Dobutamine Echocardiography in Patients With Aortic Stenosis and Left Ventricular Dysfunction*

Predicting Outcome as a Function of Management Strategy

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Study objective: To prospectively address the question whether the assessment of valvular hemodynamics and myocardial function during low-dose dobutamine infusion can guide decision making in patients with aortic stenosis and left ventricular (LV) dysfunction.

Patients and measurements: Twenty-four patients with aortic stenosis and LV dysfunction (mean ejection fraction, 28%; New York Heart Association class, II to IV) were studied by dobutamine echocardiography assessing mean pressure gradient, aortic valve area, and aortic valve resistance. Patients were prospectively divided into severe and nonsevere aortic stenosis groups according to the response of the valve area to the augmentation of systolic flow. The clinical decision was considered to be concordant with the results of dobutamine echocardiography, when patients with severe aortic stenosis and preserved contractile function were referred by a specialist for aortic valve replacement and when patients with nonsevere aortic stenosis were not. Patients were observed for up to 3 years.

Results: All eight patients with severe aortic stenosis who were referred for surgery survived and had good cardiovascular outcomes, and six of eight patients who were not initially referred for surgery had poor outcomes, including heart failure and sudden cardiac death. The eight patients with nonsevere aortic stenosis did comparatively well without valve replacement. Cardiac death or pulmonary edema occurred in 4 of 16 patients (25%) when the clinical decision was concordant with the results of the dobutamine echocardiogram and occurred in 6 of 8 patients (75%) when the clinical decision was discordant (p = 0.019 [χ² test]).

Conclusion: Patients with aortic stenosis, LV dysfunction, and relatively low gradients have better outcomes when management decisions are based on the results of dobutamine echocardiograms. Those patients identified as having severe aortic stenosis and preserved contractile reserve by dobutamine echocardiography should undergo surgery, while patients identified as having nonsevere aortic stenosis can be managed conservatively.

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Key words: aortic stenosis; dobutamine echocardiography; left ventricular dysfunction

Abbreviations: LV = left ventricle ventricular; NS = not significant; NYHA = New York Heart Association

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atients with significant aortic stenosis and left ventricular (LV) dysfunction have poor prognoses. Aortic valve replacement, which reduces the excessive afterload burden imposed on the LV, can improve outcome and normalize LV function.1–3 Therefore, surgery is generally recommended in these patients. However, perioperative mortality and morbidity are high in patients with LV dysfunction who also have relatively low transvalvular pressure gradients.3–7 This discrepancy traditionally has been attributed to the difficulty of assessing the true severity of the stenotic lesion at low cardiac output.8–11 Because the pressure gradient and the calculated aortic valve area are flow-dependent,8–14 they may be disproportionately reduced in patients with LV dysfunction and may reflect the presence of

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low transvalvular flow rather than significant valvular disease. Cannon et al \(^\text{15}\) therefore introduced the infusion of vasodilators during cardiac catheterization in order to reassess the pressure gradient and valve area at an augmented cardiac output. Pharmacologic intervention could discriminate between severe fixed aortic stenosis causing LV dysfunction and coincidental nonsevere aortic valve disease in patients with LV dysfunction that is unrelated to aortic stenosis.\(^\text{11,15}\) DeFillippi et al \(^\text{16}\) first demonstrated the safety and usefulness of dobutamine echocardiography in distinguishing these two hemodynamic subsets in order to select surgical candidates. In 1997, however, a retrospective study \(^\text{17}\) found an excess of surgical mortality in patients with aortic stenosis, low ejection fraction, and low gradients who previously had experienced myocardial infarctions. The benefit of aortic valve replacement, therefore, has been questioned again in this patient group. \(^\text{17}\) Because withholding aortic valve replacement from suitable candidates will have detrimental consequences, the identification of patients within this high-risk population who might still benefit from surgery remains an important challenge.

Therefore, we prospectively addressed the question of whether the assessment of valvular hemodynamics and myocardial function during low-dose dobutamine infusion can guide decision making about patients with aortic stenosis and LV dysfunction, and whether it can predict outcome as a function of management strategy. In particular, we hypothesized that patients with relatively low transvalvular gradients who have been identified as having severe aortic stenosis and preserved contractile reserve by dobutamine echocardiography would have better outcomes when undergoing surgery and that patients identified as having nonsevere aortic stenosis by dobutamine echocardiography could be managed conservatively. In addition, we sought to identify whether a hemodynamic parameter exists that can distinguish between severe and nonsevere aortic stenosis in patients with LV dysfunction at baseline.

