgery seems beneficial for most of the patients with left ventricular contractile reserve. In contrast, the postoperative outcome of patients without reserve is compromised by a high operative mortality. Thus, dobutamine stress Doppler hemodynamics may be factored into the risk-benefit analysis for each patient. (Circulation. 2003;108:319-324.)

Key Words: valves | hemodynamics | surgery | cardiomyopathy | echocardiography

Patients with severe aortic stenosis (AS), left ventricular (LV) dysfunction, and low transaortic pressure gradients (low-gradient AS) represent a common medical challenge considering their high operative mortality¹–⁶ and dismal spontaneous prognosis.³,⁵ Dobutamine stress hemodynamics can differentiate between patients with true severe (fixed) AS, who are likely to benefit from valve replacement, and those with primary cardiomyopathy and nonsevere (relative) AS, for whom medical therapy may be indicated.⁷,⁸ Previous studies³–⁴ have also suggested that dobutamine stress Doppler data can help stratify operative risk in this setting. Unfortunately, the four latter studies were relatively small, single-center studies.³,⁴,⁷,⁸ Therefore, we conducted a multicenter study including a large cohort of patients with low-gradient AS to (1) confirm the value of dobutamine stress Doppler data for operative risk stratification; (2) define better the prevalence of relative AS; and (3) identify independent predictors for long-term outcome in these patients.

Study Population
All consecutive patients with symptomatic, severe AS (valve area ≤1 cm²)⁹ and a low cardiac index (≤3.0 L·min⁻¹·m⁻²) were eligible if their mean transaortic pressure gradient (MPG) was ≤40 mm Hg.¹ Exclusion criteria were severe comorbidities, more than mild aortic or mitral regurgitation, and atrial fibrillation. The study was approved by local review boards, and informed consent was obtained from the patients before all procedures. From April 1994 to January 2002, 136 patients were prospectively enrolled in 6 centers in France. Preliminary data from one center were published in a previous report¹; 43 patients from this series (with extended follow-up data) were included in the present report.

Dobutamine Stress Hemodynamic Studies
All patients underwent a comprehensive Doppler echocardiographic study using commercially available ultrasound systems. Details of the dobutamine stress hemodynamic protocol have been previously described.³ Briefly, after the baseline measurements, dobutamine was infused up to a maximal dose of 20 μg/kg per minute. LV
LV ejection fraction (EF) was calculated according to the biplane Simpson's rule in 100 patients. Transaortic gradients were calculated using the simplified Bernoulli equation. Aortic valve area was calculated according to standard formulae. LV contractile reserve was present in 92% (n=68) of patients, absent in 44 patients (group II, 32%). Baseline data by group are presented in Table 1; outcomes were considered statistically significant. Analyses were done using STATA software (version 7.0, Stata Corp).

Clinical Decisions and Follow-Up
Therapeutic decisions for each patient were left to the discretion of the referring physicians who had knowledge of individual dobutamine stress hemodynamic data. Clinical data at follow-up were obtained in all patients at a median interval of 14 months (range, 7 to 29 months) by direct patient examination or telephone interview. Evaluated end points at follow-up were survival and New York Heart Association functional class.

Data Analysis
The dobutamine stress hemodynamic studies were evaluated off-line in each center by a single experienced echocardiographer who was blinded to the clinical data. All data from each center were then centralized in Liège, Belgium, for statistical analysis. LV contractile reserve during dobutamine infusion was defined by an increase in stroke volume of ≥20% compared with baseline values; patients were then divided into 2 groups according to the presence (group I) or absence (group II) of contractile reserve. Relative AS was defined by an increase in valve area ≥0.3 cm², with a final valve area >1 cm² on dobutamine stress hemodynamics.

Statistical Analysis
Continuous data are presented as median values and corresponding 25th and 75th percentiles. Univariate analysis was performed using nonparametric statistical tests. To identify the cut point in baseline transaortic MPG that would define the ranges of severity, MPG was plotted against perioperative mortality (ie, death within 30 days after valve replacement), and the lowest smoothing function, using locally weighted least squares, was used. Survival curves were established by the Kaplan-Meier estimation method. Variables that were significantly associated with perioperative mortality by univariate analysis were entered into a multiple logistic regression model to allow for the determination of independent parameters. Variables that were significantly associated with long-term survival were included in a Cox proportional hazards model to assess their independent association with survival. Two-tailed probability values <0.05 were considered statistically significant. Analyses were done using STATA software (version 7.0, Stata Corp).

