

Low-Output, Low-Gradient Aortic Stenosis in Patients With Depressed Left Ventricular Systolic Function

The Clinical Utility of the Dobutamine Challenge in the Catheterization Laboratory

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Background—Although aortic valve replacement can be performed at an acceptable risk level in selected patients with left ventricular systolic dysfunction and low-output, low-gradient aortic stenosis, not all patients presenting with these hemodynamics will benefit from the operation. Some patients may have only mild aortic stenosis, despite a small calculated valve area. We report on the clinical utility of diagnostic dobutamine stimulation during cardiac catheterization in these diagnostically challenging patients.

Methods and Results—Thirty-two patients with low-output, low-gradient aortic stenosis and an ejection fraction <40% had dobutamine infusion in the catheterization laboratory. On the basis of the results of the dobutamine test, 21 patients underwent aortic valve replacement. All patients with a final aortic valve area ≤ 1.2 cm² at peak dobutamine infusion and a mean gradient of >30 mm Hg were found to have severe calcific aortic stenosis at operation. In the 15 patients in whom contractile reserve was identified during dobutamine challenge (increase in stroke volume >20%), 1 patient died perioperatively (7% mortality) and 12 patients were alive in New York Heart Association class I or II status at follow-up.

Conclusions—In patients with left ventricular systolic dysfunction and aortic stenosis with a low output and a low mean gradient, dobutamine challenge may aid in selecting those who would benefit from an aortic valve operation. (*Circulation*. 2002;106:809-813.)

Key Words: valves ■ cardiomyopathy ■ hemodynamics ■ inotropic agents ■ surgery

In patients with anatomically severe aortic stenosis and a low ejection fraction, aortic valve replacement (AVR) will relieve symptoms and improve survival. However, a subset of patients who present with low-output, low-gradient aortic stenosis and a small calculated valve area may not have true severe, fixed aortic stenosis but rather a concomitant cardiomyopathy and only mild aortic stenosis.^{1,2} In such patients, the calculated effective valve area may be small because of inaccuracy of the standard valve area formula at low flow states or because of a lack of contractile force to fully open the aortic valve.^{3,4} The American College of Cardiology/American Heart Association (ACC/AHA) guidelines have suggested that determining the hemodynamic response of the aortic valve gradient and valve area to inotropic stimulation may aid in differentiating these 2 subgroups of patients.⁵ There has been limited information on (1) criterion for differentiating these patients with low-output, low-gradient aortic stenosis and (2) the clinical outcome based on this response to inotropic stimulation.⁶⁻⁸ The purpose of the

present study is to report on the clinical utility of the hemodynamic results obtained with dobutamine stimulation at the time of cardiac catheterization in patients with low-output, low-gradient aortic stenosis.

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Methods

Patient Selection

The study was reviewed and approved by the Mayo Clinic Institutional Review Board. All patients provided informed consent for entry into the Mayo Clinic cardiac catheterization laboratory database. This study consisted of 32 patients who underwent dobutamine infusion as an extension of the clinical assessment of aortic stenosis severity by cardiac catheterization over an 8-year study period (October 1992 through October 2000) in the Mayo Clinic catheterization laboratory database. Patients were selected for catheterization on the basis of the initial clinical and echocardiographic findings of aortic stenosis and left ventricular dysfunction.⁹ Criteria for selection included (1) diagnosis of aortic stenosis with a calculated valve area <1.0 cm² by the continuity equation, (2) mean aortic valve gradient