### MATERIALS AND METHODS

#### Patient Selection

Twenty-four patients with aortic stenosis and LV dysfunction were consecutively referred to our laboratory for dobutamine echocardiography from December 1995 to June 1998. Their clinical data are detailed in Table 1. Twenty-two patients were referred for the assessment of myocardial reserve. There were 15 men and 9 women with an age range of 53 to 93 years. Ejection fractions ranged from 15 to 45%, with an average value of 25%. All patients had calculated valve areas of < 0.9 cm\(^2\) (mean ± SD) area, 0.69 ± 0.13 cm\(^2\) and mean gradients of < 35 mm Hg (mean gradient, 28 ± 9 mm Hg), except for the two patients who were referred for assessment of myocardial reserve, who had higher gradients. Nineteen patients (79%) had proven coronary artery disease, and 17 patients (71%) had experienced a previous myocardial infarction. Ten patients (42%) were in pulmonary edema 3 days to 6 months prior to the examination, and 10 patients were categorized as being in functional New York Heart Association (NYHA) class III and IV at the time of the test. Significant comorbidity was present in more than half of the study group (54%).

#### Examination Protocol

The examination protocol included a complete Doppler echocardiographic baseline study and continuous monitoring of heart rate, BP, oxygen saturation, ECG, and wall motion. IV dobutamine infusion was started at a dose of 5 \(\mu\)g/kg/min and was increased by increments of 5 \(\mu\)g/kg/min every 3 min to up to 20 \(\mu\)g/kg/min.

#### Measurements

Stroke volume was calculated as the LV outflow tract area multiplied by the time-velocity integral of the outflow tract velocity (pulsed-wave Doppler). For the assessment of the LV outflow tract area, outflow tract diameter (D) was measured from a zoomed systolic freeze-frame in the parasternal long-axis view as the distance between the insertion points of the aortic cusps. Outflow tract area then was calculated as \(D^2\pi/4\). Systolic flow was calculated as aortic stroke volume divided by systolic ejection time. The mean pressure gradient was determined from the continuous-wave Doppler signal using the modified Bernoulli equation. Aortic valve area was calculated by the continuity equation as outflow tract area times the ratio of the time-velocity integrals of outflow tract and stenotic orifice Doppler signals. \(^\text{18,19}\) Aortic valve resistance was calculated from the ratio of mean gradient and systolic flow (times 1.33 to convert millimeters of mercury to dynes per second per square centimeter).\(^\text{15,20–23}\)

The measurements were repeated during dobutamine infusion. Because the LV outflow tract area has been shown to remain constant during flow changes both in normal subjects \(^\text{24,25}\) and in patients with valve disease, \(^\text{26}\) the resting value of LV outflow tract area was used to calculate stroke volume both at rest and during dobutamine infusion. Thus, changes in stroke volume, systolic flow, and aortic valve area could be assessed as intraventricular changes of the ratio of time-velocity integrals, eliminating the confounding influence of two different outflow tract measurements (squared in the calculation) on the comparison of rest and peak dobutamine values.

#### Definitions

**Aortic Stenosis Severity:** Aortic stenosis 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 aortic valve area did not increase by > 0.29 cm\(^2\) \(^\text{216,27}\) and remained < 1.0 cm\(^2\).\(^\text{15,27}\) Aortic stenosis was defined as nonsevere when systolic flow increased more than the maximal orifice velocity, because the effective aortic valve area had increased by at least 0.3 cm\(^2\) \(^\text{216,27}\) to at least 1.0 cm\(^2\).\(^\text{15,27}\)

