CME

iREVIEWS

STATE-OF-THE-ART PAPER

Imaging of Low-Gradient Severe Aortic Stenosis

Anumeha Tandon, MD, Paul A. Grayburn, MD

Dallas, Texas

JACC: CARDIOVASCULAR IMAGING CME

CME Editor: Ragavendra R. Baliga, MD

This article has been selected as this issue's CME activity, available online at http://imaging.onlinejacc.org by selecting the CME tab on the top navigation bar.

Accreditation and Designation Statement

The American College of Cardiology Foundation (ACCF) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The ACCF designates this Journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Method of Participation and Receipt of CME Certificate

To obtain credit for this CME activity, you must:
1. Be an ACC member or *JACC: Cardiovascular Imaging* subscriber.
2. Carefully read the CME-designated article available online and in this issue of the journal.
3. Answer the post-test questions. At least 2 out of the 3 questions provided must be answered correctly to obtain CME credit.
4. Complete a brief evaluation.
5. Claim your CME credit and receive your certif-icate electronically by following the instructions given at the conclusion of the activity.

CME Objective for This Article: At the end of this activity the reader should be able to: 1) understand the hemodynamic mechanisms underlying low gradient severe aortic stenosis (LGSAS); 2) understand how dobutamine stress echocardiography can be useful in evaluating whether LGSAS is due to true aortic stenosis or pseudo-aortic stenosis (failure of moderately thickened leaflets to fully open because of low forward stroke volume); and 3) apply current guidelines for determining when surgery is indicated for patients with LGSAS.

CME Editor Disclosure: *JACC: Cardiovascular Imaging* CME Editor Ragavendra R. Baliga, MD, has reported that he has no relationships to disclose.

Author Disclosure: Dr. Tandon has reported that he has no relationships relevant to the contents of this paper to disclose. Dr. Grayburn has received grant support from Abbott Vascular and Medtronic, has consulted for Abbott Vascular and Bracco Diagnostics, and serves as the Echo Core Lab for ValTech Cardio and Guided Delivery Systems.

Medium of Participation: Print (article only); online (article and quiz).

CME Term of Approval:
Issue Date: February 2013
Expiration Date: January 31, 2014

Imaging of Low-Gradient Severe Aortic Stenosis

Although most patients with severe aortic stenosis (AS) have high peak velocity and mean transvalvular gradient, there is a subset of patients with low-flow, low-gradient severe AS (LGSAS). Assessment and management of such patients can be difficult and dobutamine echocardiography has been recommended to distinguish those with pseudo-AS (low calculated AVA due to insufficient flow to fully open the valve) from those with contractile reserve and true LGSAS, who may have good outcomes with surgery. More recently, a group of patients with LGSAS and preserved LV function have been identified. These patients are often elderly with hypertension, small left ventricular cavities, and concentric left ventricular hypertrophy. Because cardiac imaging plays a vital role in hemodynamic classification of patients with suspected LGSAS and determining appropriate management, this review was undertaken to summarize the current state of knowledge of this important but complex condition.   (J Am Coll Cardiol Img 2013;6:184–95) © 2013 by the American College of Cardiology Foundation

Aortic stenosis (AS) is one of the most common valvular disorders encountered in clinical practice, and its prevalence is expected to increase in the United States as the "baby boomer" generation ages (1,2). It is the most common indication for aortic valve replacement (AVR), which is recommended for symptomatic severe AS (3,4). Severe AS has been defined as a calculated aortic valve area (AVA) ≤ 1.0 cm^2, mean pressure gradient (MPG) ≥ 40 mm Hg and peak velocity ≥ 4 m/s (3,4). It is often recommended to index the AVA for body surface area (≤ 0.6 cm^2/m^2), which corresponds better with left ventricular stroke work loss than AVA.

Most patients with severe AS maintain normal left ventricular ejection fraction (LVEF) despite significant afterload mismatch. In such patients, the presence of an elevated MPG and/or peak velocity, along with a decreased calculated AVA is sufficient to diagnose severe AS. However, there is a subset of patients with depressed LVEF, either due to long-standing severe AS or due to other causes such as ischemic cardiomyopathy, in whom the calculated AVA, MPG, and peak velocity are all low. This condition was first described in 1980 by Carabello et al. (5) and has been termed low-flow, low-gradient AS. A more appropriate term might be low-gradient severe aortic stenosis (LGSAS), as mild AS is expected to have a low gradient. More recently, LGSAS has been shown to also occur in patients with preserved LVEF and low forward stroke volume (6). Although much has been learned about LGSAS since 1980, it remains a complicated problem for which cardiac imaging plays a crucial

role. This review will cover the use of various imaging modalities to evaluate hemodynamics, LV function, and outcomes in patients with LGSAS.

Hemodynamics. By definition, LGSAS includes both severe AS and a low gradient, which may seem contradictory. To fully understand the relationship between AVA, flow, and gradient in LGSAS, it is helpful to consider the Gorlin hydraulic orifice equation (7). It is based on the principle that effective orifice area (EOA) is dependent on flow and velocity across the valve as shown in Equation 1, where

$$EOA = Flow/Velocity$$

Gorlin and Gorlin used cardiac output to derive systolic flow across the aortic valve and velocity was estimated from the MPG using Torricelli's law. Thus, the Gorlin equation describes the relationship between AVA, flow, and gradient in AS derived by Equation 2,

$$AVA = CO \div (HR \times SEP)/44.3 \times \sqrt{MPG}$$

where CO = cardiac output, HR = heart rate, and SEP = systolic ejection period.

The constant value 44.3 is empirical and includes both a contraction coefficient and a discharge coefficient. The discharge coefficient accounts for the energy loss that occurs from conversion of potential energy (pressure) to kinetic energy (velocity). The calculated AVA is the EOA of the flow stream, which is smaller than the anatomic orifice area

(AOA). The ratio of EOA to AOA is the contraction coefficient, which can vary with flow and orifice geometry. The denominator of the Gorlin equation equals velocity across the stenotic valve, which is calculated from MPG. Doppler echocardiography, which had not been invented at the time of the Gorlin paper, can be used to directly measure aortic valve velocity. Had Doppler echocardiography been available in 1951, it is likely that the denominator of the Gorlin equation would be velocity rather than the square root of MPG.

Continuity equation. Equation 1, from which the Gorlin equation was derived, is also the basis for the continuity equation, which is the preferred modality for measuring AVA according to the American Heart Association (AHA)/American College of Cardiology (ACC) and European Society of Cardiology (ESC)/European Association of Thoracic Surgery (EATS) guidelines (3,4). The continuity equation uses Doppler velocity-time integral (VTI) and left ventricular outflow tract (LVOT) measurements to calculate stroke volume proximal to the aortic stenosis and the VTI of the AS jet as shown in Equation 3:

$$AVA = (Area_{LVOT} \times VTI_{LVOT})/VTI_{AS}$$

Peak velocity can be substituted for VTI, but the latter value is more accurate and reproducible. The continuity equation is mathematically equivalent to the Gorlin equation, but the numerator (flow or flow rate) is determined by Doppler echocardiography instead of Fick or thermodilution, and the denominator (velocity) is directly measured instead of calculated from the MPG.