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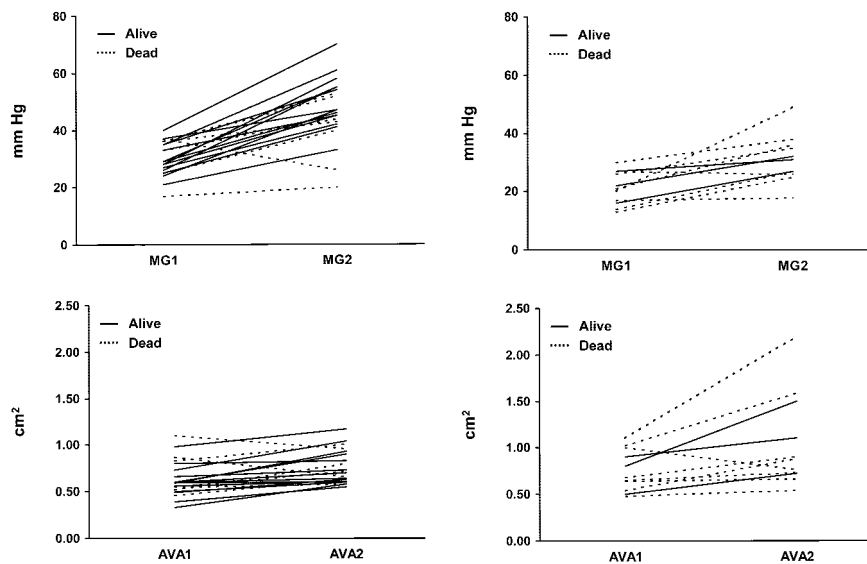


Figure 1. Response of mean aortic valve gradient (MG; top) and aortic valve area (AVA; bottom) at baseline (1) and during peak dobutamine infusion (2). Left, Patients who underwent aortic valve replacement. Right, Patients who underwent medical therapy only. Solid line indicates patients who were alive at follow-up; dotted line, those who were dead at follow-up.

<40 mm Hg,⁶ and (3) ejection fraction <40%. These patients were prospectively sent to cardiac catheterization so that a clinical decision on the need for aortic valve operation could be made.

Catheterization Procedure

Hemodynamic catheterization was performed with simultaneous measurement of left ventricular and ascending aortic pressures. Aortic pressure was measured from a 6-French pigtail catheter passed retrogradely into the ascending aorta and placed within 2 to 3 cm above the aortic valve.² Left ventricular pressure was obtained from either a transeptal approach or a second arterial access with a pigtail catheter placed retrogradely across the aortic valve. The mean gradient was measured from 8 to 10 consecutive beats of simultaneous left ventricular and ascending aortic pressures. Cardiac output was determined by the thermodilution method in 27 patients and green-dye dilution method in the 5 remaining patients. Coronary angiography was performed, and significant coronary artery disease was defined as a diameter stenosis >70%.

Dobutamine Study Protocol

Baseline measurements of cardiac output, left ventricular pressure, aortic pressure, and mean aortic pressure gradient were recorded. Dobutamine infusion was started at $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and was increased with increments of 3 to $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ every 5 minutes. The predetermined end points were a maximal dose of $40 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, mean gradient >40 mm Hg, 50% increase in the cardiac output, heart rate >140 beats per minute, or intolerable symptoms or side effects.

Calculations

Aortic valve area was calculated by the Gorlin equation,¹⁰ and the aortic valve resistance was calculated from the formula of Cannon et al.⁴ Contractile reserve during dobutamine challenge was defined as an increase in stroke volume of $\geq 20\%$.⁶

Treatment and Follow-Up

The results of the acute hemodynamic study were available to the clinician caring for the patient. The decision to proceed with AVR was made by the clinician after the results of the dobutamine study were known. Clinical follow-up, obtained by either a return visit to our institution or a telephone questionnaire, was available in all patients. The median follow-up was 32 months.

Statistical Analysis

Data are expressed as mean \pm SD for continuous variables. To determine whether dobutamine infusion resulted in a change in

hemodynamic parameters, comparisons of data before and after dobutamine infusion were performed with the paired Student's *t* test for data with a gaussian distribution and a Wilcoxon signed rank test for a nongaussian distribution.

Results

Patient Population

Of the 32 patients who met the criteria for the study, 30 (94%) were male and 2 (6%) were female, with a mean age of 74 ± 9 years. Eight patients had prior coronary artery bypass surgery, and 2 had prior mitral valve replacement. Coronary angiography was performed in 31 (97%) of the studies. Nine patients (28%) had no significant coronary artery disease. Atrial fibrillation or atrial flutter was present in 11 patients (34%), and 1 patient had a permanent pacemaker for complete heart block. The mean ejection fraction by echocardiography for the entire group was $23 \pm 7\%$, with a range of 10% to 39%. All patients presented with New York Heart Association (NYHA) class III or IV heart failure symptoms.