**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).
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr/Sex</th>
<th>Cardiac Status</th>
<th>Significant Noncardiac Comorbidity</th>
<th>AS by DE</th>
<th>Initial Decision</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63/M</td>
<td>NYHA III–IV, EF 25%, PAPsys 55 mm Hg, S/P posterolateral MI, S/P CABG × 3, mod MR</td>
<td>NIDDM</td>
<td>Severe</td>
<td>AVR</td>
<td>NYHA I, EF 45%, walks 5 miles/d, mod MR, F/U 7 mo</td>
</tr>
<tr>
<td>2</td>
<td>53/M</td>
<td>NYHA III, CC III, EF 15%, HTN</td>
<td>S/P chemotherapy and radiotherapy (Hodgkin’s disease), CLL (untreated)</td>
<td>Severe</td>
<td>AVR</td>
<td>NYHA I, EF 60%, F/U 35 mo</td>
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<tr>
<td>3</td>
<td>76/F</td>
<td>NYHA II–III, CC II, EF 28%, S/P pulmonary edema, S/P anterior MI, LBBB, HTN</td>
<td>Pancycopenia (vitamin B-12 deficiency), NIDDM</td>
<td>Severe</td>
<td>AVR</td>
<td>NYHA I–II, EF 38%, F/U 17 mo: leukopenia, sepsis (no endocarditis), death</td>
</tr>
<tr>
<td>4</td>
<td>73/F</td>
<td>NYHA II–III, CC III–IV, EF 30%, S/P anterior wall MI, 3VCAD</td>
<td>No</td>
<td>Severe</td>
<td>AVR + CABG</td>
<td>NYHA I F/U 25 mo</td>
</tr>
<tr>
<td>5</td>
<td>62/M</td>
<td>NYHA II–III, EF 45%</td>
<td>No</td>
<td>Severe</td>
<td>AVR</td>
<td>NYHA I, EF 60%, F/U 28 mo</td>
</tr>
<tr>
<td>6</td>
<td>87/F</td>
<td>NYHA III, EF 19%, 2VCAD PAPsys 80 mm Hg, S/P DDD-pacemaker implantation, exertional syncope</td>
<td>No</td>
<td>Severe</td>
<td>AVR + CABG</td>
<td>NYHA I, F/U 36 mo</td>
</tr>
<tr>
<td>7</td>
<td>87/M</td>
<td>NYHA III–IV, EF 25%, S/P anterior wall MI, 3-VCAD, mod MR</td>
<td>Ca of prostate, low-grade B cell lymphoma (retroperitoneal nodes, chlorambucil [Leukeran] tx)</td>
<td>Severe</td>
<td>AVR + CABG</td>
<td>NYHA I, EF 35%, mod MR, F/U 30 mo, death (pneumonia, dl lymphatic spread)</td>
</tr>
<tr>
<td>8</td>
<td>71/M</td>
<td>NYHA III, EF 28%, S/P pulmonary edema, S/P anterior wall MI</td>
<td>No</td>
<td>Severe</td>
<td>AVR</td>
<td>Minor perioperative stroke, complete recovery, medication inadvertently stopped—transient pulmonary edema, since then NYHA II, F/U 14 mo</td>
</tr>
<tr>
<td>9</td>
<td>82/M</td>
<td>NYHA II–III, CC II–III, EF 38%, HTN</td>
<td>CML, CRF (crea 3.2), PVD</td>
<td>Severe</td>
<td>No AVR</td>
<td>NYHA III–IV, EF 30%, F/U 7 mo death (CHF)</td>
</tr>
<tr>
<td>10</td>
<td>73/M</td>
<td>NYHA III–IV, EF 35%, S/P CABG (1 graft), S/P anteroseptal MI</td>
<td>Morbid obesity (240 lb), COPD, S/P CVA</td>
<td>Severe</td>
<td>No AVR</td>
<td>NYHA IV, pulmonary edema → AVR, NYHA I, weight loss, F/U 22 mo</td>
</tr>
<tr>
<td>11</td>
<td>57/F</td>
<td>NYHA II, EF 20%, S/P pulmonary edema, S/P extensive anterior MI, HTN</td>
<td>CRF (crea 4.0), NIDDM</td>
<td>Severe</td>
<td>No AVR</td>
<td>NYHA II, F/U 24 mo</td>
</tr>
<tr>
<td>12</td>
<td>48/M</td>
<td>NYHA II–III, EF 33%, PAPsys 50 mm Hg, S/P anteroseptal MI, S/P CABG (2 grafts)</td>
<td>COPD</td>
<td>Severe</td>
<td>No AVR</td>
<td>NYHA III–IV pulmonary edema → AVR moderate leak and redo, NYHA II, F/U 10 mo</td>
</tr>
<tr>
<td>13</td>
<td>65/F</td>
<td>NYHA II–III, EF 20%, doxorubicin (Adriamycin) cardiomyopathy, HTN</td>
<td>Bleomycin-induced pulmonary fibrosis (S/P Hodgkin’s disease), NIDDM</td>
<td>Severe</td>
<td>No AVR</td>
<td>NYHA IV, pulmonary edema, FU 11 mo</td>
</tr>
<tr>
<td>14</td>
<td>65/M</td>
<td>NYHA III–IV, EF 25%, 3-VCAD, (diffuse, no revascularization possible), S/P inferior MI, HTN</td>
<td>No</td>
<td>Severe</td>
<td>No AVR</td>
<td>NYHA III, reasonably stable, F/U 8 mo</td>
</tr>
<tr>
<td>Patient No.</td>
<td>Age, yr/Sex</td>
<td>Cardiac Status</td>
<td>Significant Noncardiac Comorbidity</td>
<td>Initial Decision</td>
<td>Outcome</td>
<td></td>
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<tr>
<td>15</td>
<td>93/M</td>
<td>NYHA IV, EF 15%, S/P anterior MI, LBBB, HTN, severe MR.</td>
<td>S/P CVA</td>
<td>Severe</td>
<td>No AVR</td>
<td>F/U 3 mo, death (CHF)</td>
</tr>
<tr>
<td>16</td>
<td>70/F</td>
<td>NYHA IV, EF 38%, S/P pulmonary edema, S/P MVR</td>
<td>Interstitial lung disease, COPD, S/P mastectomy for Ca (no recurrence), acquired hemophilia</td>
<td>Severe</td>
<td>No AVR</td>
<td>NYHA III–IV, recurrent pulmonary edema, F/U 9 mo, sudden death</td>
</tr>
<tr>
<td>17</td>
<td>86/M</td>
<td>CC II–III, EF 37%, S/P inferior and apical MI, HTN</td>
<td>No</td>
<td>Nonsevere</td>
<td>No AVR</td>
<td>CC II–III, stable, F/U 8 mo</td>
</tr>
<tr>
<td>18</td>
<td>77/F</td>
<td>NYHA II, CC II, EF 38%, S/P anterior wall MI, S/P PTCA to LAD, moderate MR</td>
<td>No</td>
<td>Nonsevere</td>
<td>No AVR</td>
<td>Stable during F/U of 1 mo, then pulmonary edema (atrial fibrillation)</td>
</tr>
<tr>
<td>19</td>
<td>70/F</td>
<td>CC II, EF 35%, S/P anterior wall MI and pulmonary congestion, 3-VCAD</td>
<td>No</td>
<td>Nonsevere</td>
<td>No AVR</td>
<td>Underwent CABG without problems, CC I, F/U 23 mo</td>
</tr>
<tr>
<td>20</td>
<td>77/M</td>
<td>NYHA II–III, CC II, EF 20%, S/P anterior wall MI, S/P CABG and redo—CABG, S/P PTCA and stenting to LAD, S/P PTCA to LAD, diagonal branch, septal branch</td>
<td>S/P sigmoidectomy for Ca of colon</td>
<td>Nonsevere</td>
<td>No AVR</td>
<td>NYHA II–III, CC II, stable, F/U 3 mo, severe USAP with cardiogenic shock, unsuccessful PTCA to LAD, and death</td>
</tr>
<tr>
<td>21</td>
<td>74/F</td>
<td>NYHA I–II, S/P CABG, S/P MVR, S/P pacemaker implantation, S/P MI (indeterminate), HTN. Diagnosis of AS on admission for anteroseptal MI, EF 35%, DE on third day of MI</td>
<td>S/P CVA</td>
<td>Nonsevere</td>
<td>No AVR</td>
<td>Recovered well from MI, hypertensive crisis after 12 mo, NYHA I, EF 40%, F/U 16 mo</td>
</tr>
<tr>
<td>22</td>
<td>75/M</td>
<td>NYHA II, CC II, EF 35%, S/P PTCA and stenting (USAP with pulm congestion), S/P CABG, S/P infarction and inferopost wall MI</td>
<td>S/P hemicolecotomy S/P CVA NIDDM (insulin tx)</td>
<td>Nonsevere</td>
<td>No AVR</td>
<td>NYHA II, CC II, small non-Q-wave MI after F/U of 12 mo, otherwise stable</td>
</tr>
<tr>
<td>24</td>
<td>74/M</td>
<td>NYHA III, CC II, EF 28%, DE on third day after extubation (pulmonary edema, recurrent over 2 yr), HTN, diffuse CAD (no revascularization feasible)</td>
<td>Chronic renal failure</td>
<td>Nonsevere</td>
<td>No AVR</td>
<td>F/U 6 mo, death during local anesthesia for minor surgical procedure</td>
</tr>
</tbody>
</table>