Low-Flow, Low-Gradient Aortic Stenosis

True AS versus pseudo-AS. Accurate assessment of AVA in patients with LGSAS is difficult because the Gorlin constant varies at low-flow states and the calculated AVA is directly proportional to forward flow (8,9). Cannon et al. (10) reported that some patients with LGSAS were found to have mild AS at surgery despite a calculated AVA by the Gorlin equation suggesting severe AS. Thus, a low calculated AVA could represent pseudo-AS, in which the calculated value is artificially low because forward flow is too low to open a mildly or moderately diseased aortic valve, or an error in the calculated

AVA. The first step in evaluating a patient with LGSAS is to carefully evaluate the possibility of a measurement error. Thermodilution cardiac output may be erroneous in low output states or tricuspid regurgitation (11), leading to a falsely low AVA by the Gorlin equation. With the continuity equation, underestimation of the LVOT diameter can significantly underestimate AVA because any error in its measurement is squared (12). It is best to make this measurement at the base of the aortic annulus rather than the mid-LVOT level. It is important for the sonographer to position the scan plane in the center of the LVOT to find the largest diameter. In addition, the continuity equation assumes circular geometry, but recent studies using computed tomography (CT) demonstrate that both the LVOT and aortic annulus are often noncircular (13–15). This may lead to an average 17% underestimation of LVOT area, and hence, AVA (13). The measurement error at the annulus level may be less than 17%, as the annulus is sometimes more circular than the LVOT. It is common to encounter very low AVA in patients with nearly normal aortic valve morphology on echocardiography due to underestimation of the LVOT area. This is particularly problematic in small elderly women with measured LVOT diameters of 1.6 to 1.8 cm. In such cases, the use of 3-dimensional (3D) echocardiography, CT, or cardiac magnetic resonance may be helpful in obtaining a more accurate measure of aortic annulus area (Fig. 1). It can also be helpful to corroborate LV stroke volume by calculation of LV end-diastolic and end-systolic volumes, which works well in the absence of significant mitral regurgitation. This is often done by biplane method of disks, a technique that is prone to underestimation by foreshortening. The most accurate and reproducible methods for LV volumes are 3D echocardiography (16) or cine magnetic resonance imaging (17). Most studies of LGSAS have used the continuity equation, and despite its potential to underestimate AVA, it remains the reference standard (4).

Role of dobutamine echocardiography. The ACC/AHA guidelines on management of valvular heart disease recommend dobutamine echocardiography (DE) to distinguish between true LGSAS and pseudo-AS (Class 2a recommendation) (3). Figure 2 illustrates the rationale for the use of DE in LGSAS, based on Gorlin formula plots of the relationship of transvalvular flow, MPG, and AVA (18). At low transvalvular flow rates (dashed line at 125 ml/s), MPG is low regardless of AVA. At normal transvalvular flow (250 ml/s), MPG is able
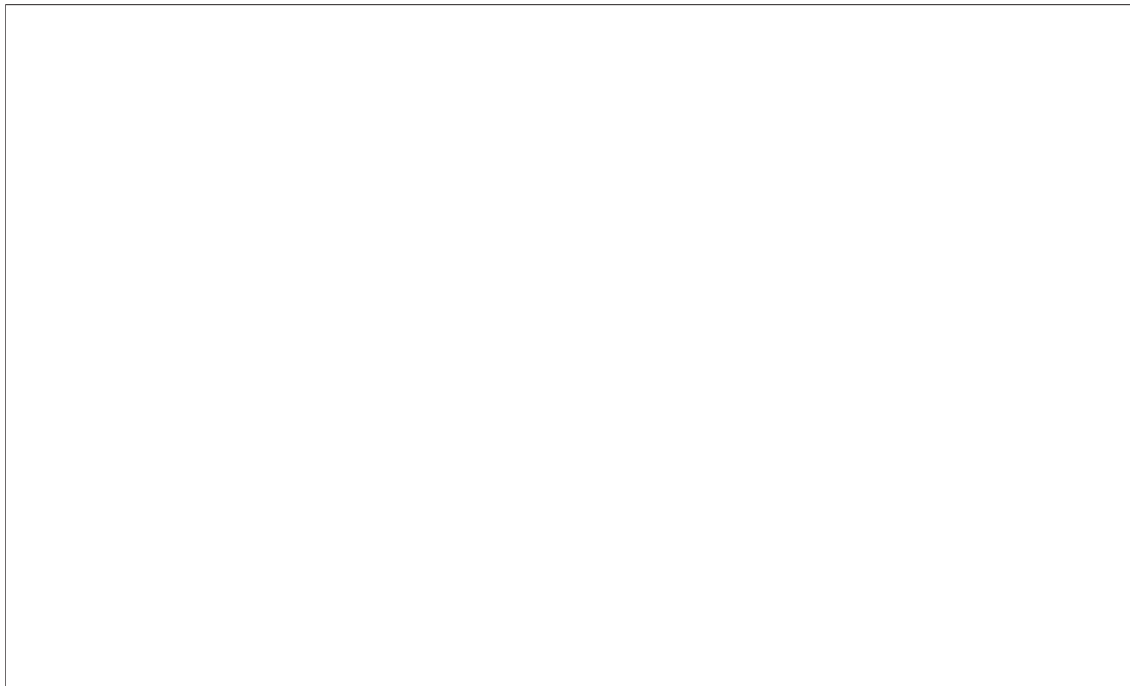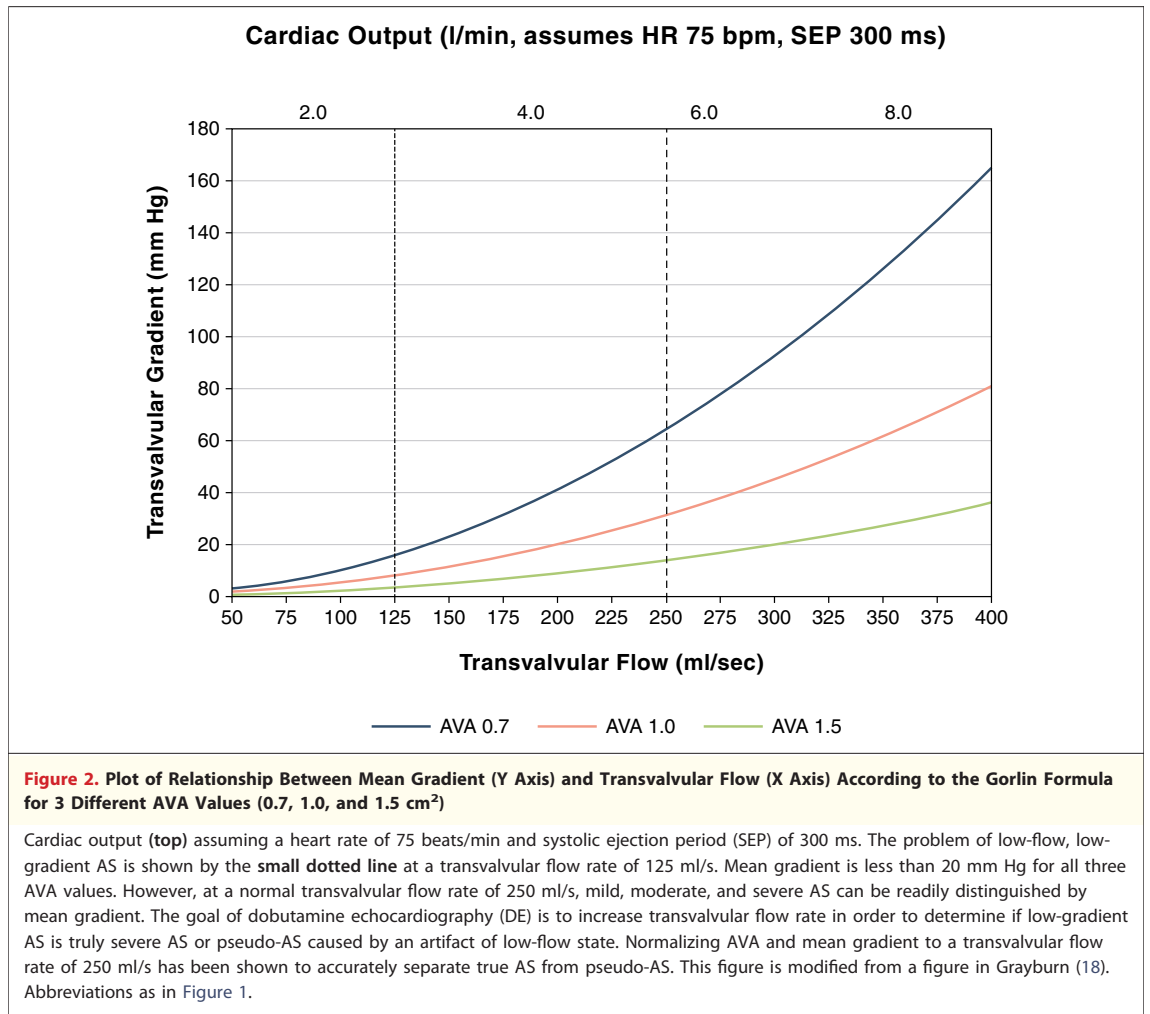
Figure 1. Example of Underestimation of LVOT Diameter by 2D Echocardiography in a Patient with Aortic Stenosis

