

Low gradient “severe” aortic stenosis with preserved left ventricular ejection fraction

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Abstract: In developed nations, aortic stenosis (AS) is the most common valvular heart disease presentation, and its prevalence is increasing due to aging populations. Accurate diagnosis of the disease process and determination of its severity are essential in clinical decision-making. Although current guidelines recommend measuring transvalvular gradients, maximal velocity, and aortic valve area in determining the disease severity, inconsistent grading of disease severity remains a common problem in clinical practice. Recent studies suggest that patients with paradoxical low-flow and/or low-gradient, severe AS are at a more advanced stage of the disease process and have a poorer prognosis. This mode of presentation may lead to an undervaluation of symptoms and inappropriate delay of AVR. Therefore, this challenging clinical situation should be carefully assessed in particular in symptomatic patients and clinical decisions should be tailored individually.

Key Words: Aortic stenosis; transvalvular gradients; maximal velocity; aortic valve area



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Introduction

In developed nations, aortic stenosis (AS) is the most common valvular heart disease presentation, and its prevalence is increasing due to aging populations. Our understanding of calcific AS has changed dramatically, from a concept of a “mechanical” disease of aging strictly limited with the valve, to a modern concept of a progressive disease process, with similarities to atherosclerosis. Because AS is a fatal disease when left untreated, replacement of the degenerative and stenotic valve with an artificial valve (bio-prosthetic or mechanical) is the recommended treatment for patients with symptomatic, severe AS. Therefore, the accurate diagnosis of the disease and determination of its hemodynamic severity are clinically essential in clinical decision-making. Current ACC/AHA guidelines recommend cut-off values for Doppler-echocardiographic measurements of severe aortic stenosis (AS) as follows: aortic valve area (AVA) $<1.0 \text{ cm}^2$ and/or indexed for body surface area $<0.6 \text{ cm}^2/\text{m}^2$,

mean gradient $>40 \text{ mmHg}$ and peak velocity $>4.0 \text{ m/s}$ (1). Similarly, ESC guidelines set the mean transvalvular gradient of $>50 \text{ mmHg}$ (2) (Table 1). However, inconsistent grading of AS remains a common problem in clinical practice, both in patients with impaired and normal LV functions. A common pattern is the combination of an AVA $<1 \text{ cm}^2$ with a gradient $<40 \text{ mmHg}$.

This pattern of “low-flow/low-gradient aortic stenosis” is relatively well known and accepted in AS patients with depressed LV function, where it was assumed that the failing LV cannot generate a high-flow/high-gradient across the stenotic valve. However, more recent observations demonstrate that “low-flow/low-gradient aortic stenosis” is not infrequently encountered in the setting of preserved LV EF (LV EF $>50\%$). This clinical entity was therefore named “Paradoxical low flow and/or low gradient severe AS”. In a study of 2427 patients with aortic stenosis and preserved left ventricular systolic function evaluated at a referral centre, such discrepancies in grading were found in a surprisingly

Table 1 Severity of Aortic Stenosis in Adults

| | AVA (cm ²) | Mean TVG (mmHg) | Peak Aortic Velocity (m/sec) |
|----------|--|-----------------|------------------------------|
| Mild | >1.5 | <25 | <3 |
| Moderate | 1-1.5 | 25-40 | 3-4 |
| Severe | <1 or iAVA≤0.6 cm ² /m ² | >40* | >4 |

Aortic Valve Area, AVA; Aortic Valve Area indexed for iAVA; Transvalvular Gradient, TVG; *ESC guideline accepts 50 mmHg as cut off to be severe.

high percentage of almost one third of patients (30%). In these patients, valve area calculated by the continuity equation to less than 1 cm², but the mean gradient was less than 40 mmHg (3). A subgroup of this cohort with inconsistent grading of AS interestingly represents with low flow across the valve, despite maintained LV function. Recent studies suggest that such patients are characterized by severe LV concentric hypertrophy with small LV cavity, restrictive filling pattern, and subtle myocardial dysfunction. Data suggest that these patients are at a more advanced stage of the disease process and have a poorer prognosis, if treated medically rather than surgically (4,5). This creates a challenging scenario for the clinicians by raising uncertainty regarding the actual severity and complicating an appropriate timely decision for AVR.

This review article, will discuss the reasons of inconsistent grading of aortic valve stenosis and possible pathophysiological mechanisms underlying low flow/low gradient severe AS, despite preserved LV EF, based on an illustrative case presentation.