Acute Hemodynamic Study

The mean dose of dobutamine at peak response was $22 \pm 8 \mu\text{g}/\text{min}$ (8 to $40 \mu\text{g}/\text{min}$). Reasons for terminating the test included achieving a mean gradient >40 mm Hg (22 patients; 69%), doubling of the cardiac index (4 patients; 12%), reaching maximal dose of dobutamine (4 patients; 12%), heart rate >140 beats per minute (1 patient; 3%), and hypotension (1 patient; 3%). The systolic blood pressure of the patient who developed hypotension decreased from 111 to 83 mm Hg. Five patients (16%) experienced isolated premature ventricular contractions, but none had complex ventricular arrhythmias that would have required termination of the study. There were no other adverse effects of the dobutamine infusion in this group (Figure 1).

Overall, during dobutamine infusion, heart rate increased by $27 \pm 20\%$ and left ventricular systolic pressure by $13 \pm 16\%$. The ascending aortic pressure and left ventricular end-diastolic pressure did not change significantly. Overall, cardiac output increased from 3.1 ± 0.9 to 5.4 ± 1.2 L/min

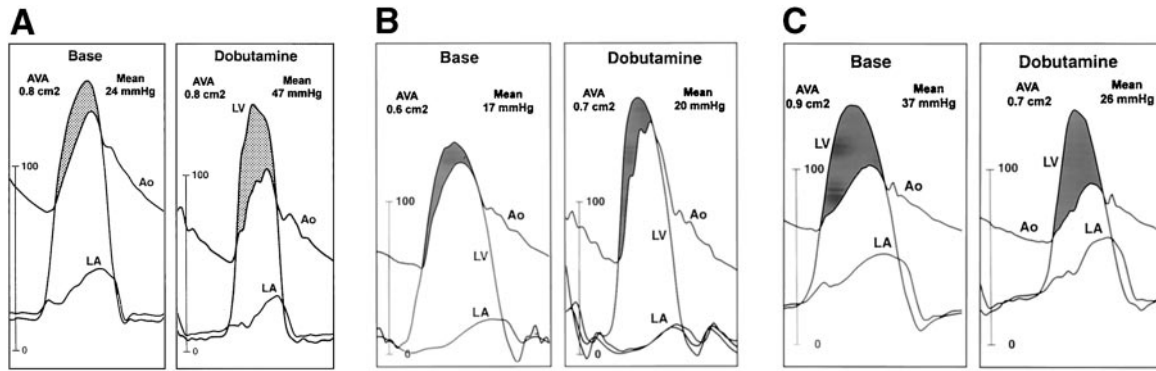


Figure 2. Representative hemodynamic tracings from 3 patients representing 3 different responses to dobutamine. A, This patient responded to dobutamine infusion with an increase in cardiac output and an increase in aortic valvular mean gradient from 24 to 47 mm Hg. The aortic valve area (AVA) remained 0.8 cm². This patient had severe aortic stenosis at the time of aortic valve replacement and is alive in NYHA class I after the operation. B, The patient responded to dobutamine infusion with an increase in cardiac output and an increase in mean aortic valvular gradient from 17 to 20 mm Hg. The final aortic valve area was 0.7 cm². This patient was found to have only mild aortic stenosis at the time of operation. C, This patient had no change in cardiac output, and the mean aortic valvular gradient decreased from 37 to 26 mm Hg in response to dobutamine infusion. The test was terminated because of hypotension. This patient had severe aortic stenosis at the time of aortic valve replacement but died 2 years postoperatively because of heart failure. Ao indicates aortic; LA, left atrial; LV, left ventricular; and base, baseline.

($P < 0.01$) and the mean aortic valve gradient from 27 ± 7 to 41 ± 13 mm Hg ($P < 0.01$). The stroke volume increased from 38 ± 14 to 51 ± 13 mL ($P < 0.01$). There was an increase in aortic valve area from 0.70 ± 0.20 to 0.86 ± 0.35 cm² ($P < 0.01$).

