# Editorial

# Assessment of Low-Gradient Aortic Stenosis With Dobutamine

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Low-gradient aortic stenosis (AS) has been a vexing problem for cardiologists since its original description in 1980 by Carabello et al.[1] In that study, 3 of 4 patients with low-gradient AS died at surgery, and the other patient had persistent severe heart failure postoperatively. Subsequent studies showed that although operative mortality is high, most patients survive aortic valve replacement (AVR), and some have dramatic improvement in symptoms and left ventricular (LV) function.[2,3] The challenge facing clinicians is how to accurately distinguish those patients who will benefit from AVR from those who will not. The American College of Cardiology/American Heart Association guidelines for valvular heart disease recommend hemodynamic evaluation of low-gradient AS with dobutamine echocardiography to distinguish patients with fixed anatomic AS from those with flow-dependent ("relative") AS in patients with LV dysfunction.[4] In the latter case, aortic valve area (AVA) is spuriously low because there is not enough forward flow to fully open the leaflets.[5–7] To understand how dobutamine infusion helps sort out the dilemma of low-gradient AS, it is useful to revisit the hemodynamic principles that govern the relationship between AVA, flow, and gradient.

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## The Gorlin Formula

In 1951, Gorlin and Gorlin proposed the "hydraulic orifice equation" for calculation of valve area in valvular stenosis.[8] The Gorlin formula was based on the fundamental equation:

$$A = \frac{F}{V},$$

in which valve area (A) is equal to transvalvular flow (F), divided by transvalvular velocity (V). In AS, the Gorlin formula is used to calculate AVA as:

$$AVA = \frac{CO \div (HR \cdot SEP)}{C_d \cdot \sqrt{MPG}}.$$

Because transvalvular flow occurs during systole in AS, the numerator (flow) becomes the cardiac output (CO) divided by heart rate times systolic ejection period (SEP), or stroke volume

divided by SEP. The denominator (velocity) could not be measured in 1951 (Doppler echocardiography did not exist), so it was calculated from the pressure drop across the valve as the product of the discharge coefficient ($C_d$) times the square root of the mean pressure gradient (MPG). The discharge coefficient accounts for energy losses that occur when potential energy (pressure) is converted to kinetic energy (velocity) as flow accelerates across the stenosis. For AS, the Gorlin formula uses an empiric discharge coefficient of 44.5.

## Low-Gradient AS

Figure 1 illustrates the relationship between MPG and transvalvular flow according to the Gorlin formula for 3 fixed values for AVA, representing mild, moderate, and severe AS. Below a transvalvular flow of 175 mL/s, mean gradient is <20 mm Hg regardless of AVA. Thus, a low gradient does not exclude anatomically severe AS in the setting of low transvalvular flow (ie, severe LV dysfunction). Conversely, a low calculated AVA in such patients does not necessarily indicate anatomically severe AS. Some patients with low-gradient AS have a low calculated AVA because there is not enough forward flow to fully open the valve. In these patients, AVA is not fixed but is flow dependent.

## Rationale for Dobutamine Challenge

The rationale for using a dobutamine challenge is also illustrated in Figure 1. The open circle labeled "Bsl" (for "baseline") illustrates a patient with a low transvalvular flow of 150 mL/s, a mean gradient of 23 mm Hg, and AVA of 0.7 cm². Two possible responses to dobutamine are shown. In one scenario ("dob 1"), transvalvular flow increases to 225 mL/s, mean gradient more than doubles to 52 mm Hg, and AVA remains 0.7 cm². This hemodynamic response indicates fixed anatomic AS, and it is thought that such patients will generally benefit from AVR. In a second scenario ("dob 2"), transvalvular flow increases to 275 mL/s, mean gradient increases modestly to 38 mm Hg, and AVA increases to 1.0 cm². Such patients have "relative" AS or "pseudo-AS," in which AVA is not anatomically fixed but simply does not open fully at a low-flow state.[9,10] It is thought that such patients have severe LV dysfunction out of proportion to the degree of AS and are therefore less likely to benefit from AVR. A third scenario (not shown) is that dobutamine fails to elicit a significant increase in transvalvular flow, such that it is impossible to determine whether there is fixed AS or pseudo-AS. Such patients lack LV contractile reserve and have a poor prognosis (more on this later).