*AVR = aortic valve replacement; Ca = carcinoma; CABG = coronary artery bypass graft; CAD = coronary artery disease; CC = Canadian Cardiovascular Society functional classification of angina pectoris; CHF = congestive heart failure; CLL = chronic lymphatic leukemia; CVA = cerebrovascular accident; EF = ejection fraction; F/U = follow up; HTN = arterial hypertension; LBBB = left bundle branch block; MI = myocardial infarction; mod = moderate; MR = mitral regurgitation; MR = mitral valve replacement; NIDDM = non-insulin-dependent diabetes mellitus; PAF = paroxysmal atrial fibrillation; PAPsys = systolic pulmonary artery pressure; USAP = unstable angina pectoris; VCAD = vessel coronary artery disease; M = male; F = female; DE = dobutamine echocardiography; AS = aortic stenosis; dd = differential diagnosis; crea = creatinine; S/P = status post; tx = therapy.
Concordant and Discordant Clinical Decision: Applying the above-mentioned criteria, dobutamine echocardiography identified 16 of the 24 patients as having severe aortic stenosis and 8 of the patients as having nonsevere aortic stenosis (Fig 1). The clinical decision of the referring physician (who would have knowledge of the test results) was defined as being concordant with the result of the dobutamine echocardiogram in patients with severe aortic stenosis who were referred for aortic valve replacement and in patients with nonsevere aortic stenosis who were not referred for aortic valve replacement. The clinical decision of the referring physician was defined as discordant with the test result in patients who were initially not referred for surgery despite severe aortic stenosis or in patients who were referred for surgery despite having nonsevere aortic stenosis. In all patients who were reported as having nonsevere aortic stenosis, the treating cardiologist decided against aortic valve replacement (including one patient who underwent coronary artery bypass grafting). Half of the patients who were reported to have severe aortic stenosis were directly referred for aortic valve replacement (in three cases, this was combined with coronary artery bypass grafting), whereas half of the patients were initially managed conservatively because the comorbidity was considered to be prohibitive by the referring physician. Thus, the clinical decision was concordant with the result of the dobutamine echocardiography in 16 patients and was discordant in 8 patients.