Results
Clinical Characteristics
The study population included 40 women and 96 men aged a median of 72 years (range, 65 to 77 years) with a median aortic valve area of 0.7 cm² (range, 0.6 to 0.8 cm²), median MPG of 29 mm Hg (range, 23 to 34 mm Hg), median LVEF of 0.30 (range, 0.24 to 0.35), median cardiac index of 2.11 L·min⁻¹·m⁻² (range, 1.75 to 2.55 L·min⁻¹·m⁻²), and median aortic valve resistance of 216 dyne·s·cm⁻⁵ (range, 181 to 283 dyne·s·cm⁻⁵). Symptoms at first presentation were congestive heart failure in 133 patients, with associated angina or syncope in 11 and 2 patients, respectively; isolated angina or syncope were reported in 1 and 2 patients, respectively. Coronary angiography was performed in 121 patients, with no significant stenosis in 65 patients (54%); single-, double- or triple-vessel disease was present in 18, 12, and 21 patients, respectively. Five patients had patent coronary artery bypass grafts (CABG). According to dobutamine stress hemodynamics, LV contractile reserve was present in 92 patients (group I, 68%) and absent in 44 patients (group II, 32%). Baseline data by group are presented in Table 1;
patients from group II had significantly more extensive coronary artery disease ($P = 0.03$), and the difference in aortic valve area was of borderline significance ($P = 0.045$). Otherwise, there was no significant difference between groups.

**Dobutamine Stress Hemodynamic Studies: Differences Between Groups**

Dobutamine stress Doppler data were obtained in all consecutive patients, and stress hemodynamic studies were well tolerated in all cases (premature ventricular or atrial contractions in 28 patients, no sustained arrhythmia). Dobutamine peak dose and heart rate acceleration were strictly comparable between the groups. In group I, stroke volume increased by 33% (range, 26% to 46%), LVEF by 12 ejection fraction (EF) units (range, 7 to 15 EF units), aortic valve area by 0.1 cm$^2$ (range, 0.1 to 0.2 cm$^2$), and MPG by 47% (range, 33% to 67%). The corresponding increases in group II were as follows: stroke volume, 10% (range, 2% to 13%); LVEF, 7 EF units (range, 3 to 13 EF units); aortic valve area, 0.0 cm$^2$ (range, 0.0 to 0.1 cm$^2$); and MPG, 32% (range, 21% to 56%; all $P < 0.006$ compared with group I). Valve resistance remained relatively unchanged in both groups (2% versus 12%; $P = 0.23$).

**Clinical Outcome: Therapeutic Decisions**

In group I, 70% of patients (64 of 92) underwent aortic valve replacement, with associated CABG in 30% (19 of 64). In this group, one patient died preoperatively of acute coronary occlusion during coronary angiography; the 27 remaining patients were treated medically for the following reasons: older age or comorbidities (n=10), patient refusal for surgery (n=8), and patients thought to have none severe AS (n=9). In group II, 70% of patients (31 of 44) underwent valve replacement, with CABG in 26% (8 of 31). The 13 remaining patients from group II were treated medically for older age or comorbidities (n=7) or patient refusal for surgery (n=6).

**Perioperative Mortality**

Overall perioperative mortality was 14% (13 of 95 patients); it was 5% in group I (3 of 64 patients) compared with 32% (10 of 31 patients) in group II. Relative risk for perioperative death in group II was 6.88 (95% confidence interval [CI], 2.0 to 23.2; $P = 0.0002$). With associated CABG, operative mortality was 11% in group I (2 of 19 patients) compared with 62% in group II (5 of 8 patients; relative risk in group II, 5.9; 95% CI, 1.4 to 24.5; $P = 0.005$). Considering baseline MPG, the cut point for ranges of operative risk was 20 mm Hg; thus, operative mortality was 10% (9 of 86 patients) in patients with a MPG $\geq$20 mm Hg compared with 44% (4 of 9 patients) in patients with a MPG $<20$ mm Hg. In the entire population, 53 patients had a baseline MPG $\geq$30 mm Hg, 64% of these (34 of 53) were in group I and 36% were in group II (19 of 53). In this latter subgroup, operative mortality was 11% (5 of 47); it was none (0 of 29) in group I compared with 28% (5 of 18) in group II. By univariate analysis (Table 2), LV contractile reserve, MPG $<20$ mm Hg, and associated CABG were related to perioperative mortality. According to multivariate analysis, independent predictors for operative mortality were the lack of contractile reserve (odds ratio for perioperative death, 10.9; 95% CI, 2.6 to 43.4; $P = 0.001$) and a baseline MPG $<20$ mm Hg (odds ratio for perioperative death, 4.7; 95% CI, 1.1 to 21.0; $P = 0.04$).