(A) Parasternal long-axis view showing a left ventricular outflow tract (LVOT) diameter measured at the base of leaflet insertion of 2.4 cm, resulting in a calculated aortic valve area (AVA) 0.9 cm², consistent with severe aortic stenosis (AS). (B) Computed tomography (CT) scan in the same patient showing a noncircular LVOT, with the same diameter of 2.4 in the minor axis plane. Using actual LVOT area by planimetry, calculated AVA is 1.1 cm². (C) CT scan from a different patient at the level of the aortic annulus. The annulus is elliptical with minor and major axis diameters of 2.4 cm and 3.0 cm, respectively. (D) Three-dimensional transesophageal echocardiography images at the aortic annulus in the same patient also show elliptical geometry with minor and major axis diameters of 2.4 cm and 2.8 cm, closely matching the CT scan. 2D = 2-dimensional.

to clearly separate mild, moderate or severe AS. In 1995, deFilippi et al. (19) first reported the use of DE to evaluate LGSAS in 18 patients with severe symptoms and LV dysfunction. All patients had a calculated AVA $\leq$0.5cm²/m², mean gradient $\leq$30 mm Hg and LVEF $\leq$45%. Dobutamine was started at 5 μg/kg/min and increased to a peak of 20 μg/kg/min at 3-min intervals. Three types of responses were observed: true AS, pseudo-AS, and absence of contractile reserve. True AS was characterized by dobutamine-induced increase in peak velocity, MPG and valve resistance with no significant change in AVA. Pseudo-AS was characterized by an increase in AVA by $\geq$0.3 cm² with no significant change in MPG and peak velocity. Presence of contractile reserve was defined as increase in peak velocity of $\geq$0.6m/s, stroke volume $\geq$20% and MPG $\geq$10 mm Hg with dobutamine. Absence of contractile reserve did not help differentiate between true AS or pseudo-AS because there was no change in forward stroke volume. Figure 3 shows Doppler spectra from a patient with true AS, in whom peak velocity increases from 3.2

to 4.1 m/s after dobutamine. Figure 4 shows continuous wave and pulsed wave Doppler with dobutamine infusion with no significant increase in peak velocity and MPG but increase in aortic valve area by continuity equation consistent with pseudo-AS. The ability of DE to distinguish true LGSAS from pseudo-AS, and to identify contractile reserve has been reported by many authors. However, the exact criteria that optimally distinguish true AS from pseudo-AS have not been rigorously studied, nor is there an established reference standard for comparison. The most recent guidelines indicate that true AS is characterized by <0.2 cm² increase in AVA, while still <1.0 cm² with an increase in MPG to >40 mm Hg (4). Conversely, pseudo-AS has "a marked increase in valve area but only minor changes in gradients" (4). However, outcomes studies (as will be discussed) indicate that DE is a valuable diagnostic tool in LGSAS.

Technical aspects of DE. As noted above, accurate measurement of the LVOT diameter is of paramount importance (12–15). CT scans done prior to transcatheter aortic valve implantation (TAVI)

Figure 2. Plot of Relationship Between Mean Gradient (Y Axis) and Transvalvular Flow (X Axis) According to the Gorlin Formula for 3 Different AVA Values (0.7, 1.0, and 1.5 cm²)

Cardiac output **(top)** assuming a heart rate of 75 beats/min and systolic ejection period (SEP) of 300 ms. The problem of low-flow, low-gradient AS is shown by the **small dotted line** at a transvalvular flow rate of 125 ml/s. Mean gradient is less than 20 mm Hg for all three AVA values. However, at a normal transvalvular flow rate of 250 ml/s, mild, moderate, and severe AS can be readily distinguished by mean gradient. The goal of dobutamine echocardiography (DE) is to increase transvalvular flow rate in order to determine if low-gradient AS is truly severe AS or pseudo-AS caused by an artifact of low-flow state. Normalizing AVA and mean gradient to a transvalvular flow rate of 250 ml/s has been shown to accurately separate true AS from pseudo-AS. This figure is modified from a figure in Grayburn (18). Abbreviations as in Figure 1.

show elliptical LVOT and aortic annulus geometry (14,15). 3D echocardiography may prove to be useful in measuring the actual LVOT cross-sectional area to obtain more accurate values of AVA by the continuity equation (13). Peak aortic velocity should be measured from multiple views including apical, right parasternal and suprasternal views. Continuous wave and pulsed wave Doppler should be measured at each stage. For each Doppler measurement 3 to 5 cycles should be averaged and post–premature ventricular contraction beats should be discarded. The infusion rate of dobutamine does not need to exceed 20 μg/kg/min as the inotropic effect is maximal at this dose and further increases in dose merely add to the chronotropic response and can provoke ischemia and arrhythmia in these patients (14). Ischemia is counter-productive in evaluating LGSAS, as it may depress global LV systolic function and reduce transvalvular flow rate rather than augment it. In patients with AS and severe coronary artery disease, dobutamine may provoke ventricular arrhythmias. This can result in hemodynamic

compromise and even death. Dobutamine should be turned off as soon as the hemodynamic classification of LGSAS is established, or once a peak dose of 20 μg/kg/min is completed.

