Dobutamine Challenge for Low-Gradient Aortic Stenosis

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In adults with valvular aortic stenosis (AS), valve replacement is recommended in the presence of symptoms and severely reduced aortic valve area (AVA).1 In such patients, valve replacement improves symptoms and survival, even in the setting of left ventricular (LV) dysfunction. LV dysfunction in severe AS is usually due to afterload mismatch; valve replacement relieves the afterload excess imposed by the stenotic valve and improves LV performance.2 However, a subset of patients with “severe” AS, LV dysfunction, and low-transvalvular gradient has been reported to have a relatively high operative mortality and poor prognosis.2–4 This clinical scenario has been termed “low-flow, low-gradient AS.” Accurate assessment of AVA in such patients is difficult because (1) calculated AVA is directly proportional to forward stroke volume, and (2) the Gorlin constant varies at low-flow states.5–7 Some patients with low-flow, low-gradient AS have a reduced AVA as a result of inadequate forward stroke volume rather than anatomic stenosis, a situation analogous to reduced anterior mitral leaflet excursion in dilated cardiomyopathy where there is not enough forward flow to fully open the valve. For example, Cannon et al8 showed that some patients with low-gradient AS were found to have only mild AS at surgery despite a Gorlin AVA indicating critical AS. Obviously, surgical therapy is unlikely to benefit such patients because their primary pathology is a cardiomyopathy. On the other hand, patients with severe anatomic AS may benefit from valve replacement despite the increased operative risk associated with a low-flow, low-gradient hemodynamic state. The recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines for managing valvular heart disease recommends hemodynamic evaluation of low-flow, low-gradient AS using dobutamine echocardiography to distinguish patients with fixed anatomic AS from those with flow-dependent (“relative”) AS in patients with LV dysfunction and low-transvalvular gradients.1

Role of Dobutamine Echocardiography
DeFilippi et al9 first reported dobutamine echocardiography in 18 patients with symptomatic severe native valve AS (AVA ≤0.5 cm²/m², mean gradient ≤30 mm Hg, and LV ejection fraction ≤0.45). Mean aortic gradient, AVA, and aortic valve resistance were measured at baseline and peak dobutamine (up to 20 μg/kg per minute). Three basic patterns of dobutamine responsiveness were observed: fixed AS, relative AS, and absence of contractile reserve (ie, failure of dobutamine to elicit a significant increase in forward stroke volume). Fixed AS was characterized by dobutamine-induced increases in peak velocity, mean gradient, and valve resistance with no change in AVA. All patients with contractile reserve and fixed AS had an increase of ≥0.6 m/s in peak velocity and ≥10 mm Hg in mean gradient. In contrast, relative AS was characterized by a significant increase in calculated AVA (≥0.3 cm²) without a significant change in peak velocity, mean gradient, or valve resistance. No hemodynamic variable changed significantly in the patients without contractile reserve. Although the study was too small to draw conclusions regarding outcome, fixed AS generally fared well with valve replacement.

Subsequent studies have shown similar results. Monin et al10 studied 45 patients with low-flow, low-gradient AS by dobutamine echocardiography. Operative mortality at 30 days was only 8% (2 of 24) in patients with contractile reserve compared with 50% (3 of 6) in those without contractile reserve. LV ejection fraction and NYHA functional class improved significantly in patients with contractile reserve who survived valve replacement.

Schwammenthal et al11 studied 24 patients with low-flow, low-gradient AS by dobutamine echocardiography and followed them for a mean of 17±10 months. Contractile reserve with fixed AS was reported in 16 subjects, 8 of whom subsequently underwent valve replacement. All 8 survived surgery with improved functional class.

Dobutamine Challenge in the Catheterization Laboratory
In this issue of Circulation, Nishimura et al12 report for the first time the use of dobutamine infusion during cardiac catheterization to evaluate the hemodynamics of low-flow, low-gradient AS. Patients were enrolled if they had AVA <1.0 cm², a mean gradient <40 mm Hg, and LV ejection fraction <40%. A total of 32 patients with NYHA III-IV heart failure were evaluating using careful hemodynamic evaluation with dual 6-French pigtail catheters, one in the LV and one in the ascending aorta. Cardiac output was measured by thermodilution in 27 patients and green dye in the other 5. After the initial hemodynamic recordings, dobutamine was started at 5 μg/kg per minute and increased to either a peak dose of 40 μg/kg per minute, an increase in mean gradient to >40 mm Hg, an increase in heart rate >140 minutes⁻¹, or a 50% increase in cardiac output. The dobutamine infusion was well tolerated, with 5 patients experiencing isolated prema-
ture ventricular contractions and 1 patient experiencing hypotension. For the entire group of 32 patients, significant increases were observed for stroke volume (38±14 to 51±13 mL), cardiac output (3.1±0.9 to 5.2±1.0 L/min), mean gradient (27±7 to 41±13 mm Hg), and AVA (0.7±0.2 to 0.9±0.4 cm²). In contrast, aortic valve resistance was unchanged (283±122 versus 276±99 dynes · cm · cm⁻¹).