Illustrative case

A 72-year-old woman with a history of hypertension, dyslipidemia and coronary artery disease presented with exertional dyspnea and angina. Four years ago, she was diagnosed with moderate aortic stenosis (Max/Mean Gradient 42/21 mmHg with a valve area 1.52 cm²) and coronary artery disease. At that time a lesion in the LAD was stented successfully.

Transthoracic echocardiography was repeated to evaluate the current status of the patient. Severely calcified aortic stenosis was observed by 2D echo with transvalvular gradients measured at 53/32 mmHg and calculated AVA of 0.7 cm² by continuity equation (*Figure 1*). There was normal LV systolic function with an ejection fraction (LV EF) of 64% by the biplane Simpson method. There was grade 2 diastolic dysfunction (Pseudo normal pattern with an E/E' ratio: 22)

detected by a dedicated Doppler diastolic examination. Her blood pressure was 160/90 mmHg at the time of echo exam and her body surface area was 1.7 cm². Coronary angiography and invasive left heart catheterization were performed to evaluate current coronary status and to determine AS severity (*Figure 1*). There was no severe coronary lesion for revascularization and LAD stent was patent.

How should this case be further evaluated?

A. Prevalence and clinical importance of low flow/low gradient severe AS with preserved LV EF

Hachicha *et al.* studied the clinical and Doppler echocardiographic data of 512 consecutive patients with severe aortic stenosis (iAVA ≤0.6 cm²/m²) and preserved LV EF (>50%) (6). Of these patients, 331 (65%) had normal LV flow output defined as a stroke volume index >35 mL/m², and 181 (35%) had paradoxically low-flow output defined as stroke volume index ≤35 mL/m². When compared with normal flow patients, low-flow patients had a higher prevalence of female gender (P<0.05), a lower transvalvular gradient (32±17 versus 40±15 mmHg; P<0.001), a lower LV diastolic volume index (52±12 versus 59±13 mL/m²; P<0.001), lower LV ejection fraction (62±8% versus 68±7%; P<0.001), a higher level of LV global afterload reflected by a higher valvulo-arterial impedance (5.3±1.3 versus 4.1±0.7 mm Hg·mL⁻¹·m⁻²; P<0.001). Importantly, compared with normal flow patients, low-flow patients had a lower overall 3-year survival (76% versus 86%; P<0.006). The authors concluded that a subgroup of patients with severe aortic stenosis presents with low transvalvular flow and low gradients despite normal LV ejection fraction. Further, while the results of grading may lead to an undervaluation of severity with inappropriate delay of AVR, this pattern of the disease is in fact consistent with a more advanced stage of the disease and has a poorer prognosis (5). However, this study was a retrospective analysis and more importantly the symptomatic status of the included