The baseline aortic valve resistance was 274 ± 109 dyne · s · cm⁻⁵. There was no significant change in aortic valve resistance during dobutamine infusion. The aortic valve resistance of the patients with a final aortic valve area > 1.2 cm² was not significantly different from that of patients with a final aortic valve area ≤ 1.2 cm² (283 ± 122 versus 276 ± 99 dyne · s · cm⁻⁵).

Figure 2 shows illustrative hemodynamic tracings before and after dobutamine infusion from 3 patients.

Clinical Course

Twenty-one patients had AVR on the basis of the results of the dobutamine test (Figure 3). These patients all had an aortic valve

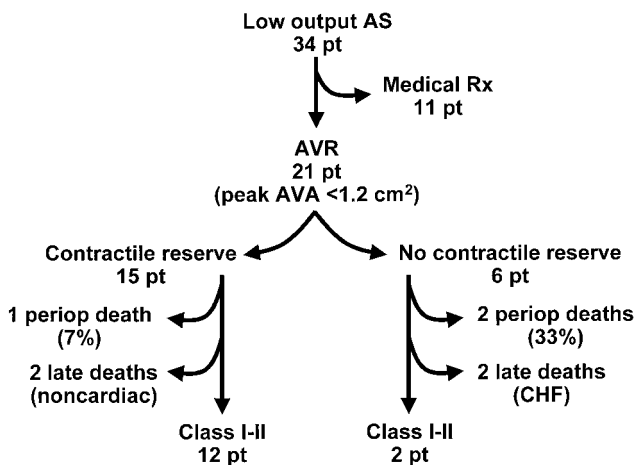


Figure 3. Clinical outcome of the patients (pt) with low-output aortic stenosis (AS) who underwent AVR. Contractile reserve was defined as an increase in stroke volume $> 20\%$ during dobutamine infusion. CHF indicates congestive heart failure; AVA, aortic valve area; periop, perioperative; and Rx, treatment.

area of ≤ 1.2 cm² at peak dobutamine infusion. Seven of these patients had undergone prior open heart surgery: coronary artery bypass grafting (CABG) in 6 and mitral valve replacement in 1. Concomitant CABG was performed in 9 patients at the time of AVR. The surgical findings were reviewed in the 21 patients who had AVR. In 1 patient, direct inspection of the valve revealed findings consistent with mild-to-moderate aortic stenosis. The peak aortic valve gradient during dobutamine infusion was only 22 mm Hg in this patient. Twenty of the patients had severe calcific aortic stenosis on inspection of the valve at operation. Nineteen patients had aortic valve gradients > 30 mm Hg during dobutamine infusion. The remaining patient with severe calcific aortic stenosis on inspection had a mean gradient of 32 mm Hg at rest, which decreased to 26 mm Hg during dobutamine infusion.

There were 3 perioperative deaths within 30 days of the operation (14%). One patient could not be weaned off the pump, and 2 patients died in the hospital 1 month postoperatively, both from multiorgan failure. Follow-up was obtained in all patients for a median duration of 32 months. During follow-up, 2 patients died of heart failure and 2 of noncardiac causes. At last follow-up, 14 patients were alive and all were in NYHA class I or II. In 13 patients in whom an ejection fraction was measured at least 6 months postoperatively, it had increased from 21% to 39% ($P < 0.001$).

Eleven patients did not undergo AVR. Seven patients were thought not to have severe aortic stenosis on the basis of the dobutamine infusion. Three of these patients had a final aortic valve area > 1.2 cm², and 4 had a final mean gradient < 30 mm Hg at peak dobutamine infusion. Four patients had a final mean gradient with dobutamine of 30 to 40 mm Hg but were thought to be at too high risk for operation. At follow-up, 7 of these patients had died from progressive heart failure and one died suddenly.