Contractile reserve by DE. Before the use of DE became standard of care, studies of LGSAS patients undergoing AVR demonstrated improved functional class and LVEF, but at the cost of increased perioperative mortality (20,21). Subsequently, it was found that the presence or absence of contractile reserve by DE strongly predicts operative mortality (22–27) and long-term mortality (Table 1). Monin et al. (24) enrolled 136 patients with AVA ≤1.0 cm², cardiac index ≤3.0 l/min/m² and MPG <40 mm Hg in a multicenter study. LV contractile reserve was present in 92 patients and absent in 44 patients. Operative mortality was 5% in patients with contractile reserve, whereas it was 32% if contractile reserve was absent (24). Other predictors of operative mortality and decreased long-term survival after AVR are older age, presence of co-
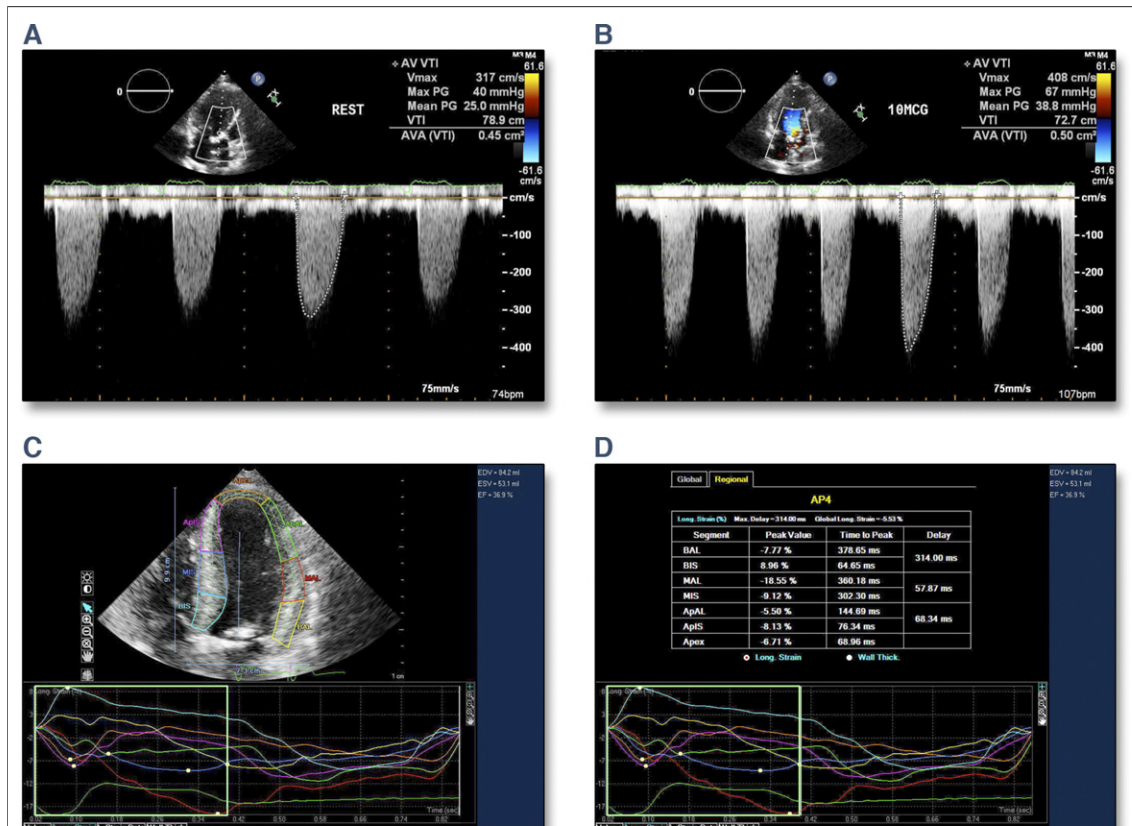
Figure 3. Example of DE in a Patient With True LGSAS

(A) Baseline continuous wave (CW) Doppler tracing with peak velocity 3.2 m/s, mean gradient 25 mm Hg, calculated AVA 0.45 cm². (B) CW Doppler during dobutamine infusion at 10 μg/kg/min. Peak velocity increased to 4.1 m/s, mean gradient to 39 mm Hg, and AVA remained at 0.5 cm². (C) Speckle tracking in an apical 4-chamber view. (D) Results of global longitudinal strain, which was −5.5%, indicating severely abnormal myocardial function. LGSAS = low-gradient severe aortic stenosis; other abbreviations as in Figures 1 and 2.

morbidities, very low pressure gradients (<20 mm Hg), presence or absence of atrial fibrillation and severe associated coronary artery disease (25).

Quere et al. (26) showed that in those patients who had no contractile reserve on pre-operative DE, but survived the perioperative period, 90% had an improvement in their functional class and 65% showed a post-operative increase in LVEF by at least 10%. Tribouilloy et al. (27) found that 5-year survival after AVR compared to medical therapy in patients with LGSAS and no contractile reserve was 54% versus 13%, despite a high operative mortality of 22%. Thus, absence of contractile reserve should not preclude AVR, even though it clearly portends a higher operative mortality.

Projected AVA at normal flow. One of the limitations of DE is the different transvalvular flow rates achieved in different patients with dobutamine. As shown already in Figure 2, at low-flow rates, there is little difference in mean gradient between AVA values corresponding to mild, moderate, or severe AS. Similarly, AVA is flow-dependent, which is the underlying basis for pseudo-AS. Therefore, it would be ideal to compare AVA in different patients at a common, normalized flow rate. Blais et al. (28) proposed the attractive idea of using DE to calculate projected AVA at normal transvalvular flow rate of 250 ml/s. This is simply done by plotting transvalvular flow and AVA at baseline and peak dobutamine and extrapolating the value for AVA at a flow rate of 250 ml/s (29). This allows comparison of AVA (and mean gradient) between patients at a standardized normal flow rate. Clavel et al. (30) have shown that projected AVA at normal transvalvular flow is an important predictor of outcome in LGSAS and depressed LVEF.