Follow-up was performed by regular visits in our outpatient clinic, review of hospital records, and phone interviews. The following two combined end points were prospectively determined: (1) cardiac death and pulmonary edema; and (2) all-cause death and pulmonary edema.

Statistical Analysis

Results were expressed as the mean ± SD. Comparisons of proportions between groups were made using the χ² test, and a p value of < 0.05 was considered to be significant. Differences between groups in hemodynamic parameters were explored by unpaired two-way comparisons (Student’s t test), and changes of hemodynamic parameters during dobutamine infusion were tested for significance by a paired two-tailed Student’s t test. In order to account for multiple comparisons applying the same type of test, the p value indicating statistical significance was conservatively set at p < 0.01 (Bonferroni correction).

Results

Safety

There were no serious side effects, arrhythmia, or patient discomfort during the low-dose dobutamine infusion. The mean heart rate was 76 ± 12 beats/min at rest and increased to 99 ± 17 beats/min (p < 0.000002) during dobutamine infusion; the mean arterial BP was 92 ± 16 mm Hg at baseline and decreased mildly to 85 ± 17 mm Hg (p < 0.009).

Valvular Hemodynamics

Systolic flow at baseline was similar in patients with severe and nonsevere aortic stenosis (164 ± 26 mL/s vs 178 ± 33 mL/s, respectively; not significant [NS]) (Fig 2 and 3, Table 2). During dobutamine infusion, systolic flow increased significantly (p < 0.000001 and p < 0.0001, respectively) in both groups (248 ± 58 vs 285 mL/s, respectively; NS). The mean pressure gradient at baseline was 31 ± 10 mm Hg in patients with severe aortic stenosis (27 ± 4 mm Hg without the two patients with resting pressure gradients of > 35 mm Hg who were referred for assessment of contractile reserve) and 24 ± 6 mm Hg in patients with nonsevere aortic stenosis (p = 0.09; NS). The mean pressure gradient

increased significantly to 46 ± 12 mm Hg in patients with severe aortic stenosis (p < 0.000002) and to 33 ± 9 mm Hg in patients with nonsevere aortic stenosis (p < 0.005). The difference between the mean gradients during dobutamine infusion in both groups (p = 0.011; NS) was of marginal significance at the conservatively set threshold. The mean aortic valve area at baseline was 0.65 ± 0.1 cm² in patients with severe aortic stenosis (0.69 ± 0.1 cm² without the two patients with gradients of > 35 mm Hg) and 0.76 ± 0.1 cm² in patients with nonsevere aortic stenosis (p = 0.047; NS). The aortic valve area in-
increased significantly to 1.11 ± 0.08 cm² in patients with nonsevere aortic stenosis (p < 0.00001), and to 0.75 ± 0.15 cm² in patients with severe aortic stenosis (p < 0.000001).

The mean valvular resistance was 270 ± 139 dyne·s·cm⁻⁵ at baseline in patients with severe aortic stenosis (217 ± 32 dyne·s·cm⁻⁵ when excluding the two patients with resting gradients of >35 mm Hg) and remained unchanged during dobutamine infusion (264 ± 139 and 233 ± 31 dyne·s·cm⁻⁵, respectively). In patients with nonsevere aortic stenosis, the mean valvular resistance was 179 ± 28 dyne·s·cm⁻⁵ at baseline and declined to 154 ± 28 dyne·s·cm⁻⁵ during dobutamine infusion (p = 0.011; NS). Due to the large SDs, there was no significant difference between the two groups concerning the baseline values of valvular resistance (p = 0.069; NS). In contrast, the difference between the two groups concerning valvular resistance during dobutamine infusion was statistically significant (p < 0.007).

Outcome

Follow-up was completed in all patients during an observational period of up to 36 months (mean, 17 ± 10 months). The individual courses of the patients during follow-up are detailed in Table 1.

All patients with severe aortic stenosis who were referred for aortic valve replacement survived surgery and virtually all of them experienced symptomatic benefits. One patient had a minor perioperative stroke from which he completely recovered; the same patient had transient pulmonary edema after inadvertently stopping treatment with his heart failure medication. Two patients died during follow-up. One patient who had mild pancytopenia preoperatively developed leukopenia and sepsis without clinical or echocardiographic evidence of endocarditis after a follow-up period of 17 months and died. One physically active 87-year-old patient with a low-grade lymphoma who became asymptomatic following aortic valve replacement and continued to work in the store he owned died from pneumonia after a follow-up period of 30 months.

Patients with severe aortic stenosis who were initially not referred to aortic valve replacement had poor outcomes. Two patients died from heart failure after 3 months and 7 months, and one died suddenly after 9 months. Three patients had recurrent episodes of pulmonary edema and worsening of heart failure; two of them ultimately were referred for aortic valve replacement (both patients survived surgery and improved clinically). Only two patients remained in fairly stable condition.