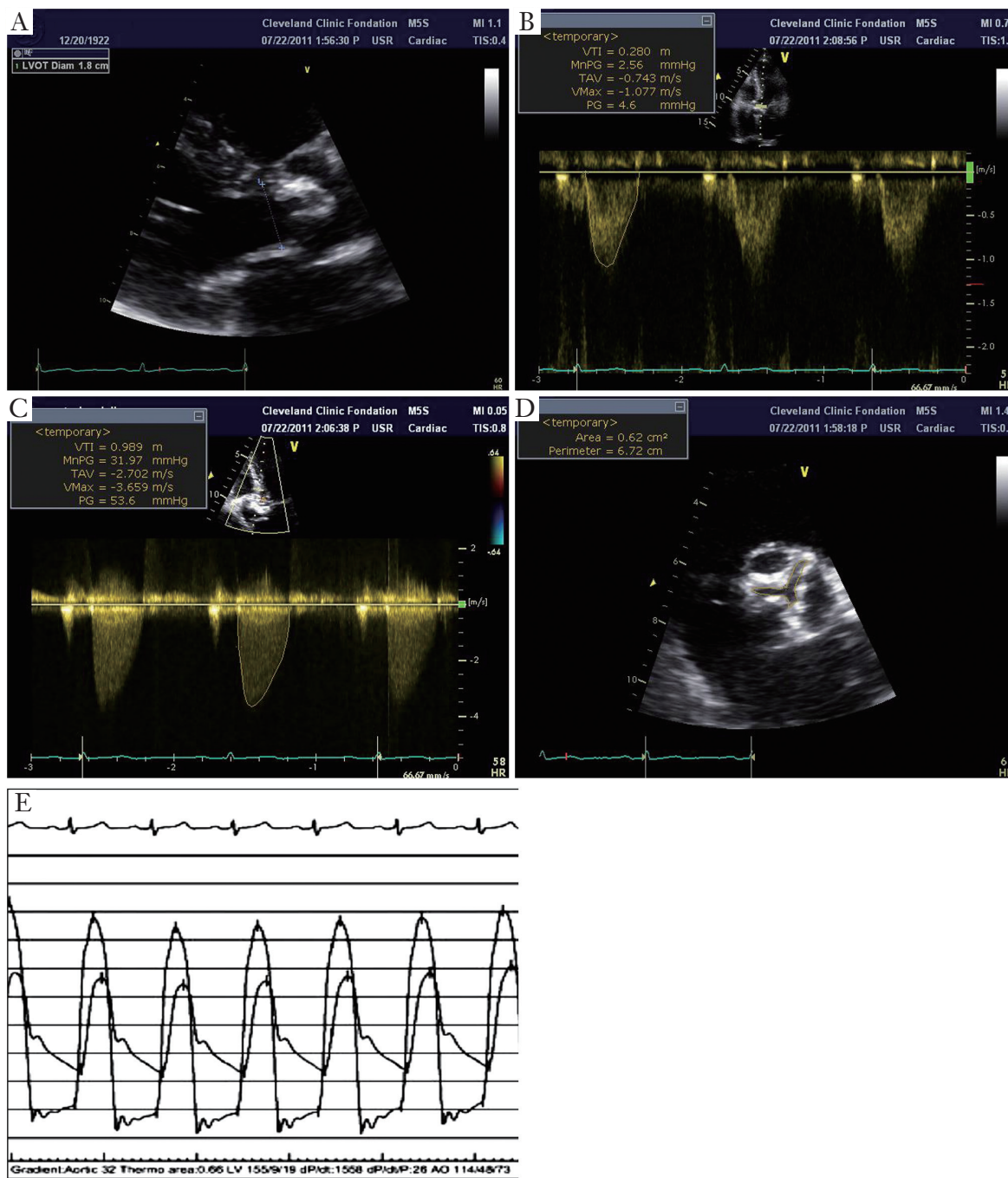


Figure 1 An illustrative case. A. LVOT diameter was measured from parasternal long axis, during mid-systole as to be 1.8 cm which yields 2.54 cm² CSA of LVOT; B. LVOT VTI was measured 28 cm from apical 5 chamber view and C. Max/mean transvalvular gradients and AV VTI were calculated by Doppler echocardiography as 53/32 mmHg and 99 cm respectively. By using continuity equation, AVA was calculated 0.71 cm² and indexed valve area adjusted for BSA (1.7 cm²) was 0.41 which indicates severe AS; D. AVA was also measured by planimetric method as 0.62 cm²; E. Catheter study revealed mean gradient was 32 mmHg with an AVA 0.66 cm² by thermodilution method that findings confirmed echo measurements

patients and details of the decision process leading to possible AVR were not comprehensively discussed.

Confirming prior results, data from Barasch *et al.* also demonstrated the impact of low gradient AS on outcome, reporting a two-fold increase in mortality and an almost 50% lower referral rate for AVR in the low-gradient AS compared to the high gradient group (4). In another report of 150 patients with severe AS and a normal LVEF, 12 patients with an invasively measured peak-to-peak gradient <50 mmHg were identified. Despite symptomatic status, AVR was not recommended. During 2.5 years of follow up, six patients had died (50% mortality) and three developed severe heart failure within (6). Contrary to these studies, Jander *et al.* found that patients with low-gradient “severe” aortic stenosis and normal ejection fraction have an outcome similar to that in patients with moderate aortic stenosis (7). The discordant results between these studies likely derive from differences in patient population and symptomatic status. Specifically, Jander *et al.* included asymptomatic AS patients from SEAS study (CAD, PAD, and DM were exclusion criteria), whereas 51 of the prospectively enrolled patients in the study by Barasch *et al.* were symptomatic. In a prospective trial, Rosenheck *et al.* demonstrated that outcomes of asymptomatic severe AS patients were almost the same with normal control in terms of event free survival (8).

B. Pathophysiology of low gradient severe AS in patients with preserved ejection fraction

Is the problem systolic dysfunction, although LV EF apparently appears normal?