Other imaging modalities. DE is not able to distinguish true AS from pseudo-AS in patients who fail to increase transvalvular flow in response to inotropic stimulation (absent contractile reserve). Other
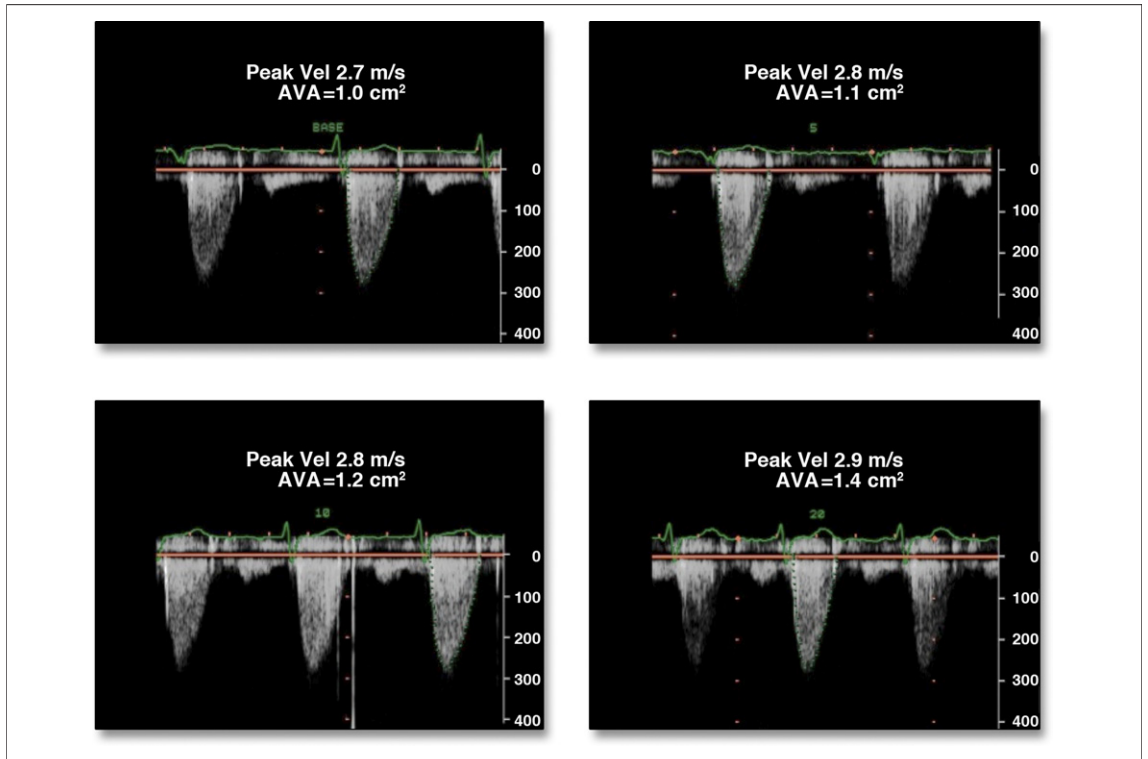
Figure 4. Example of DE in a Patient With Pseudo-AS

CW Doppler spectra at baseline, 5 μg/kg/min, 10 μg/kg/min, and 20 μg/kg/min, respectively. At increasing levels of forward flow with dobutamine, peak velocity remained fairly constant, but AVA increased from 1.0 cm² to 1.4 cm², demonstrating both contractile reserve and absence of severe AS. Abbreviations as in Figures 1, 2, and 3.

imaging modalities can be helpful in such patients. One simple, and often overlooked, method is simply evaluating aortic valve morphology on echocardiography. True AS would be expected to have significant calcification and immobility of the aortic cusps. A morphologically normal or nearly normal aortic valve would indicate that AVA was calculated erroneously, or the velocity profile is coming from a different location than the aortic valve, such as subvalvular or supravalvular obstruction. Occasion-

ally, a continuous wave Doppler profile from mitral regurgitation can be mistaken for AS. Fluoroscopy or CT scanning would be expected to show significant aortic valve calcification in true AS (Fig. 5). Aortic valve calcium score measured by multislice CT has been useful in differentiating true AS from pseudo-AS in patients with depressed LVEF (31). A calcium score >1,651 had 93% sensitivity and 75% specificity in identifying patients with true AS. Further validation of aortic valve calcium by CT,

Table 1. Perioperative Mortality and Long-Term Survival in Operated Patients of LGSAS With and Without Contractile Reserve

First Author (Ref. #)	Presence of Contractile Reserve by DE		Absence of Contractile Reserve by DE	
	Perioperative Mortality Rate for Patients With AVR With/Without CABG	Long-Term Survival in Operated Patients	Perioperative Mortality Rate for Patients With AVR With/Without CABG	Long-Term Survival in Operated Patients
Monin et al. (22)	8%	88% at 5 years	50%	—
Schwammenthal et al. (23)	0%	—	—	—
Monin et al. (24)	5%	79% at 3 years	32%	—
Levy et al. (25)	8%		38%	
Quere et al. (26)	6%	92% at 2 years	33%	90% at 2 years
Tribouilloy et al. (27)	—	—	22%	54% at 5 years

CABG = coronary artery bypass graft; DE = dobutamine echocardiography; LGSAS = low-gradient severe aortic stenosis.
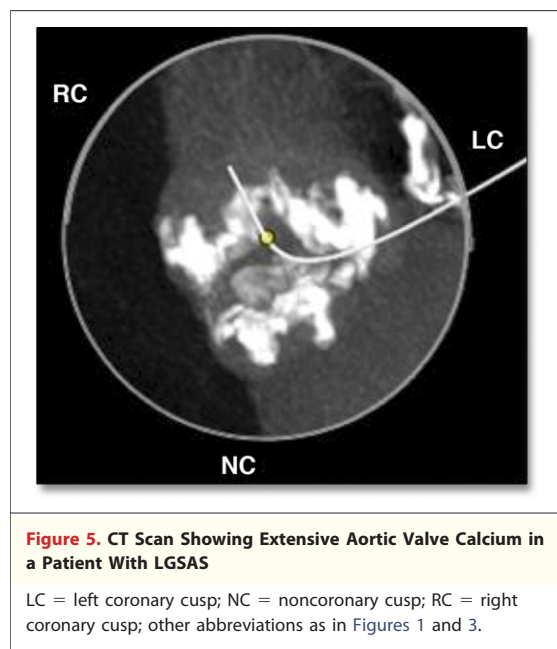
Figure 5. CT Scan Showing Extensive Aortic Valve Calcium in a Patient With LGSAS