**Long-Term Survival**

Kaplan-Meier survival estimates by group are shown in the Figure; estimated 3-years survival after valve replacement was 79% in group I (95% CI, 62% to 89%), and survival after

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors After Valve Replacement (n=82)</th>
<th>Death Within 30 Days After Valve Replacement (n=13)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center of origin, Amiens/Bordeaux/ Créteil/ Lorient/Reims/Strasbourg, n</td>
<td>15/6/39/5/15/12</td>
<td>4/1/7/0/1/0</td>
<td>0.60</td>
</tr>
<tr>
<td>Age, y</td>
<td>71 (63–75)</td>
<td>72 (70–78)</td>
<td>0.14</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>55 (67)</td>
<td>11 (84)</td>
<td>0.20</td>
</tr>
<tr>
<td>NYHA class, I/II/III/IV, n</td>
<td>0/14/44/24</td>
<td>0/2/6/5</td>
<td>0.80</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>13 (16)</td>
<td>4 (31)</td>
<td>0.22</td>
</tr>
<tr>
<td>Coronary artery disease, 0/1/2/3-vessel, n</td>
<td>53/15/5/9</td>
<td>5/2/2/4</td>
<td>0.12</td>
</tr>
<tr>
<td>Associated coronary bypass surgery, n (%)</td>
<td>20 (24)</td>
<td>7 (54)</td>
<td>0.03</td>
</tr>
<tr>
<td>Contractile reserve, n (%)</td>
<td>61 (74)</td>
<td>3 (23)</td>
<td>0.001</td>
</tr>
<tr>
<td>MPG $&gt;20$ mm Hg, n (%)</td>
<td>3 (4)</td>
<td>4 (31)</td>
<td>0.006</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.32 (0.27–0.36)</td>
<td>0.30 (0.20–0.31)</td>
<td>0.08</td>
</tr>
<tr>
<td>End-diastolic LV diameter, mm</td>
<td>58 (55–63)</td>
<td>62 (58–67)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>14 (17)</td>
<td>2 (15)</td>
<td>0.88</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>16 (19)</td>
<td>4 (31)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Values are median (range), n (%), or as indicated.
surgery was significantly improved compared with medical treatment (Table 3). In contrast, improvement in long-term survival after valve replacement was not significant in group II ($P=0.07$). Survival duration under medical therapy was not different between the groups. According to Cox proportional hazard analysis, two parameters were independently associated with long-term survival: aortic valve replacement (hazard ratio, 0.30; 95% CI, 0.17 to 0.53; $P=0.001$) and LV contractile reserve (hazard ratio, 0.40; 95% CI, 0.23 to 0.69; $P=0.001$).

**Functional Outcome**

In group I, postoperative improvement in functional status occurred in nearly all surviving patients; only 1 patient with prosthesis-patient mismatch remained in New York Heart Association class III after valve replacement. Thus, good functional results after valve replacement occurred in 84% of patients (54 of 64) in group I compared with 45% of patients (14 of 31) in group II ($P=0.002$). Functional outcome under medical therapy was equally poor in both groups; good functional results occurred in 18% (5 of 28) and 7% (1 of 14) of patients from groups I and II, respectively ($P=0.15$).

**Patients With Relative AS**

Seven patients met the criteria for relative AS; their main characteristics and outcomes are outlined in Table 4. Outcomes were favorable without valve replacement in 3 of 6 patients. After 65 months of follow-up, patient 2 finally underwent aortic valve replacement for progression of AS. In contrast, 2 patients under medical therapy died from cardiac causes, and one patient who had undergone isolated CABG died suddenly 22 months after surgery. Finally, patient 7 underwent valve replacement, revealing a moderately calcified aortic valve.