In patient with AS, assessment of LV function plays a central role in the decision to proceed with AVR, and patients with preserved systolic function have an excellent outcome after AVR (9). However, it is well known that LV EF is a limited marker of systolic function, in particular in the setting of co-morbidities that affect LV mechanics (10,11). Calcific AS should not be considered as an isolated disease limited to the valve, but rather a manifestation of a more systemic disease process (12). Hypertension (13), the metabolic syndrome (14), atherosclerosis and aging are highly prevalent in AS patients. These conditions cause direct alterations of LV mechanics and also contribute to vascular stiffness and increased afterload.

Briand *et al.* suggested that increased afterload should be taken into account when assessing AS severity (15). The authors demonstrate that valvuloarterial impedance (Z_{va}), which is calculated by dividing the total systolic pressure

(systolic blood pressure plus mean transvalvular gradient) by the stroke volume index (SVi) reflects increased afterload in AS patients. Z_{va} , in fact, represents the cost in mmHg for each systemic millimeter of blood indexed for the body size. The data demonstrates that increased afterload is strongly associated with LV systolic and diastolic dysfunction in AS patients. Hachica *et al.* further demonstrated that increased Z_{va} (>3.5 mmHg·mL⁻¹·m²) identifies poor outcome in asymptomatic severe AS patients (16). Low gradient severe AS with preserved LV EF patients were also evaluated in a SEAS sub study and interestingly Z_{va} was found as the main determinant of LV dysfunction in asymptomatic patients (17). These data suggest that measures of afterload, including an increased Z_{va} can guide risk stratification and follow up decisions and are incremental to measures of LVEF.

The development of myocardial fibrosis, independent of prior myocardial infarction, has been well established in severe AS patients and a direct relationship has been shown between severity of fibrosis and adverse outcome (18). In a recent study with severe symptomatic AS patients, low gradient was found to be associated with higher degree of fibrosis and decreased longitudinal function and poorer clinical outcome despite preserved LV EF (19). Mitral ring displacement was shown to differentiate between moderate AS and low gradient severe AS with preserved EF. Subtle myocardial dysfunction and decreased longitudinal deformation have been demonstrated in studies using different techniques such as M mode echocardiography (20), tissue Doppler imaging (TDI) (21) and 2D Speckle Tracking Echocardiography (2D STE) (22,23) (Figure 2). In patients with low-flow/low-gradient AS despite preserved EF, decreased global longitudinal strain was found and it was inversely related with increased global afterload as calculated by Z_{va} (24).

Is the problem “simply” LV diastolic dysfunction?

Diastolic dysfunction in varying degrees is highly prevalent in aging populations due to associated co-morbid factors such as coronary artery disease, hypertension, and diabetes mellitus. Both impaired myocardial relaxation and increased stiffness are contributing to impaired LV diastolic filling. Increased filling pressure with severe LV diastolic dysfunction has been associated with worse outcome in AS patients. A restrictive filling pattern with a small LV cavity has been found to be more common in LGAS patient (5). However, each factor including atrial fibrillation, mitral annular calcification, severe pulmonary hypertension etc. can affect LV filling negatively and this may results with low