LC = left coronary cusp; NC = noncoronary cusp; RC = right coronary cusp; other abbreviations as in Figures 1 and 3.
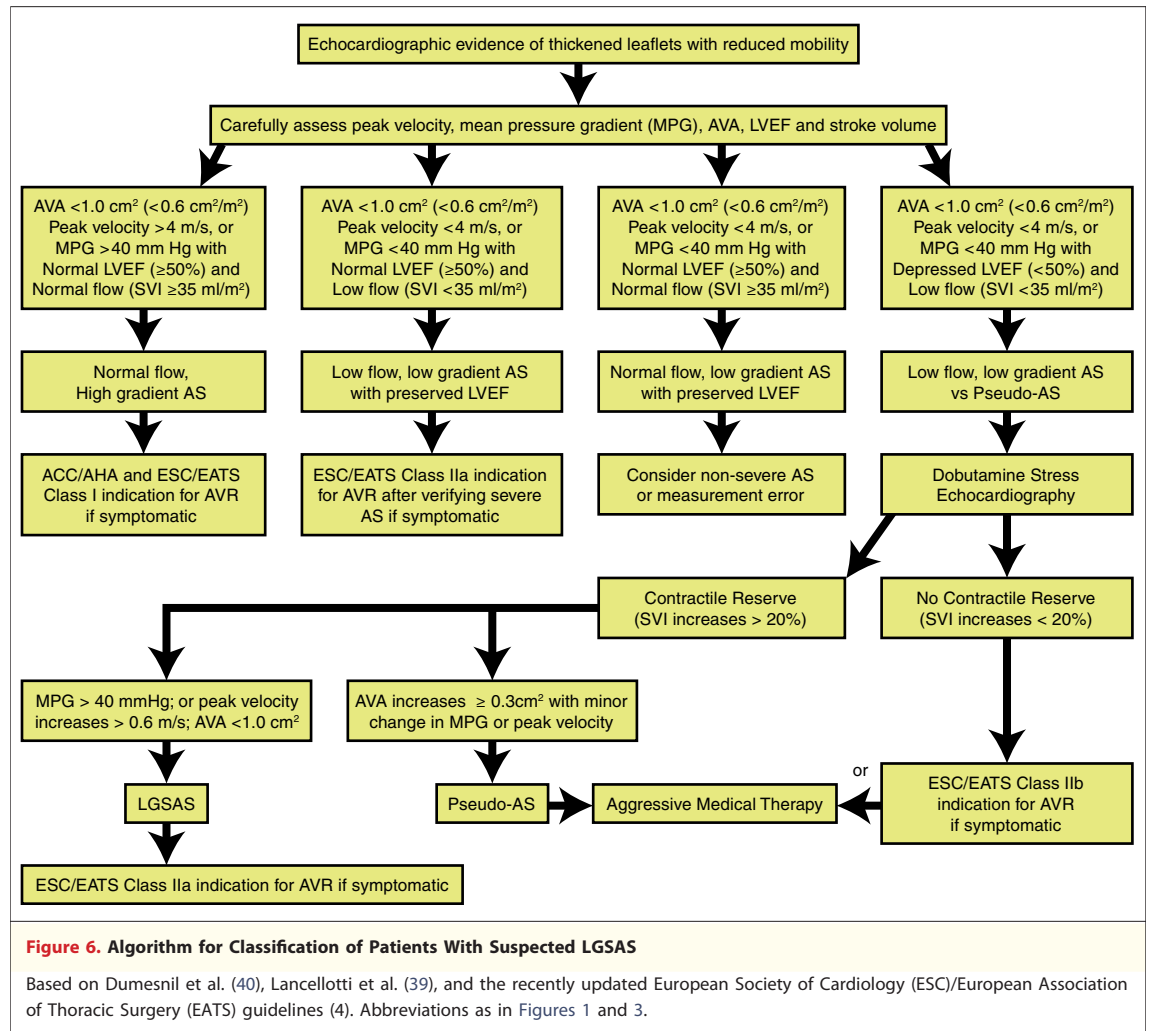
including outcomes endpoints, is needed. Cine magnetic resonance imaging is also capable of calculating AVA by continuity equation using phase velocity encoding with good correlation to echocardiography (32–34). Positron emission tomography has shown smaller resting myocardial flow reserve in patients with true stenosis compared to pseudo-AS (35), although this does not directly assess aortic valve pathology and is not available in many centers.

Paradoxical LGSAS with Preserved LVEF

Up to 30% of patients who undergo echocardiographic assessment of AS severity have discrepancy in echocardiographic parameters such that AVA indicates severe stenosis but mean gradient is in the nonsevere range despite a normal LVEF (36). One potential cause is paradoxical LGSAS with preserved LVEF, defined as indexed AVA $\leq$0.6 cm^2/m^2) and LVEF $\geq$50% (6). "Paradoxically" low transvalvular flow rate (defined as a stroke volume index $\leq$35 ml/m^2) was present in 35% of 512 subjects. Compared with normal flow patients, low-flow patients had a higher prevalence of female gender, lower MPG ($<$40 mm Hg), lower LV diastolic volume index, lower LVEF (but still $>$50%), higher level of LV global afterload and lower 3 year survival (76% vs. 86%). Barasch et al. (37) also showed that patients with severe AS with AVA index of $<$0.46 cm^2/m^2 and low mean gradient ($<$30 mm Hg) with preserved LV function had a

higher mortality and a lower rate of referral ($<$50%) for surgery compared to patients with mean gradients $>$30 mm Hg. Clavel et al. (38) have shown that paradoxical low-flow LGSAS patients have 1.7-fold increase in total mortality and a 2-fold increase in cardiovascular mortality compared to patients with severe AS with high gradient. AVR was associated with improved outcomes (HR: 0.50; p = 0.04) in these patients (38). Recently, Lancellotti et al. (39) have shown that prognosis is better with normal flow, low-gradient AS than with low-flow, low-gradient or high-gradient AS. Such patients are common and most likely represent moderate rather than severe AS. Figure 6 presents a flow diagram for classification of patients as first proposed by Dumesnil et al. (40). Proper classification of these patients can be challenging, as clinical scenario of LGSAS with preserved LVEF may arise in different situations as described by Zoghbi (41). These disparate situations include: 1) mildly reduced stroke volume in patients with normal LV size; 2) small LV cavity with a small body habitus; 3) calculation errors by underestimating LVOT diameter or malposition of Doppler sample volume; 4) presence of systemic hypertension; or 5) inconsistency in the definition of AS by current guidelines because AVA of 1 cm^2 does not correspond to a mean gradient $>$40 mm Hg by the Gorlin equation (Fig. 2). Jander et al. (42) investigated the prognostic impact and progression rate of LGSAS in the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial and showed that the outcome of patients with LGSAS and normal LVEF was similar to patients with moderate AS. Although these data seem to conflict with those of the studies of Hachicha et al. (6) and Barasch et al. (37), patients in the SEAS study were asymptomatic and had less LV hypertrophy for a given level of AVA, indicating minimal pressure overload. SEAS patients were also selected for having nonsevere AS and no immediate indication for AVR.