**TABLE 3. Cox Proportional Hazard Analysis of the Effect of Surgical Treatment on Survival Duration in the 2 Groups**

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2, medical</td>
<td>1.0</td>
<td>Reference</td>
</tr>
<tr>
<td>Group 1, medical</td>
<td>0.61</td>
<td>0.27–1.35</td>
</tr>
<tr>
<td>Group 2, surgical</td>
<td>0.47</td>
<td>0.31–1.05</td>
</tr>
<tr>
<td>Group 1, surgical</td>
<td>0.12</td>
<td>0.05–0.3</td>
</tr>
</tbody>
</table>

**Definition of Low-Gradient AS**

As stated in current practice guidelines, severe AS with normal cardiac output generally implies a transaortic MPG $\geq 50$ mm Hg. Thus, in any given patient, a calculated valve area $\leq 1$ cm$^2$ with a MPG $\leq 40$ mm Hg may be related to reduced stroke volume. In previous studies, low-gradient AS was defined by a MPG $\leq 30$ mm Hg and from 11% to 18% when MPG was $\leq 40$ mm Hg. In recent studies, operative risk for valve replacement varied from 8% to 21% when MPG was $\leq 30$ mm Hg and from 11% to 18% when MPG was $\leq 40$ mm Hg. Thus, it was important to determine the cut point for ranges of operative risk in terms of MPG; this cut point was a MPG $\leq 20$ mm Hg in the present study. Interestingly, in the 53 patients with a MPG between 30 and 40 mm Hg, the proportion of patients without LV contractile reserve was the same as in the whole population, and operative mortality was 28% (5 of 18) in the patients without reserve compared with zero (0 of 29) in patients with contractile reserve. Thus, our results, supported by others, demonstrate that operative risk stratification is justified in patients with a MPG between 30 and 40 mm Hg.

**Predictors for Operative Mortality**

In the setting of low-gradient AS, known predictors for operative mortality were previous myocardial infarction, small-sized aortic prosthesis, or LV contractile reserve. We published a previous report on operative risk stratification by dobutamine stress hemodynamics, but the subgroup of operated patients without contractile reserve in that study was very small (6 patients), and thus no definitive conclusions could be drawn. In the present study, 31 patients without reserve underwent valve replacement, and the high operative mortality in this subgroup was confirmed with much improved statistical power compared with the earlier report. The other independent predictor for operative mortality was a baseline mean transaortic gradient $\leq 20$ mm Hg. Neither previous myocardial infarction nor associated CABG was an independent predictor for operative mortality in this series.

**Predictors for Long-Term Survival**

In case of low-gradient AS, postoperative improvement in LV function due to the release of afterload mismatch may be

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The Kaplan-Meier survival estimates by group and treatment are shown in the figure. The table outlines the Cox proportional hazard analysis of the effect of surgical treatment on survival duration in the 2 groups. The hazard ratio for death and its 95% confidence interval are provided for each group, along with the associated $P$ value. The results indicate that aortic valve replacement and LV contractile reserve are independent predictors of long-term survival. The Kaplan-Meier survival curve shows a significant difference in survival duration between the groups. The figure also displays Kaplan-Meier survival estimates by group and treatment, illustrating the improved survival outcomes in the group undergoing valve replacement compared to medical therapy.
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TABLE 4. Hemodynamic Parameters and Outcomes in the 7 Male Patients With Relative AS

<table>
<thead>
<tr>
<th>Patient/ Age, y</th>
<th>MPG, mm Hg</th>
<th>Valve Area, cm²</th>
<th>Coronary Artery Disease</th>
<th>Treatment</th>
<th>Outcome, Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/66</td>
<td>12/25</td>
<td>0.8/1.2</td>
<td>1-vessel</td>
<td>Medical</td>
<td>Stable, NYHA II, 14 months</td>
</tr>
<tr>
<td>2/47</td>
<td>9/19</td>
<td>0.9/1.3</td>
<td>No significant stenosis</td>
<td>Medical</td>
<td>NYHA IV to I, 65 months</td>
</tr>
<tr>
<td>3/70</td>
<td>13/20</td>
<td>1.0/1.3</td>
<td>1-vessel</td>
<td>PTCA</td>
<td>NYHA III to II, 6 months</td>
</tr>
<tr>
<td>4/83</td>
<td>18/24</td>
<td>0.9/1.3</td>
<td>Angiography not performed</td>
<td>Medical</td>
<td>Death (congestive heart failure), 14 months</td>
</tr>
<tr>
<td>5/69</td>
<td>27/43</td>
<td>0.6/1.1</td>
<td>1-vessel</td>
<td>Medical</td>
<td>Death (congestive heart failure), 1 month</td>
</tr>
<tr>
<td>6/57</td>
<td>12/15</td>
<td>0.8/1.2</td>
<td>3-vessel</td>
<td>Isolated CABG</td>
<td>Sudden death, 22 months</td>
</tr>
<tr>
<td>7/68</td>
<td>37/40</td>
<td>1.0/1.4</td>
<td>3-vessel</td>
<td>Valve replacement + CABG</td>
<td>NYHA IV to I, 14 months</td>
</tr>
</tbody>
</table>