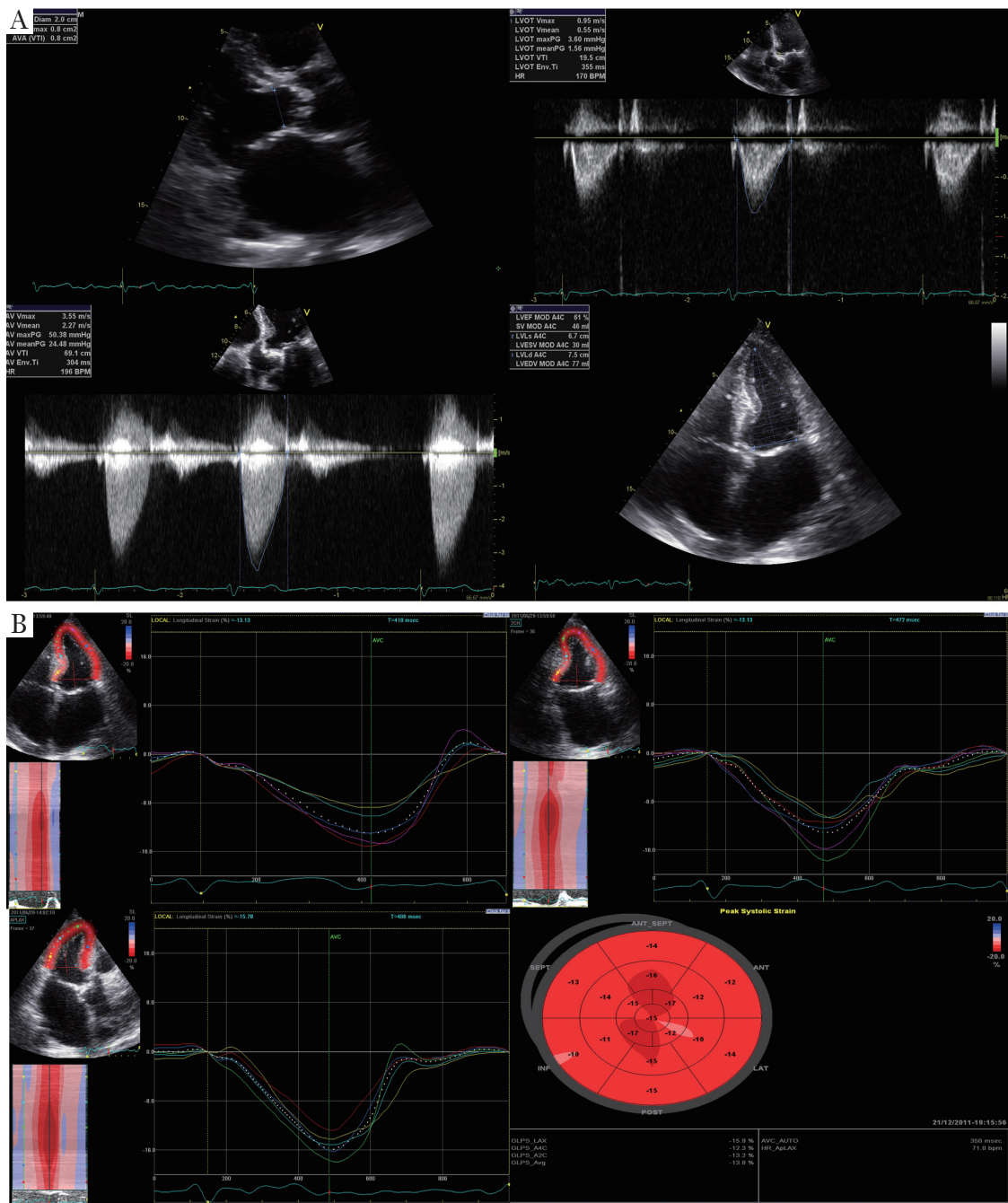


Figure 2 (A) Low Flow/low gradient severe AS despite preserved LV EF. A 78 year old man who had history of hypertension and AS presented with exertional dyspnea and chest pain. AVA was calculated as 0.88 cm² (iAVA was 0.44 cm²/m² with a BSA of 2 m²) but gradients were measured as 50/24 mmHg. SV_i was calculated 30.6 mL/m², Z_{va} was 5.8 mmHg·mL⁻¹·m⁻²; (B). Assessment of segmental and global strain by 2D STE. Global longitudinal strain was found 13.3% indicating mildly decreased LV function. The patient was also symptomatic and diagnosed with low flow/low gradient severe AS despite preserved LV EF. Increased Z_{va} and decreased global strain indicate possible impaired LV function. Since the patient was not a good candidate for surgical AVR due to multiple comorbidities, transcatheter aortic valve replacement (TAVi) was performed via transfemoral approach