Patients with nonsevere aortic stenosis were treated conservatively except for one patient who underwent coronary artery bypass grafting (without concomitant aortic valve replacement). One patient with diffuse coronary artery disease (which was not suitable for revascularization) died while under local anesthesia for a minor surgical procedure after a follow-up period of 6 months, and one patient was admitted to the hospital for severe unstable angina with cardiogenic shock after 3 months, underwent unsuccessful emergency angioplasty of a left anterior descending artery stenosis, and died. One patient was admitted to the hospital for pulmonary edema during an episode of paroxysmal atrial fibrillation with rapid ventricular response.

In the 10 patients who ultimately underwent aortic valve replacement, the mean pressure gradient across the aortic prosthesis was 17 ± 9 mm Hg.

![Figure 3](http://publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21963/)
at the first follow-up and 16.6 mm Hg (median, 15 mm Hg) at the second follow-up. This represents a decrease in the pressure gradient of 50% (mean, 32.6 mm Hg; median, 28 mm Hg) despite the postoperative increase in the LV ejection fraction (Table 1). During the first year of follow-up, both the first combined end point (ie, cardiac death or pulmonary edema) and the second combined end point (ie, all-cause death or pulmonary edema) occurred in 3 of the 16 patients (19%) in whom the clinical decision was concordant with the result of the dobutamine echocardiography, and in 6 of 8 patients (75%) when it was discordant (p = 0.0073 [χ2]). In the group of patients for whom the clinical decision was discordant with the dobutamine study, all end points occurred during the first year (average, 7 ± 2 months; range, 3 to 11 months), and all deaths were cardiovascular in origin.

During the complete study period, the first combined end point (ie, cardiac death or pulmonary edema) occurred in 4 of 16 patients (25%) in whom the clinical decision was concordant with the result of the dobutamine echocardiography, and in 6 of 8 patients (75%) when it was discordant (p = 0.019 [χ2]). The second combined end point (ie, all-cause death or pulmonary edema) occurred in 6 of 16 patients (37%) in whom the clinical decision was concordant with the result of the dobutamine echocardiography and in 6 of 8 patients (75%) when it was discordant (p = 0.083 [χ2]).

**Discussion**

Decision making in patients with aortic stenosis, LV dysfunction, and relatively small transvalvular pressure gradients is particularly difficult if an additional non-valve-related cause of LV impairment is...
present, such as coronary artery disease. Powell et al.\textsuperscript{17} reported poor outcomes for patients who had undergone aortic valve replacement in a group of patients who had experienced prior myocardial infarctions, with a perioperative mortality rate of 47%, and a 2-year survival rate of 20%, suggesting that irreversible myocardial damage following myocardial infarction may render the LV incapable of recovering following aortic valve replacement. Since a minimal myocardial reserve may be necessary simply to survive cardiopulmonary bypass surgery and cardioplegia, operative mortality may be prohibitive in individual patients. However, in other patients with similar baseline characteristics, the removal of the excessive afterload imposed on the ventricle by the stenotic orifice may be the only way to stop the process of ventricular remodeling and progressive LV dysfunction, and to improve symptoms and survival rate.

The present study demonstrates that dobutamine echocardiography can answer the following two fundamental questions for decision making in these patients: (1) is there severe aortic stenosis with a low gradient resulting from low cardiac output across a severely stenotic valve, or is there nonsevere aortic stenosis with a small calculated aortic valve area reflecting low cardiac output in LV dysfunction unrelated to valvular disease?; and (2) is there sufficient myocardial (contractile) reserve to indicate a potential benefit and a reasonable perioperative risk that justify surgery? Therefore, the assessment of valvular hemodynamics and myocardial function during a low-dose dobutamine infusion lasting 9 to 12 min can predict the outcomes of these patients with different management strategies.

Outcome

To our knowledge, this is the first study of patients with aortic stenosis, LV dysfunction, and relatively low pressure gradients that demonstrates a better outcome when management decisions are based on the result of a dobutamine echocardiogram. In contrast to previous data,\textsuperscript{16,17} the present study prospectively followed three arms of management decisions, as follows: surgery for patients identified as having severe aortic stenosis; medical therapy in patients identified as having severe stenosis, but not referred to surgery; and medical therapy in patients identified as having nonsevere aortic stenosis and LV dysfunction that is unrelated to valvular disease. Patients with severe aortic stenosis did extraordinarily well when undergoing surgery (despite the fact that almost all of them had previously experienced myocardial infarctions), particularly considering the poor outcome of patients with severe congestive heart failure without correctable cause. In the long run, these patients then were limited by comorbidity. Not less important is the fact that patients with severe aortic stenosis who were not considered to be surgical candidates because of significant comorbidity had a low event-free survival rate with a prognosis limited by their cardiac disease and not by the comorbid factors. Two of these patients, one of them with severe lung disease and morbid obesity, ultimately underwent aortic valve replacement for severe progressive symptoms and are alive and well (the patient with morbid obesity, who previously was severely limited, was able to increase his physical activity, to reduce his weight significantly, and thus also to improve his respiratory condition). In the 10 patients who ultimately underwent aortic valve replacement, the mean pressure gradient across the aortic prosthesis was 16 ± 8 mm Hg (median, 15 mm Hg), which represents a decrease in the pressure gradient of 50% (from 32 ± 17 mm Hg; median, 28 mm Hg) despite the postoperative increase in LV ejection fraction (Table 1). This further corroborates the hemodynamic benefit of aortic valve replacement in this patient group and the validity of the selection criteria. Considering their low ejection fractions, patients identified as having nonsevere aortic stenosis did comparably well without undergoing aortic valve replacement. This includes one patient who underwent coronary artery bypass surgery without valvular intervention as a result of the findings on the dobutamine echocardiography test. This patient group seemed to be limited mainly by coronary events (Table 1). It must be emphasized that all of the patients studied in this series, both the surgical candidates as well the conservatively treated patients, had preserved contractile reserves. The results of the study therefore cannot be applied to patients lacking improvement of LV function during low-dose dobutamine infusion.\textsuperscript{16}