The pathophysiology of LGSAS with preserved LVEF has been explained as being similar to restrictive physiology. Dumesnil et al. (40) described the decrease in stroke volume due to a deficiency in ventricular filling in relation to a smaller cavity size. In patients with increased afterload, sarcomeres are added in parallel causing increased LV thickness such that they have normal LVEF despite myocardial dysfunction and low stroke volume index. In a study of 208 patients, combination of decreased systemic arterial compliance (measured as stroke volume index divided by

Figure 6. Algorithm for Classification of Patients With Suspected LGSAS

Based on Dumesnil et al. (40), Lancellotti et al. (39), and the recently updated European Society of Cardiology (ESC)/European Association of Thoracic Surgery (EATS) guidelines (4). Abbreviations as in Figures 1 and 3.

pulse pressure) and moderate AS was similar with regard to total LV afterload to patients with severe AS and normal arterial compliance (43). Myocardial strain, measured by echocardiographic speckle tracking, was abnormal despite preserved LVEF. Abnormalities in myocardial strain and strain rate provide a more sensitive marker for LV dysfunction than LVEF. Delgado et al. (44) have shown reduced longitudinal, circumferential and radial strain in patients with severe AS and preserved LVEF, which improved after AVR without change in LVEF. In a multicenter prospective study of 340 patients with severe AS (AVA index <0.6 cm^2/m^2) and preserved LVEF ($>50\%$), 9% of patients were identified as having true low-flow (systolic volume index: <35 ml/m^2) LGSAS (45). They found that longitudinal strain was particularly abnormal in 2 groups of patients with high afterload-low-flow high-gradient and low-flow, low-gradient AS. An abnormality in longitudinal strain appears to be the

earliest marker of LV dysfunction in patients with increased afterload. Cardiac cine-magnetic resonance imaging with delayed hyperenhancement using gadolinium contrast agents has shown myocardial fibrosis in at least one segment in patients with severe LGSAS, either with preserved or depressed LVEF (46). Late enhancement has been mainly observed in the subendocardial layers of the basal segments (46). Mitral ring displacement decreases gradually with increasing number of hyperenhancing segments. The longitudinal fibers are mainly present in the subendocardium and are most susceptible to the effects of ischemia and increased wall stress under conditions of increased afterload. It is reasonable to hypothesize that patients with extensive fibrosis/scarring would be less likely to demonstrate improved LV function after AVR.

Guidelines for management of LGSAS. The recent 2012 European Society of Cardiology guidelines for valvular heart disease are the first to specifically

mention indications for AVR in patients with LGSAS (4). AVR may be considered a Class IIa recommendation in the following two circumstances: 1) "symptomatic patients with low-flow, low-gradient (<40 mm Hg) AS with normal EF only after careful confirmation of severe AS"; and 2) "symptomatic patients with severe AS, low flow, low gradient with reduced EF, and evidence of flow reserve" (4).

Furthermore, AVR may be considered a Class IIb recommendation in "symptomatic patients with severe AS, low flow, low gradient with LV dysfunction without flow reserve." In patients with pseudo-AS, management should be targeted to the underlying LV dysfunction (47), and should include aggressive heart failure therapy and cardiac resynchronization if indicated by LVEF <35% and left bundle branch block.

Role of TAVI in LGSAS. The development of TAVI as an alternative to AVR for high-risk patients may be well suited to this group of patients. Clavel et al. (48) reported that TAVI was superior to AVR in a subset of patients with low LVEF at baseline, although not all of the patients had LGSAS. Ben-Dor et al. (49) reported the outcomes of high risk patients with LVEF ≤40% undergoing either TAVI or AVR. Late mortality was higher with LGSAS (54%) than with high gradient (41%) but LV functional recovery occurred with both TAVI and AVR in survivors. Lauten et al. (50) published their results of TAVI in 149 patients (from the German TAVI registry) with LGSAS (<40 mm Hg) with low LVEF (<40%). The mortality at 1 year was 37% for the LGSAS group compared with 18% in patients with normal LV function. This clearly demonstrates that TAVI is feasible in this group of patients, although the mortality rate was high and typical of that expected for open AVR. The ultimate role of TAVI in LGSAS without contractile reserve will need to be evaluated in a randomized controlled trial.

Conclusions

Low-gradient AS presents a challenging clinical situation. In patients who have depressed LV systolic function (LVEF <45%), DE helps in differentiating true AS from pseudo-AS and also gives valuable prognostic information. In general, patients with true AS can undergo surgery with a low operative mortality and improved long-term outcomes. In patients with preserved LVEF (LVEF >50%) it is important to determine the cause of low forward stroke volume, and to distinguish LGSAS from an erroneous calculation of AVA. Other imaging techniques, including speckle tracking to evaluate LV myocardial performance, cine-magnetic resonance imaging to evaluate LV scarring/fibrosis and CT scanning to assess aortic valve morphology may help in evaluating LGSAS.

Reprint requests and correspondence: Dr. Paul A. Grayburn, Baylor Heart and Vascular Institute, 621 North Hall Street, Suite H030, Dallas, Texas 75226. *E-mail:* paulgr@baylorhealth.edu.

REFERENCES

1. Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. Nat Rev Cardiol 2011;8:162–72.

2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart disease: a population-based study. Lancet 2006;368:1005–11.

3. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 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 (Writing Committee to Develop Guidelines for the Management of Patients With Valvular Heart Disease). J Am Coll Cardiol 2006;48;1–148.

4. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2012;42:S1–44.

5. 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;62:42–8.

6. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. Circulation 2007;115:2856–64.

7. 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.

8. Cannon SR, Richards KL, Crawford M. Hydraulic estimation of stenotic orifice area: a correction of the gorlin formula. Circulation 1985;71:1170–8.

9. Burwash IG, Thomas DD, Sadahiro M, et al. Dependence of Gorlin formula and continuity equation valve areas on transvalvular volume flow rate in valvular aortic stenosis. Circulation 1994;89:827–35.

10. 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 1992:20:1517–23.

11. Cigarroa RG, Lange RA, Williams RH, Bedotto JB, Hillis LD. Underestimation of cardiac output by thermodilution in patients with tricuspid regurgitation. Am J Med 1989;86:417–20.

12. Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler quantification task force of the nomenclature and standards committee of the American Society of Echocardiography. J Am Soc Echocardiogr 2002;15:176–84.

13. Gaspar T, Adawi S, Sachner R, et al. Three-dimensional imaging of the left ventricular outflow tract: impact on aortic valve area estimation by the continuity equation. J Am Soc Echocardiogr 2012;25:749–57.

14. Leipsic J, Gurvitch R, Labounty TM, et al. Multidetector computed tomography in transcatheter aortic valve implantation. J Am Coll Cardiol Img 2011;4:416–29.

15. Altiok E, Koos R, Schroder J, et al. Comparison of two-dimensional and three-dimensional imaging techniques for measurement of aortic annulus diameters before transcatheter aortic valve implantation. Heart 2011;97:1578–84.

16. Lang RM, Badano LP, Tsang W, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. J Am Soc Echocardiogr 2012;25:3–46.

17. Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE. Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. J Am Coll Cardiol Img 2011;4:98–108.