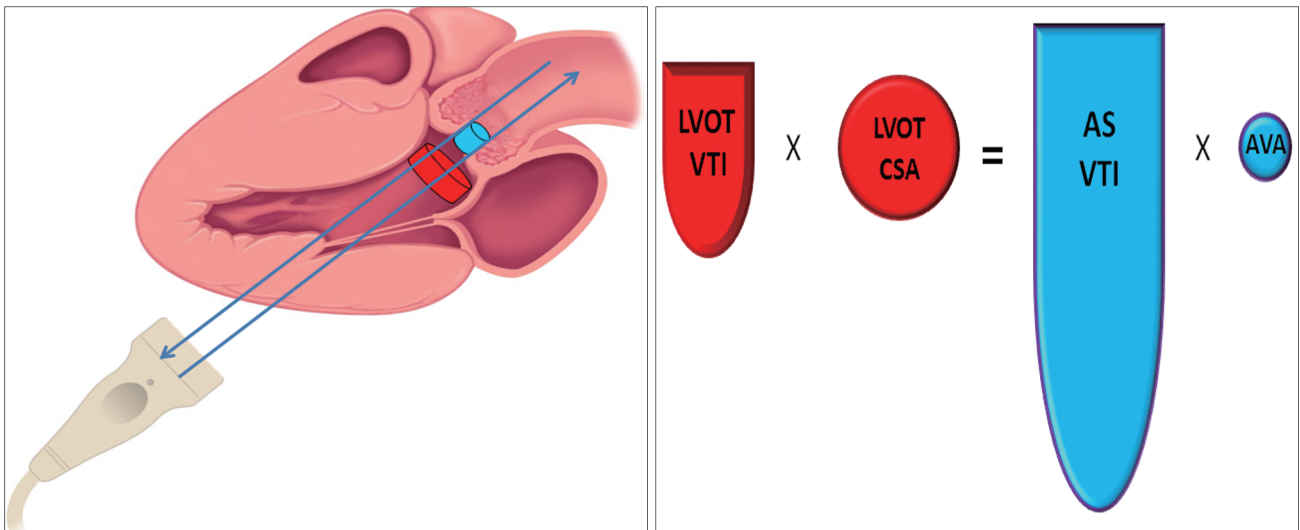


Figure 3 Continuity Equation. The continuity equation is derived from the basic principles of conservation of mass. The stroke volume below the valve must be the same as the stroke volume through the valve. The flow in LVOT can be calculated from the product of the cross sectional area of the LVOT (red circle) and the velocity time integral (VTI) of the pulsed Doppler of LVOT (area of the red waveform). That flow must be constant through the valve, so the effective orifice area of the stenotic valve can be easily calculated by dividing this stroke volume by the VTI of the continuous Doppler of AVA (area of the blue waveform)

cardiac output.

C. Methodological explanations for inconsistent grading of severity of aortic stenosis

Definition of cut off values

Current guidelines state that “when AS is severe and cardiac output is normal, the mean transvalvular pressure gradient is generally >40 mmHg”. However as described above, discrepancy between the valve area (<1 cm²) and transvalvular gradients (<40 mmHg) are frequent in both invasive measurements during catheterization and non invasive calculation by echocardiography.

Some of this inconsistency may be related matching of the cut-off values, as has been suggested based on invasive measurements. The Gorlin formula calculates AVA as:

$$AVA_{\text{Gorlin}} = [\text{Cardiac Output} / (\text{Systolic Ejection Period} \times \text{Heart Rate})] / (44.3 \times \sqrt{\text{Mean Gradient}})$$

Carabello demonstrated the potential mismatch of the cutoff values with the following assumption (25). A cardiac output of 6 L/min, systolic ejection period of 0.33 seconds, and heart rate of 80 beats per minute, a mean gradient of 26 mmHg actually yields to an AVA of 1.0 cm², whereas a mean gradient >40 is corresponding with a AVA of 0.8 cm².

These values are similar to data observed in the above cited

study of 2427 patients with aortic stenosis and preserved left ventricular systolic function (3). In this study a substantial proportion of patients (30%) had a valve area calculated by the continuity equation less than 1 cm², but a mean gradient also less than 40 mmHg (3). Similar to the results by Carabello, an AVA of 1 cm² was found to be correlated with a mean gradient of 22.8 mmHg. Conversely, a mean gradient of 40 mmHg was found to be correlated with an in vivo AVA of 0.75 cm² and maximum velocity of 4 cm/sec was corresponding with an in vivo AVA of 0.82 cm².

These data suggest that the echocardiographic and invasive results for AVA and trans-valvular gradient are actually consistent, but that the proposed cut-off values have limitations.