Although the 2 scenarios presented above are unambiguous, it may be difficult to interpret the response to dobutamine in individual patients, particularly if the increase in transvalvular
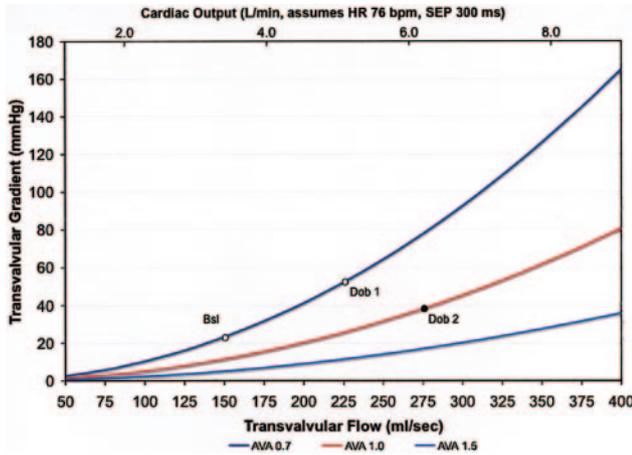
**Figure 1.** Plot of the relationship between mean gradient (y-axis) and transvalvular flow (x-axis, bottom) according to the Gorlin formula for 3 different values of AVA (0.7, 1.0, and 1.5 cm²). Cardiac output (x-axis, top) is also shown, assuming a heart rate of 75 bpm and systolic ejection period of 300 ms. At low transvalvular flows, mean gradient is low at all 3 valve areas. Two different responses to dobutamine challenge are illustrated for a hypothetical patient (○; Bsl) with a baseline flow of 150 mL/s, mean gradient of 23 mm Hg, and calculated AVA 0.7 cm². In one scenario (dob 1), flow increases to 225 mL/s, mean gradient increases to 52 mm Hg, and AVA remains 0.7 cm², consistent with fixed AS. In a second scenario, flow increases to 275 mL/s, mean gradient increases to 38 mm Hg, and AVA increases to 1.0 cm². This patient has changed to a different curve, consistent with relative or pseudo-AS. HR indicates heart rate; SEP, systolic ejection period.



**Figure 2.** Plot of the relationship between AVA and transvalvular flow at 3 different values for mean gradient (10, 20, and 40 mm Hg). The relationship is linear provided the gradient remains fixed. At a normal flow rate of 250 mL/s, there is good separation between calculated values for AVA; however, at low flow rates, calculated AVA is low, with little separation between values. HR indicates heart rate; SEP, systolic ejection period; and MPG, mean pressure gradient.

flow is small. Furthermore, the exact criteria for interpreting the response to dobutamine are different among published studies.[7,11–14] In this issue of *Circulation*, Blais et al[15] suggest a new parameter for classifying the hemodynamic response to dobutamine based on the projected AVA at a common transvalvular flow of 250 mL/s. This concept is theoretically attractive because it offers a rational solution to the common problem of achieving different transvalvular flows with dobutamine in different patients. Unfortunately, there are a number of issues that limit the practical applicability of these data. The first of these involves the accuracy of projecting AVA at a flow rate that may not be actually achieved by dobutamine infusion. Figure 2 plots AVA against transvalvular flow according to the Gorlin formula. The vertical dotted line represents a transvalvular flow rate for 250 mL/s. As can be seen, AVA increases linearly with transvalvular flow, provided mean gradient is constant. This is a problem because both AVA and gradient often change with increasing transvalvular flow.[7,11–14] Because the authors have used a linear formula to project AVA at a transvalvular flow of 250 mL/s, their formula inherently assumes a constant mean gradient. This formula appeared to work well in their small patient population, wherein mean gradient increased by a mean value of only 9 mm Hg in patients with pseudo-AS and 14 mm Hg in those with fixed AS. In patients with larger changes in mean gradient, it may not be possible to accurately project AVA at 250 mL/s using the linear formula proposed. Nonetheless, a large change in mean gradient is consistent with fixed AS and generally answers the clinical question satisfactorily.