Criteria

Contractile reserve was defined as the ability to increase transvalvular flow and was not defined by an improvement in wall motion score or measured ejection fraction. This has both theoretical and practical advantages. In contrast to measuring the ejection fraction, the accuracy of assessing systolic flow is not influenced by the degree of geometric distortion of the LV shape following myocardial infarction. In contrast to wall motion score, improvement in systolic flow does not necessarily require the improvement of segments with abnormal wall motion at rest (ie, evidence of regional viability). Thus, patients who can improve their global LV function, even if this is achieved primarily by an increase in the
contractility of normal segments, are still correctly categorized as having the ability to hemodynamically adapt to increased stress. For practical purposes, the assessment of systolic flow does not require any additional measurement, so that all relevant parameters (ie, mean gradient, systolic flow, aortic valve area, and resistance) can be obtained from the three following recordings: a pulsed-wave Doppler signal of the outflow tract velocity; a continuous-wave Doppler signal of the maximal stenotic orifice velocity; and a two-dimensional systolic frame for the assessment of the outflow tract diameter.

**Aortic Stenosis Severity:** The following two criteria have been proposed to distinguish between patients with severe and nonsevere aortic stenosis who have LV dysfunction: the presence or absence of significant flow variations during dobutamine infusion and the achievement of an absolute cutoff value for the aortic valve area during pharmacologic intervention. We used a combination of both criteria to determine the severity of aortic stenosis. Only when both criteria were concordant was the categorization of patients as severe and nonsevere considered to be conclusive for suggesting a management recommendation, which was the case for all patients.

**Mechanism and Physiology**

The following three possible mechanisms have been proposed to explain the observed variation of the calculated aortic valve area: (1) variation of the coefficient of contraction with flow leading to a decrease in the effective valve area at low flow states despite an essentially unchanged anatomic valve area; (2) variation of the anatomic valve area itself; and (3) variation of the velocity flow profile across the orifice with flow, changing from flat to parabolic as the flow rate decreases due to viscous effects at the edges of the vena contracta. Therefore, continuous-wave Doppler echocardiographic measurements of the peak flow velocity (the central velocity vector in the parabolic profile) may overestimate the average velocity across the orifice and, thus, underestimate the valve area at low flow rates.

The present study does not answer the question of which of the three proposed explanations for the flow variation of the aortic valve area is true, but it provides a solution for each case. No matter what the cause for the small orifice area at a low flow rate, the recalculation of the orifice area at an augmented flow rate during dobutamine infusion will definitely clarify whether aortic stenosis is severe or not and at the same time will provide information about the contractile reserve of the LV. Correspondingly, no matter what the cause for the larger orifice area during dobutamine infusion, it can explain why these patients do comparatively well when treated conservatively. If an observed increase in the calculated aortic valve area represents a true increase in the effective valve area, then such patients are likely to increase their effective valve area also during normal daily physical activity, preventing the excessive increase in LV afterload that may occur in patients with a fixed aortic valve area during exercise. Of interest, in a prospective study of outcomes in individuals with asymptomatic aortic stenosis, patients with an end point (death or aortic valve surgery) showed smaller increases in valve area during exercise while undergoing the initial stress echocardiogram. However, if the observed increase results from the underestimation of valve area at baseline, then valve area calculated at a higher flow rate will simply reflect more accurately the lesser severity of the stenosis.