Small body size

AVA indexed for the body size is an important step in the assessment of discrepant measurement. In current guidelines, an indexed AVA cut off value of 0.6 cm²/m² is recommended as the criterion for severe AS (1,2). Patients with small body surface area can be incorrectly classified as having severe AS, if the AVA is not indexed. Conversely, a large body size may cause an overestimation of AVA in terms of disease severity unless it is indexed for BSA. For example, an AVA of 0.9 cm² (iAVA= 0.7 cm²/m²) does

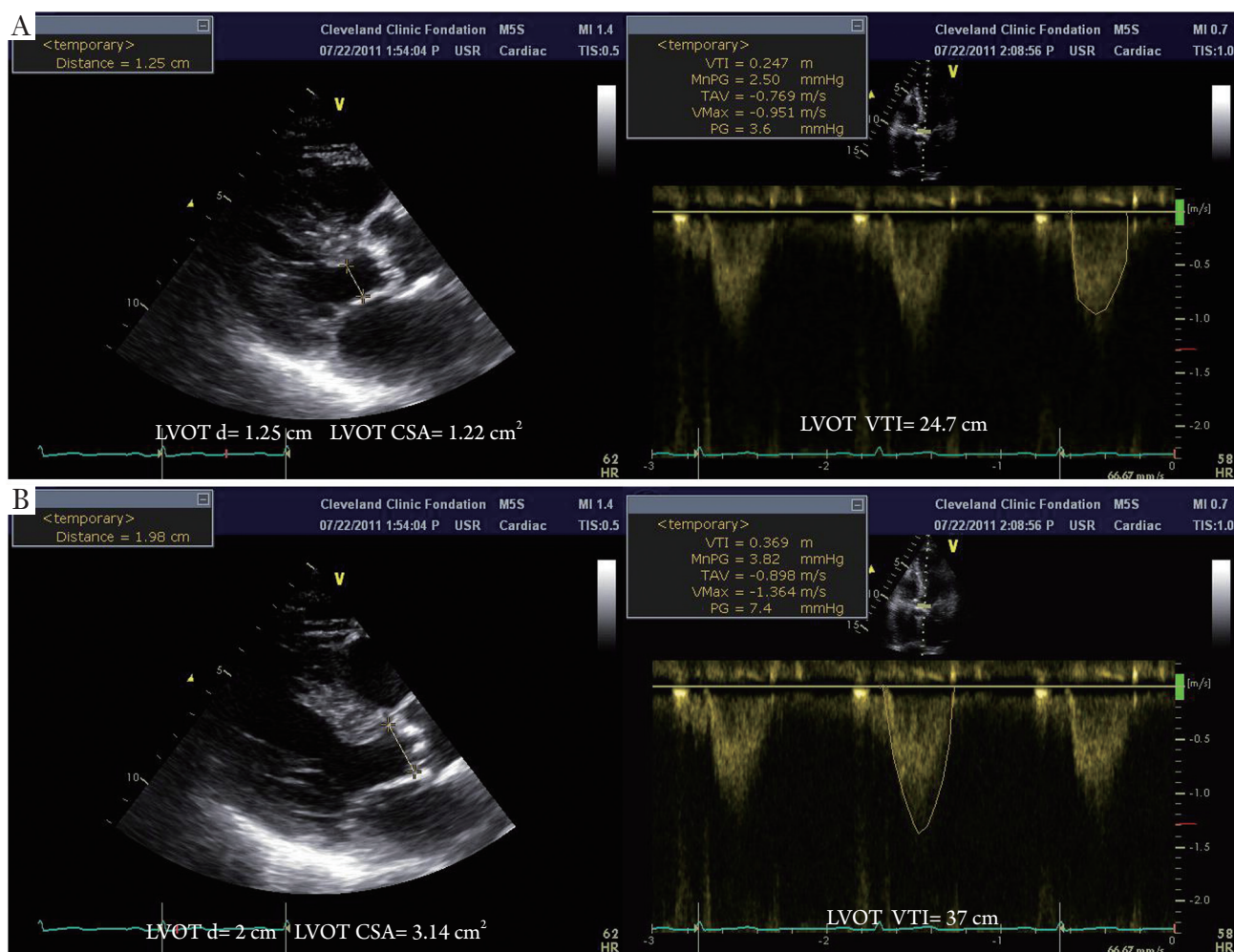


Figure 4 Importance of LVOT measurements: In the illustrative case the LV EF was 64% and gradients were 52/32 mmHg and AV VTI was 99 cm. Underestimation of LVOT measurements (**Panel A, upper**) may yield results as follows, LVOT=1.25 cm, CSA of LVOT=1.22 cm², LVOT VTI=24.7 cm, AVA=0.34 cm² and iAVA=0.24 cm²/m². Stroke volume index=17.7 cc/m² and Zva=10.8 mmHg·m²/cm². All these measurements indicate low flow, low gradient critically severe AS with rigorously increased afterload. Therefore, valve replacement is mandatory in this patient. However, overestimation of LVOT measurements (**Panel B, lower**), result as follows LVOT=2 cm, CSA of LVOT=3.14 cm², LVOT VTI=37 cm, AVA=1.17 cm² and iAVA=0.7 cm²/m². Stroke volume index=68 cc/m² and Zva=2.8 mmHg·m²/cm². These overestimated results are concluding that this case is normal flow-low gradient which is consistently with moderate AS (based on AVA) and after load is not increased. If the symptomatic status of this patient is unclear, medical therapy with careful follow-up should be recommended. Although the continuity equation is a practical and robust method for the calculation of AVA, this example demonstrates the dependency on measurement of the LVOT.