Although the authors' proposal to normalize AVA for a normal flow rate is a good one, they have not demonstrated that it is more accurate then current, simpler methods. There are 2 reasons for this. First, the sample size was extremely small. There were only 23 patients who underwent surgical confirmation of aortic valve pathology. Of these, 8 were classified as pseudo-AS and 15 as fixed AS. Thus, a sensitivity difference ranging from 67% to 100% for detecting fixed AS was based on only 5 patients (10/15 versus 15/15). This is useful for hypothesis generation but does not prove superiority of the proposed method. Moreover, the comparison of 10 different echocardiographic covariates (see Figure 6[15]) in 23 patients is not statistically meaningful owing to the play of chance. Second, the classification of pseudo-AS versus fixed AS was based on highly subjective, nonvalidated inspection of the valves at the time of operation and afterward by a pathologist. The authors incorrectly state that "there is no alternative reference method available to determine the 'actual' stenosis severity in vivo." In fact, aortic valve calcium can be quantified in vivo by electron-beam or multidetector CT scans.[16] It is unfortunate that the valves were not weighed ex vivo, because valve weight is objective and reproducible and has been shown to correlate well with catheter-derived hemodynamic data.[17] In addition, quantitative determination of calcium content in the pathological specimens could have been performed by radiographic and/or biochemical methods.[18,19] Such objective validation of the surgical pathology would have greatly improved the quality of the study.

Another caveat to the present study is the nature of the patient population. Of 46 patients enrolled, only 23 underwent surgery. The determining factors for surgical versus medical treatment are not presented; however, it is noted that 18 of the 23 operated patients also underwent coronary artery bypass surgery. It is not clear whether coronary artery disease was the primary indication for operation, and AVR was also performed, or whether AVR was the primary reason for the operation. If the former is true, it

might help explain the higher prevalence of pseudo-AS than in other studies of low-gradient AS. Finally, it is very surprising that only 3% of the valves were classified as bicuspid. A renowned cardiac pathologist recently examined 932 aortic valves surgically explanted for AS and showed that 54% were either bicuspid or congenitally unicuspid aortic valves.[20] One must wonder whether the markedly low prevalence of bicuspid valves in the present study is a result of a nonrepresentative patient population or inaccurate classification at surgical or pathological examination.

In my opinion, there are 3 major echocardiographic variables to assess in patients with low-gradient AS. The first, although intuitively obvious, is often overlooked: valve anatomy. A markedly thickened, calcified valve is likely to be fixed AS; whereas minimally thickened or even normal-appearing leaflets are likely to represent pseudo-AS. The second is the hemodynamic response to dobutamine. According to the Gorlin formula, both AVA and mean gradient may be low in the setting of low transvalvular flow rate. Therefore, it seems prudent to consider both of these variables during dobutamine challenge. As can be seen from an examination of Figures 1 and 2, there is a wider relative difference in mean gradient than in AVA at a transvalvular flow rate of 250 mL/s or higher. Perhaps a larger study in a more representative patient population would have found this to be true. Nevertheless, Blais et al[15] have offered the attractive hypothesis that normalizing AVA for transvalvular flow may avoid some of the difficulties of interpreting dobutamine echocardiography in low-gradient AS. This hypothesis remains to be tested in a large group of patients with adequate characterization of aortic pathology or, better yet, with outcomes.

The third and perhaps most important variable is LV contractile reserve. In a relatively large, prospective multicenter study of 136 patients with low-gradient AS, Monin et al[14] have shown that operative mortality was 5% and 32% ($P=0.0002$) for patients with or without LV contractile reserve, respectively. Predictors of long-term survival were AVR and LV contractile reserve. If these data are correct, the decision to operate in low-gradient AS should be based on sufficient LV myocardial viability to increase transvalvular flow with dobutamine, rather than precise distinction between fixed and pseudo-AS. Clearly, more investigation is needed before we can confidently manage the difficult problem of low-gradient AS. Hopefully, such investigation will focus on operative and long-term outcomes in large, prospective, and representative populations.