**Baseline Parameters**

Figure 3 demonstrates the complete overlap of values for the mean gradient in patients with severe and nonsevere aortic stenosis. Substantial overlap is also present for the values of the aortic valve area. All patients with an aortic valve area of < 0.65 cm² had severe aortic stenosis; however, given the flow dependence of the aortic valve area in patients from both groups (Fig 2, Table 2), this cutoff value must be a function of the severity of LV dysfunction in the examined patient group and, therefore, cannot be constant for different groups of patients. In fact, Carabello et al reported the presence of nonsevere stenosis or “pseudostenosis” of the aortic valve in a patient with a baseline aortic valve area as low as 0.6 cm². Valvular resistance not only remained stable, on average, when comparing resting and peak dobutamine values but showed somewhat less overlap than the aortic valve area (Fig 3), with a trend toward better discrimination between severe and nonsevere aortic stenosis achieved with patients already at rest. The reason for the possible advantage of using valvular resistance (calculated as the ratio of the pressure gradient to the flow rate) as a criterion in patients with LV dysfunction lies in the flow variability of the valve area. If the orifice area were completely fixed, calculated valve resistance would increase with flow, because the pressure gradient would increase disproportionately, according to Bernoulli’s Law. However, the effective aortic valve area increases mildly even in patients with severe calcified stenosis, allowing the flow rate to increase in proportion to the pressure gradient and, therefore, aortic valve resistance remains roughly in the same range in most patients. In the present series, all patients with valve resistance at a baseline of > 220
dyne⋅cm\(^{-5}\) had severe aortic stenosis (which is similar to what had been described originally by Cannon et al\(^{15}\)), while all patients with a valve resistance of < 160 dyne⋅cm\(^{-5}\) had nonsevere aortic stenosis. However, the overlap zone between 160 and 240 dyne⋅cm\(^{-5}\) still comprised 63% of the patients. Moreover, individual patients still may demonstrate sizable changes in resistance with flow, showing either an increase in resistance when the valve area remains virtually fixed and the gradient rises substantially (e.g., patients 5 and 10; Table 2)\(^{16}\) or a decrease, when the gradient rises only modestly (patients 11 and 24). Thus, pharmacologic intervention seems to be necessary in the vast majority of patients with aortic stenosis and poor LV function in order to accurately assess the severity of the valvular lesion (and in all of them to assess contractile reserve).

**Limitations and Comparisons With Other Studies**

The present study prospectively examined the course of 24 patients with aortic stenosis and LV dysfunction, of whom 10 ultimately underwent aortic valve replacement, over a follow-up period of up to 3 years. The size of the study group necessarily reflects the limitations of a single-center experience. In a feasibility and safety survey published in 1998,\(^{35}\) it took 6 years to accumulate the experience of 27 dobutamine studies in this patient group. Only seven patients underwent surgery, and no attempt was made to define the criteria of distinction between severe and nonsevere aortic stenosis in order to correlate test results with follow-up data.\(^{35}\) In fact, the recommendation to consider pharmacologic testing in patients with low gradient stenosis and LV dysfunction in order to identify true anatomically severe aortic stenosis, as published in 1998 in the American College of Cardiology/American Heart Association practice guidelines for the management of patients with valvular heart disease,\(^{37}\) is (to the best of our knowledge) based on only two published reports providing data on outcome: one retrospective study\(^{15}\) that used nitroprusside administration during cardiac catheterization in 7 patients, 3 of whom underwent surgery; and one report\(^{16}\) on 18 patients studied by dobutamine echocardiography, only 4 of whom underwent aortic valve replacement. The paucity of published data reflects the difficulty in conducting a controlled study in a group of patients with considerable cardiac and noncardiac morbidity and different comorbid factors influencing therapeutic considerations. The variation in comorbid factors and clinical profiles remains a limitation when comparing the clinical course of different subgroups. Nevertheless, the present study confirms the pathophysiologic concept outlined in the two cited studies in a prospective manner, further supporting the recommendations of the American College of Cardiology/American Heart Association practice guidelines.

Referring physicians were not blinded to the test result because withholding this information would have been unethical, particularly in light of the current recommendations.\(^{37}\) However, defining the criteria for management recommendations according to the result of the dobutamine echocardiography beforehand enabled us to compare the outcome of such decisions prospectively as a function of concordance or discordance with the test results.

Coronary artery disease has been identified as the sole independent predictor of 30-day mortality in patients with aortic stenosis and severe LV dysfunction who are undergoing aortic valve replacement,\(^{38}\) and another retrospective study\(^{17}\) found an excess of surgical mortality in patients with aortic stenosis and poor LV function who had a history of myocardial infarction. In view of these data, it is important to emphasize that > 70% of the patients in our study had experienced a myocardial infarction (in the study by DeFillipi et al,\(^{16}\) only 44% of the patients had coronary artery disease). Thus, surgery seems to be justified in this patient group, as long as the contractile reserve is retained.

**Conclusion**

The assessment of valvular hemodynamics and myocardial function during low-dose dobutamine infusion can guide decision making in patients with aortic stenosis and LV dysfunction and can predict outcome as a function of the management strategy. Such patients have a better outcome when management decisions are based on the result of a dobutamine echocardiogram. Patients with relatively low transvalvular gradients, who have been identified as having severe aortic stenosis and preserved contractile reserve by dobutamine echocardiography, have a better outcome when undergoing surgery, while patients identified as having nonsevere aortic stenosis by dobutamine echocardiography can be managed conservatively. Although aortic valve resistance is relatively flow-independent and showed a trend toward better discrimination between severe and nonsevere aortic stenosis at rest, definite assessment of lesion severity requires dobutamine echocardiography.

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