As in the previous studies with dobutamine echocardiography, clinical management of the patients was left to the discretion of the referring physician. Valve replacement was performed in 21 patients, one of whom was found to have only mild to moderate AS at surgical inspection. Interestingly, the mean gradient at peak dobutamine in this patient was only 22 mm Hg. In the 15 patients with contractile reserve, defined as a dobutamine-induced increase in stroke volume of >20%, 30-day mortality was 7% (1 death due to multisystem organ failure). Two others died later of noncardiac causes. The 12 survivors had improvement in heart failure symptoms to NYHA Class I or II. Of the 6 patients without contractile reserve who underwent operation, 2 died perioperatively (33%) and 2 more died later of progressive heart failure. The authors correctly conclude that dobutamine infusion in the catheterization laboratory may be helpful in identifying which patients with low-flow, low-gradient AS have a truly fixed anatomical stenosis that may benefit from valve replacement. The findings also confirm that contractile reserve is an important prognostic indicator in these patients.

Clinical Implications

Several clinical observations and recommendations deserve to be emphasized for the practicing cardiologist in applying the results of the present study and the previous studies using dobutamine echocardiography. First, it does not really matter whether one uses Doppler echocardiographic or invasive hemodynamic measurements of AS severity during dobutamine challenge, it is the quality of the data that counts. In the catheterization laboratory, simultaneous measurements of LV and ascending aortic pressures are essential. This can be done using a dual-tip Millar catheter or fluid-filled pigtail catheters in both the LV and ascending aorta. It is not acceptable to measure the mean gradient from a “pull-back” of the LV catheter, nor from simultaneous comparison of LV pressure to femoral sheath pressure. Likewise, the choice of method for assessing cardiac output is important. Thermodilution is convenient and accurate, provided that there is no significant tricuspid regurgitation. Fick output may offer an advantage when cardiac output is low, as is often the case in this condition. Angiographic outputs are generally less accurate. Ideally, confirmation of cardiac output by two different methods is best and increases confidence in the results.

If Doppler echocardiography is used, it is important to carefully and accurately measure the LV outflow tract diameter as recommended by the American Society of Echocardiography. The LV outflow tract velocity-time integral should be measured for 3 to 5 beats and averaged using planimetry of the modal velocity signal, not the outer edge. Peak aortic velocity should be sought from multiple windows, including apical, right parasternal, and suprasternal. In contrast to the present study, the dobutamine infusion should not be increased to more than 20 μg/kg per minute. There are two reasons for this recommendation. The first is safety. In our laboratory, we have seen ventricular tachycardia in patients with low-flow, low-gradient AS, even at doses of 15 to 20 μg/kg per minute. Therefore, a crash cart and ACLS-trained personnel should be in the room during dobutamine challenge. Second, the maximal inotropic effect of dobutamine occurs at 20 μg/kg per minute. Higher doses merely add to the chronotropic response and generally used to provoke ischemia during dobutamine echocardiography. Higher doses also cause stroke volume to decline as cardiac output becomes more dependent on heart rate. Lower doses are sufficient to elicit contractile reserve without a significant increase in heart rate, which facilitates the acquisition of accurate Doppler velocity profiles.

The definition of low-flow, low-gradient AS remains somewhat unclear. The present study and that of Monin et al enrolled patients with a mean gradient <40 mm Hg, which is certainly not “low-gradient” AS. In fact, the Nishimura study did not show a benefit of dobutamine challenge in patients with a mean gradient >30 mm Hg. We concur with the ACC/AHA guidelines that low-gradient AS should be defined by a mean gradient <30 mm Hg and a calculated AVA <1.0 cm². The definition of a low-flow state is more difficult. LV ejection fraction is not adequate. According to the Gordin equation (or continuity equation), calculated AVA is dependent on transvalvular flow and velocity. Flow is determined from the stroke volume and systolic ejection period and velocity is either measured by Doppler technique or calculated from the mean pressure gradient. Note that LV ejection fraction is not a part of the equation. One could have a normal ejection fraction and low–forward stroke volume if there were significant mitral regurgitation. Conversely, a low–ejection fraction in the setting of a very dilated LV might have a near normal stroke volume. In the latter case, the gradient would not be expected to be low and dobutamine challenge would be unnecessary. Perhaps it would be more accurate if we changed the terminology from “low-flow, low-gradient AS” to “low-stroke volume, low-gradient AS,” or simply “low-gradient AS.”

Defining the hemodynamic subsets of dobutamine responsiveness is also uncertain. Nishimura et al point out that the response should be determined both by the AVA and the mean gradient. However, their cutoff values were slightly different from those in the deFilippi study. Until much larger studies are available, the precise values for AVA and mean gradient that predict surgical outcome are uncertain and must be left to clinical judgment.

In patients with low-gradient AS, dobutamine challenge may help select patients for valve replacement. It appears that patients with contractile reserve and fixed AS have a relatively good prognosis with valve replacement. Such patients have improved LV ejection fraction and reduced heart failure symptoms. LV contractile reserve appears to be an important variable whose absence portends a poor prognosis. Unfortunately, these clinical recommendations are based on four small, single-center observational studies, two of which contain patients that do not meet the definition of low-gradient AS. Given that a randomized trial is neither ethical nor feasible, it is time to establish a registry of dobutamine
challenge for low-gradient AS to help establish specific criteria for selecting patients who will benefit from valve replacement.

References

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