## Disclosure

## References

1. Carabello BA, Green LH, Grossman W, Cohn LH, Koster JK, Collins JJ Jr. Hemodynamic determinants of prognosis of aortic valve replacement in critical aortic stenosis and advanced congestive heart failure. *Circulation*. 1980;62:42–48.
2. Brogan WC, Grayburn PA, Lange RA, Hillis LD. Prognosis after valve replacement in patients with severe aortic stenosis and a low transvalvular pressure gradient. *J Am Coll Cardiol*. 1993;21:1657–1660.
3. Connolly HM, Oh JK, Schaff HV, Roger VL, Osborn SL, Hodge DO, Tajik AJ. Severe aortic stenosis with low transvalvular gradient and sever left ventricular dysfunction: results of aortic valve replacement in 52 patients. *Circulation*. 2000;101:1940–1946.
4. Bonow RO, Carabello B, de Leon, AC Jr, Edmunds LH Jr, Fedderly BJ, Freed MD, Gaasch WH, McKay CR, Nishimura RA, O'Gara PT, O'Rourke RA, Rahimtoola SH, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A Jr, Gibbons RJ, Russell RO, Ryan TJ, Smith SC Jr. ACC/AHA guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *J Am Coll Cardiol*. 1998;32:1486–1588.
5. Burwash IG, Thomas DD, Sadahiro M, Pearlman AS, Verrier ED, Thomas R, Kraft CD, Otto CM. Dependence of Gorlin formula and continuity equation valve areas on transvalvular volume flow rate in valvular aortic stenosis. *Circulation*. 1994;89:827–835.
6. Cannon JD, Zile MR, Crawford FA, Carabello BA. Aortic valve resistance as an adjunct to the Gorlin formula in assessing the severity of aortic stenosis in symptomatic patients. *J Am Coll Cardiol*. 1992;20:1517–1523.
7. deFilippi CR, Willett DL, Brickner ME, Appleton CP, Yancy CW, Eichhorn EJ, Grayburn PA. Usefulness of dobutamine echocardiography in distinguishing severe from non-severe valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. *Am J Cardiol*. 1995;75:191–194.
8. Gorlin R, Gorlin SG. Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. *Am Heart J*. 1951;41:1–29.
9. Carabello BA. Ventricular function in aortic stenosis: how low can you go? *J Am Coll Cardiol*. 2002;39:1364–1365.
10. Grayburn PA, Eichhorn EJ. Dobutamine challenge for low-gradient aortic stenosis. *Circulation*. 2002;106:763–765.
11. Monin J-L, Monchi M, Gest V, Duval-Moulin AM, Dubois-Rande JL, Gueret P. Aortic stenosis with severe left ventricular dysfunction and low transvalvular pressure gradients: risk stratification by low-dose dobutamine echocardiography. *J Am Coll Cardiol*. 2001;37:2101–2107.
12. Schwammenthal E, Vered Z, Moshkowitz Y, Rabinowitz B, Ziskind Z, Smolinski AK, Feinberg MS. Dobutamine echocardiography in patients with aortic stenosis and left ventricular dysfunction: predicting outcome as a function of management strategy. *Chest*. 2001;119:1766–1777.
13. Nishimura RA, Grantham JA, Connolly HM, Schaff HV, Higano ST, Holmes DR Jr. 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. *Circulation*. 2002;106:809–813.
14. Monin JL, Quere JP, Monchi M, Petit H, Baleynaud S, Chauvel C, Pop C, Ohlmann P, Lelguen C, Dehant P, Tribouilloy C, Gueret P. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. *Circulation*. 2003;108:319–324.
15. Blais C, Burwash IG, Mundigler G, Dumesnil JG, Loho N, Rader F, Baumgartner H, Beanlands RS, Chayer B, Kadem L, Garcia D, Durand L-G, Pibarot P. Projected valve area at normal flow rate improves the assessment of stenosis severity in patients with low-flow, low-gradient aortic stenosis: the multicenter TOPAS (Truly or Pseudo-Severe Aortic Stenosis) Study. *Circulation*. 2006;113:711–721.
16. Kizer JR, Gefter WB, deLemos AS, Scoll BJ, Wolfe ML, Mohler ER III. Electron beam computed tomography for the quantification of aortic valvular calcification. *J Heart Valve Dis*. 2001;10:361–366.
17. Roberts WC, Ko JM. Relation of weights of operatively excised stenotic aortic valves to preoperative transvalvular peak systolic pressure gradients and to calculated aortic valve areas. *J Am Coll Cardiol*. 2004;44:1847–1855.
18. Lachman AS, Roberts WC. Calcific deposits in stenotic mitral valves: extent and relation to age, sex, degree of stenosis, cardiac rhythm, previous commissurotomy and left atrial body thrombus from study of 164 operatively-excised valves. *Circulation*. 1978;37:808–815.
19. Schoen FJ, Kujovich JL, Webb CL, Levy RJ. Chemically determined mineral content of explanted porcine aortic valve bioprostheses: correlation with radiographic assessment of calcification and clinical data. *Circulation*. 1987;76:1061–1066.
20. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation*. 2005;111:920–925.