18. Grayburn PA. Assessment of low-gradient aortic stenosis with dobutamine. Circulation 2006;113:604–6.

19. deFilippi CR, Willett DL, Brickner ME, et al. 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;75:191–4.

20. 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;21:1657–60.

21. Connolly HM, Oh JK, Schaff HV, et al. Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction: results of aortic valve replacement in 52 patients. Circulation 2000;101:1940–6.

22. 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;37:2101–7.

23. Schwammenthal E, Vered Z, Moshkowitz Y, et al. Dobutamine echocardiography in patients with aortic stenosis and left ventricular dysfunction: predicting outcome as a function of management strategy. Chest 2001;119:1766–7.

24. Monin JL, Quere JP, Monchi M, et al. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. Circulation 2003;108:319–24.

25. Levy F, Laurent M, Monin JL, et al. Aortic valve replacement for low-flow/low gradient aortic stenosis: operative risk stratification and long term outcome: a European multicenter study. J Am Coll Cardiol 2008;51:1466–72.

26. Quere JP, Monin JL, Levy F, et al. Influence of pre-operative left ventricular contractile reserve on postoperative ejection fraction in low gradient aortic stenosis. Circulation 2006;113:1738–44.

27. Tribouilloy C, Lévy F, Rusinaru D, et al. Outcome after aortic valve replacement for low flow/low gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. J Am Coll Cardiol 2009;53:1865–73.

28. Blais C, Burwash IG, Mundigler G, et al. The 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;113:711–21.

29. Clavel MA, Burwash IG, Mundigler G, et al. Validation of conventional and simplified methods to calculate projected valve area at normal flow rate in patients with low flow, low gradient aortic stenosis: the multicenter TOPAS (True or Pseudo Severe Aortic Stenosis) study. J Am Soc Echocardiogr 2010;23:380–6.

30. Clavel MA, Fuchs C, Burwash IG, et al. Predictors of outcomes in low-flow, low-gradient aortic stenosis: results of the multicenter TOPAS Study. Circulation 2008;118:234–42.

31. Cueff C, Serfaty JM, Cimadevilla C, et al. Measurement of aortic valve calcification using multislice computed tomography: correlation with hemodynamic severity of aortic stenosis and clinical implication for patients

with low ejection fraction. Heart 2011;97:721–6.

32. Caruthers SD, Lin SJ, Brown P, et al. Practical value of cardiac magnetic resonance imaging for clinical quantification of aortic valve stenosis: comparison with echocardiography. Circulation 2003;108:2236–43.

33. Yap SC, van Geuns RJ, Meijboom FJ. et al. A simplified continuity equation approach to the quantification of stenotic bicuspid aortic valves using velocity-encoded cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2007;9:899–906.

34. Garcia J, Kadem L, Larose E, Clavel MA, Pibarot P. Comparison between cardiovascular magnetic resonance and transthoracic Doppler echocardiography for the estimation of effective orifice area in aortic stenosis. J Cardiovasc Magn Reson 2011;13:25.

35. Burwash IG, Lortie M, Pibarot P, et al. Myocardial blood flow in patients with low flow, low gradient aortic stenosis: differences between true and pseudo severe aortic stenosis. Results from the multicenter TOPAS study. Heart 2008;94:1627–33.

36. Minners J, Allgeier M, Gohlke-Baerwolf C, Kienzle RP, Neumann FJ, Jander N. Inconsistent grading of aortic valve stenosis by current guidelines: haemodynamic studies in patients with apparently normal left ventricular function. Eur Heart J 2008;29:1043–8.

37. Barasch E, Fan D, Chukwu EO, et al. Severe isolated aortic stenosis with normal left systolic function and low transvalvular gradient: pathophysiologic and prognostic insights. J Heart Valv Dis 2008;17:81–8.

38. Clavel MA, Dumesnil JG, Capoulade R, Mathieu P, Sénéchal M, Pibarot P. Outcome of patients with aortic stenosis, small valve area, and low flow, low gradient despite preserved left ventricular ejection fraction. J Am Coll Cardiol 2012;60:1259–67.

39. Lancellotti P, Magne J, Donal E, et al. Clinical outcome in asymptomatic severe aortic stenosis: insights from the new proposed aortic stenosis grading classification. J Am Coll Cardiol 2012;59:235–43.

40. Dumesnil JG, Pibarot P, Carabello B. Paradoxical low flow and/or low gradient severe aortic stenosis despite preserved left ventricular ejection fraction: implications for diagnosis and treatment. Eur Heart J 2010;31:281–9.

41. Zoghbi WA. Low gradient "severe" aortic stenosis with normal systolic function: time to refine the guidelines? Circulation 2011;123:838–40.

42. Jander N, Minners J, Holme I, et al. Outcome of patients with low-gradient "severe" aortic stenosis and preserved ejection fraction. Circulation 2011;123:887–95.

43. Lancellotti P, Donal E, Magne J, et al. Impact of global left ventricular afterload on left ventricular function in asymptomatic severe aortic stenosis: a two-dimensional speckle-tracking study. Eur J Echocardiogr 2010;11:537–43.

44. Delgado V, Tops LF, van Bommel RJ, et al. Strain analysis in patients with severe aortic stenosis and preserved left ventricular ejection fraction undergoing surgical valve replacement. Eur Heart J 2009;30:3037–47.

45. Adda J, Mielot C, Giorgi R, et al. Low flow, low gradient severe aortic stenosis despite normal ejection fraction is associated with severe left ventricular dysfunction as assessed by speckle-tracking echocardiography: a multicenter study. Circ Cardiovasc Imaging 2012;5:27–35.

46. Herrmann S, Stork S, Niemann M, et al. Low-gradient aortic valve stenosis myocardial fibrosis and its influence on function and outcome. J Am Coll Cardiol 2011;58:402–12.

47. Fougeres E, Tribouilloy C, Monchi M, et al. Outcomes of pseudo-severe aortic stenosis under conservative treatment. Eur Heart J 2012;33:2426–33.

48. Clavel MA, Webb JG, Rodes-Cabau J, et al. Comparison between transcatheter and surgical prosthetic valve implantation in patients with severe aortic stenosis and reduced left ventricular ejection fraction. Circulation 2010;122:1928–36.

49. Ben-Dor I, Maluenda G, Iyasu GD, et al. Comparison of outcome of higher versus lower transvalvular gradients in patients with severe aortic stenosis and low (<40%) left ventricular ejection fraction. Am J Cardiol 2012;109:1031–7.

50. Lauten A, Zahn R, Horack M, et al. Transcatheter aortic valve implantation in patients with low-flow, low-gradient aortic stenosis. J Am Coll Cardiol Intv 2012;5:552–9.

Key Words: cardiac imaging ▪ dobutamine echocardiography ▪ low gradient aortic stenosis ▪ valvular heart disease.

To participate in this CME activity by taking the quiz and claiming your CME credit certificate, please go to **www.imaging.onlinejacc.org** and select the CME tab on the top navigation bar.