Subgroup of Patients With a Resting Aortic Valve Mean Gradient < 30 mm Hg

Twenty-two patients presented with a resting aortic valve mean gradient of ≤ 30 mm Hg. Of these, 11 patients had an

aortic valve operation. Ten patients had severe aortic stenosis at the time of operation, and all patients had an aortic valve mean gradient >30 mm Hg during dobutamine infusion. All 10 patients are alive and in NYHA class I or II at follow-up. Two of these 10 patients with severe aortic stenosis at the time of operation had an aortic valve area ≥ 1.0 cm² during dobutamine infusion. The one patient with a mean gradient <30 mm Hg during dobutamine infusion was found to have mild aortic stenosis at the time of operation, despite an aortic valve area of 0.7 cm² at peak infusion.

Contractile Reserve in Patients Undergoing AVR

The patients who had AVR were divided into 2 groups on the basis of the presence or absence of a contractile response to dobutamine infusion (Figure 3).⁶ Fifteen patients had an increase in stroke volume of $>20\%$ during dobutamine infusion (group I). The remaining 6 patients (group II) had a $<20\%$ increase in stroke volume during dobutamine infusion.

In group I, all 15 patients came off the pump and left the operating room with stable hemodynamics. There was one perioperative death (perioperative mortality rate, 7%). Two late noncardiac deaths were due to carcinoma and a neurological event. All 12 survivors are alive and in NYHA class I or II at follow-up.

In group II, 2 of the 6 patients died perioperatively (perioperative mortality rate, 33%). Two additional patients died of progressive heart failure 25 and 34 months after the operation. The 2 remaining patients are alive and in NYHA class I or II at follow-up. In these 2 survivors, the final mean aortic valve gradient during dobutamine infusion was >50 mm Hg.

Discussion

This study is the first to report on the clinical utility of a diagnostic dobutamine challenge in the catheterization laboratory for patients with low-output, low-gradient aortic stenosis. On the basis of the results of the dobutamine challenge, 21 patients were sent for AVR. All had a final aortic valve area during dobutamine stimulation ≤ 1.2 cm², and the 20 patients who had confirmed severe aortic stenosis at operation had an initial or final mean gradient of >30 mm Hg. The overall 30-day perioperative mortality was 14%. Sixty-seven percent of these patients are alive and in NYHA class I or II at follow-up. This outcome is in contrast to the initial report by Carabello et al,¹ in which all patients with low-output, low-gradient aortic stenosis either died at operation or remained severely symptomatic. The identification by inotropic stimulation of a subgroup of patients with low-output, low-gradient aortic stenosis who respond favorably to operation supports the recent recommendations proposed by the ACC/AHA guidelines on valvular heart disease.^{2,5}

Low-Output, Low-Gradient Aortic Stenosis

In patients with documented severe valvular aortic stenosis and left ventricular dysfunction, aortic valve operations can be performed with low mortality and excellent results.¹¹⁻¹⁴ However, there is a subset of patients with aortic stenosis and left ventricular systolic dysfunction who present with a low mean aortic valve gradient and have a poor outcome after an

aortic valve operation.^{1,15} The poor outcome in this subset may have been due to the inclusion of patients who had a primary contractile dysfunction that is responsible for the low ejection fraction and low cardiac output. In these patients, there may be only a mild degree of aortic stenosis, which results in a small calculated valve area for several reasons. The low output reduces the valve-opening forces, and so a mildly stenotic valve may have limited mobility.^{2,5,6,8} In addition, the Gorlin equation used for the calculation of valve area may not be applicable in the presence of a low cardiac output and low aortic valve gradient.^{3,4} This is in contrast to patients with fixed severe aortic stenosis, in whom the cardiac output is diminished because of the high afterload on the left ventricle. It is the latter subset of patients who, when carefully selected, will benefit from AVR.

More recent studies have reported a lower operative mortality in patients with low-output, low-gradient aortic stenosis^{16,17} compared with the initial report by Carabello et al,¹ presumably because of advances in operative technique and myocardial preservation. However, in the study from our own institution, 40% of these patients died after a median of 1.5 years of follow-up. Several patients in this previous study had less than severe aortic stenosis noted by the surgeon at the time of operation, and thus it has been the practice at our institution to use dobutamine stimulation to assess the severity of aortic stenosis fully in these patients.