related to LV contractile reserve, which may be paralleled with myocardial viability in chronic coronary artery disease. It is currently admitted that in chronic ischemic cardiomyopathy, long-term survival is improved by myocardial revascularization provided myocardial viability is present. Thus, it is not surprising that independent predictors for long term survival in the present study were valve replacement and LV contractile reserve. Conversely, in most of the patients without contractile reserve, LV function may be irreversibly damaged due to previous myocardial infarction or extensive myocardial fibrosis; therefore, these latter patients are less likely to benefit from valve replacement. Of course, in the absence of contractile reserve, calculated valve area remains unreliable, so heterogeneity is possible with regard to AS severity and response to valve replacement in group II. Moreover, the predictive value of the lack of contractile reserve for postoperative changes in LV function is still unknown. Nevertheless, our results demonstrate that despite a trend toward better survival after valve replacement, the outcome of patients without reserve is compromised by high operative mortality. In contrast to previous reports, associated coronary artery disease did not influence long-term survival in the present study, although operative mortality was increased in patients with associated CABG.

Relative AS

Relative AS refers to primary LV dysfunction with nonsevere AS. In such cases, AS severity may be overestimated due to the inaccuracy of both Gorlin and continuity equations at low-flow states and/or the inability of the left ventricle to open a mildly calcified valve fully due to severely decreased stroke volume. Previous studies reported up to one-third of patients meeting the criteria for relative AS and a fairly good prognosis under medical therapy at midterm follow-up in these patients. In our study, this situation was rarely encountered because only 7 of 136 patients met the criteria for relative AS; this number is reduced to 5 patients if recently revised criteria are applied. Six patients in this subgroup did not undergo valve replacement, and 3 of them died after a relatively short period of follow-up. This result is supported by Nishimura et al, who reported several deaths among medically treated patients with relative AS. In contrast, 3 patients in our series did relatively well under medical therapy, including one patient who finally underwent valve replacement for progression of AS after 65 months of follow-up. Thus, currently available data on relative AS remain too scarce to allow any definitive conclusion, and further studies are mandatory concerning this rare subset of patients.

Study Limitations

The 100% success rate of Doppler interrogation during dobutamine infusion in this study may not reflect daily practice; thus, when Doppler data are not available, a dobutamine hemodynamic study in the catheterization laboratory is also safe and effective. The lack of significant benefit of valve replacement on long-term survival in group II may be due to the relatively small number of patients in this group; therefore, we have insisted on the trend toward a benefit of valve surgery in this group. A limitation of our study is that patients were not randomized for treatment and that therapeutic decisions were made by the referring physicians, who had knowledge of dobutamine stress hemodynamic data. Our opinion is that randomization of such patients would be unethical considering their dismal spontaneous prognosis. Furthermore, in our study, the proportion of operated patients was comparable in both groups; this confirms that for the majority of physicians, the prognostic value of dobutamine stress hemodynamics is not yet fully established.

Conclusions

This first multicenter study confirms the prognostic value of dobutamine stress hemodynamics for operative risk stratification and long-term outcome in the setting of low-gradient AS. Our results confirm that patients with a contractile reserve have an acceptable operative risk and that valve replacement may improve long-term survival and functional status in most cases; thus, surgery may be recommended in most of these patients. In contrast, despite a trend toward better survival after valve replacement, the outcome of patients without reserve is compromised by high operative mortality, especially in those with a baseline MPG ≤20 mm Hg or associated coronary artery disease. Therefore, individual patients should not be denied the potential benefits of valve surgery on the basis of the absence of contractile reserve alone; however, we suggest that this important parameter should be considered, in addition to other risk factors, in the risk-benefit analysis for each patient.

Acknowledgment

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References


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