not indicate severe AS in a woman with a BSA of 1.3 m², whereas an AVA of 1.2 cm² (iAVA=0.57 cm²/m²) should be considered as severe in a man with a BSA of 2.1 m².

Measurement error and possible pitfalls of LVOT measurements

It is important to note that LVOT measurements play an

essential role for several reasons. First, calculation of AVA by continuity equation (*Figure 3*) depends on the area of the LVOT measurement (26). Second, calculation of stroke volume is derived from pulsed wave Doppler of LVOT. Third, estimation of global load by using valvuloarterial impedance (Zva) requires accurate LVOT measurements. All these parameters change substantially with variations

in LVOT measurements. Therefore, if there occurs any mistake in LVOT measurements, AVA, SV and Z_{va} will be calculated wrong. *Figure 4* depicts the importance of LVOT measurements.

Contamination of the LVOT with mitral regurgitation signal and erroneous correction for misalignment of Doppler beam can be the other potential pitfalls.

D. How should we approach a patient with low gradient and severe AS?

The accurate assessment of the hemodynamic severity of AS is clinically essential for several reasons. First, determination of the severity of the disease is critical to explain the symptomatic status. If the AS is not severe, differential diagnosis should be carefully reviewed and possible other reasons such as coronary artery disease or hypertensive heart disease should be ruled out. Second, since AS is a progressive disease, quantitative measures allow monitoring and predicting disease progression for optimal timing of valve replacement. Third, if the patient is totally asymptomatic, evaluation of disease severity provides critical data in terms of risk stratification and future therapeutic decision.

In the setting of inconsistently grading AS despite preserved LV EF, possible measurement pitfalls should be reviewed and the symptomatic status of the patients should be clarified. If the patient is symptomatic with an indexed AVA of $<0.6 \text{ cm}^2/\text{m}^2$, AVR should be recommended. If symptoms are equivocal, measures of afterload and in particular Z_{va} can be calculated in order to estimate total load. In addition measuring global LV strain can provide important data in terms of LV function and risk stratification. However, it is noteworthy that neither Z_{va} nor global longitudinal strain can differentiate moderate and severe AS. Z_{va} reflects increased global load but unfortunately cannot discriminate the load separately. Dobutamine stress echo can be carefully performed in order to assess contractile reserve. B type Natriuretic Peptide (BNP) can provide useful data regarding risk assessment, and other imaging modalities such as TEE and 3D TEE can better characterize LVOT measurement and finally calcium score of aortic valve can give us an idea about disease severity.

Since there is no prospective randomized trial about outcome of low-flow/low-gradient patients despite preserved LV to date, utility of aforementioned parameters (Z_{va} , global longitudinal strain, contractile reserve with DSE or calcium score of the valve) is incompletely

understood and clinical decision should be tailored individually.

Commentary on illustrative case

In our illustrative case the patient was symptomatic and had severe AS. Invasive study confirmed that this patient had “normal flow/low gradient and severe AS despite preserved LV EF”. SV_i was calculated as $42 \text{ mL}/\text{m}^2$ and Z_{va} was calculated as $4.5 \text{ mmHg}\cdot\text{mL}^{-1}\cdot\text{m}^{-2}$. This case is a good example of inconsistently grading AS.

Conclusions

Inconsistent results of grading AS remains a common problem in the assessment of patient with suspected severe aortic stenosis. An important subgroup of these patients has ‘paradoxically’ low-flow/low-gradient severe AS despite preserved LV EF. This pattern of the AS is consistent with a more advanced stage of the disease and has a poorer prognosis. The inconsistencies in grading may leads to an undervaluation of symptoms and inappropriate delay of AVR. Although accurate assessment of the hemodynamic severity of AS is clinically essential for decision making, symptomatic status of this cohort should be carefully evaluated and clinical decision should be tailored individually.

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