The definition of "low-gradient" aortic stenosis has varied from study to study. The original study by Carabello and coworkers¹ defined low gradient as <30 mm Hg, but subsequent studies have used the criteria of mean aortic valve gradients <35 mm Hg^{4,7} and <40 mm Hg.⁶ In this study, all patients with a mean gradient >30 mm Hg in conjunction with a small valve area were found to have severe aortic stenosis at the time of operation. Therefore, we do not believe that patients with a mean gradient >30 mm Hg and a small aortic valve area need further diagnostic testing.

Results of Dobutamine Challenge

The ACC/AHA guidelines for the management of valvular heart disease recommended the use of dobutamine challenge to differentiate between patients with true severe aortic stenosis and those with a low cardiac output and only mild aortic stenosis by examining the response of the aortic valve gradient, stroke volume, and valve area.⁵ Prior studies have reported the results of noninvasive echocardiography in response to dobutamine.⁶⁻⁸ These studies had focused only on the change in valve area (<0.3 cm² change) and absolute valve area (<1.0 cm² change) during dobutamine infusion as an indicator of severe aortic stenosis. In our data, these criteria would have misclassified 9 patients who had surgical confirmation of the severity of aortic stenosis. Eight patients had severe aortic stenosis at the time of operation, of whom 4 had an absolute aortic valve area ≥ 1.0 cm², and 5 had an increase in aortic valve area ≥ 0.3 cm² during dobutamine infusion. All these patients had a mean gradient >30 mm Hg at peak dobutamine infusion (7 of 8 had a mean gradient >40 mm Hg). One patient with mild aortic stenosis confirmed at operation met the above criteria for severe aortic stenosis by valve area but had a mean gradient <30 mm Hg

during dobutamine infusion. It is thus necessary to use both the valve area and mean gradient to interpret the results of this hemodynamic study.

The contractile reserve, as assessed by the change in stroke volume during dobutamine infusion, was of prognostic value in patients undergoing aortic valve operation. In patients with a contractile reserve, the operative mortality rate was only 7%, and no patient died as a result of heart failure either perioperatively or during follow-up. In the patients without contractile reserve, the operative mortality rate was 33%, and another 33% died of heart failure during follow-up. These findings are supported by Monin et al,⁶ who demonstrated similar operative mortality on the basis of the presence or absence of a contractile reserve assessed by dobutamine echocardiography.

Limitations

The number of patients in this clinical observational study is small. The decision to proceed with aortic valve intervention was based on results of the dobutamine challenge, and it is unknown what the outcome of the patients treated medically would have been if they had undergone the operation. In addition, these patients were referred to the cardiac catheterization laboratory only after a clinical decision had been made that the patient's comorbid factors would not preclude an operation. Other confounding factors may have played a role in the overall survival and outcome, such as concomitant coronary artery disease, severity of underlying left ventricular dysfunction, and coexisting serious medical problems. The relatively low operative mortality from our institution in these high-risk patients might not be applicable to all other institutions.

Aortic valve resistance has been shown to be less dependent on flow than the calculated aortic valve area,⁴ and the lack of overall change in resistance during hemodynamic manipulation was confirmed in this study. Because of the lack of a population for comparison, the diagnostic accuracy of valve resistance could not be assessed.

Summary

Patients who present with left ventricular systolic dysfunction and aortic stenosis with a low output and a low mean gradient present a diagnostic and therapeutic challenge. Patients with true fixed aortic stenosis must be differentiated from those with a primary myocardial process and only mild aortic stenosis. Diagnostic stimulation with dobutamine can be done safely in the cardiac catheterization laboratory and may aid in determining which patients could benefit from an aortic valve operation. Both the mean aortic valve gradient and the aortic valve area at rest and in response to stimulation should be taken into consideration. On the basis of our data, we think that patients will have true fixed aortic stenosis if they have (1) a mean aortic valve gradient >30 mm Hg at rest or dobutamine infusion and (2) an aortic valve area that remains ≤ 1.2 cm² during dobutamine infusion. The presence or absence of a contractile reserve ($>20\%$ increase in stroke

volume during dobutamine infusion) is of prognostic value in these patients undergoing an aortic valve operation. Evaluation of larger numbers of patients is necessary, and the utility of other criteria, such as aortic valve resistance,^{4,18,19} needs to be investigated.

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