



Imaging Strategies for Evaluating Low-Flow, Low-Gradient Aortic Stenosis with Reduced and Preserved Left Ventricular Ejection Fraction

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Abstract

Purpose of Review Aortic stenosis (AS) is one of the most common valvular heart diseases, and aortic valve replacement (AVR) provides both symptomatic and survival benefit in symptomatic severe AS patients. The purpose of this review is to discuss low-flow low-gradient AS which is still a challenging diagnostic entity.

Recent Findings Thirty–forty percent of patients with AS have low flow which makes it difficult to differentiate truly severe AS that benefits from AVR compared to pseudo-severe AS which is currently managed conservatively. Patients with low-flow low-gradient AS (LF-LG AS) include those with reduced left ventricular systolic function (classical LF-LG AS) and those with preserved left ventricular systolic function (paradoxical LF-LG AS). Low-dose dobutamine stress echocardiography (DSE) helps to identify truly severe stenosis in patients with classical LF-LG AS. Aortic valve calcium scoring with multidetector computed tomography plays a major role in patients with paradoxical LF-LG AS and also among classical LF-LG AS patients who have reduced contractile reserve on DSE.

Summary This article will provide an overview of imaging strategies for evaluating LF-LG AS with reduced and preserved left ventricular ejection fraction.

Keywords Aortic stenosis · Left ventricular ejection fraction · Dobutamine stress · Echocardiography · Multidetector computed tomography · Aortic valve replacement

Introduction

Aortic stenosis (AS) is one of the most common valvular heart diseases in developed countries and is the most common indication for aortic valve replacement. The prevalence of AS increases with age, affecting up to 10% of octogenarians [1]. The prognosis is excellent until the disease becomes severe and symptomatic whereupon prognosis worsens dramatically.

[2, 3]. The definition of severe AS is based on natural history studies of patients with unoperated AS, which show that the prognosis is poor once peak aortic valve velocity is > 4.0 m per second, corresponding to a mean aortic valve gradient > 40 mmHg [4, 5]. Aortic valve replacement (AVR) provides both symptomatic and survival benefits in these symptomatic severe AS patients [6–8]. However, as gradient is a squared function of flow, even a modest decrease in flow may lead to significant reduction in gradient despite the presence of severe aortic stenosis, termed low-flow, low-gradient AS (LF-LG AS), leaving aortic valve area (AVA) as the principle determinant of AS severity [4]. Patients with LF-LG AS can be either those (a) with reduced left ventricular systolic function who represent 5 to 10% of patients with AS [9–11], or (b) those with preserved left ventricular systolic function (paradoxical LF-LG) who represent 10 to 25% of patients with AS [12–14] (Fig. 1). Unfortunately, valve area is a calculated rather than a measured variable and is subject to many errors compounded by low flow because AVA is flow dependent. Thus, it is important but in some cases it is very difficult to distinguish truly

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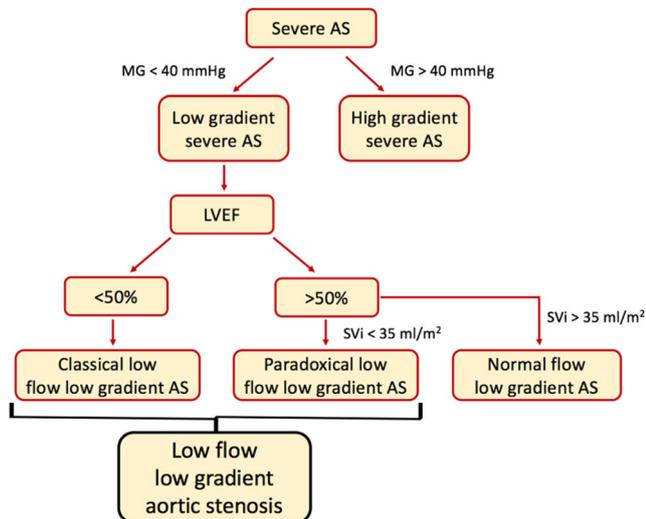


Fig. 1 Subtypes of severe aortic stenosis. *AS* aortic stenosis, *LVEF* left ventricular ejection fraction, *SVi* stroke volume index

severe AS from pseudo-severe AS where calculated AVA is small due to insufficient flow to fully open the valve [15, 16]. Cardiac imaging plays an important role in hemodynamic classification of patients with LF-LG AS. It is the intent of this article to provide an overview of LF-LG AS with case-based illustrations.

Classical Low-Flow, Low-Gradient Aortic Stenosis

Classical LF-LG AS is defined in the guidelines [4] as an aortic valve area (AVA) $< 1.0 \text{ cm}^2$, a mean gradient $< 40 \text{ mmHg}$, and a left ventricular ejection fraction (LVEF) $< 50\%$ although not all patients with reduced EF have low flow. For the purposes of classification, the most accepted definition of low flow is stroke volume index $< 35 \text{ ml/m}^2$. Stroke volume (SV) is usually measured in the LV outflow tract by Doppler echocardiography [17, 18]. Accurate SV calculations depend on precisely recording the left ventricular outflow tract (LVOT) diameter and velocity. It is essential that both measurements are made at the same distance from the aortic valve. When a smooth velocity curve can be obtained, the aortic annulus is the preferred site to measure these parameters. In case of flow acceleration at the annulus level, the sample volume must be moved apically to obtain a laminar flow curve without spectral dispersion [17].

Accurate assessment of AVA by use of the continuity equation is the crucial first step in evaluating patients with LF-LG AS. Among the parameters in the continuity equation, LVOT diameter has the highest intra and interobserver variability [17]. Because the LVOT diameter is squared for calculation of AVA, it becomes the greatest potential source of error in the continuity equation. In addition, three-dimensional imaging has shown that

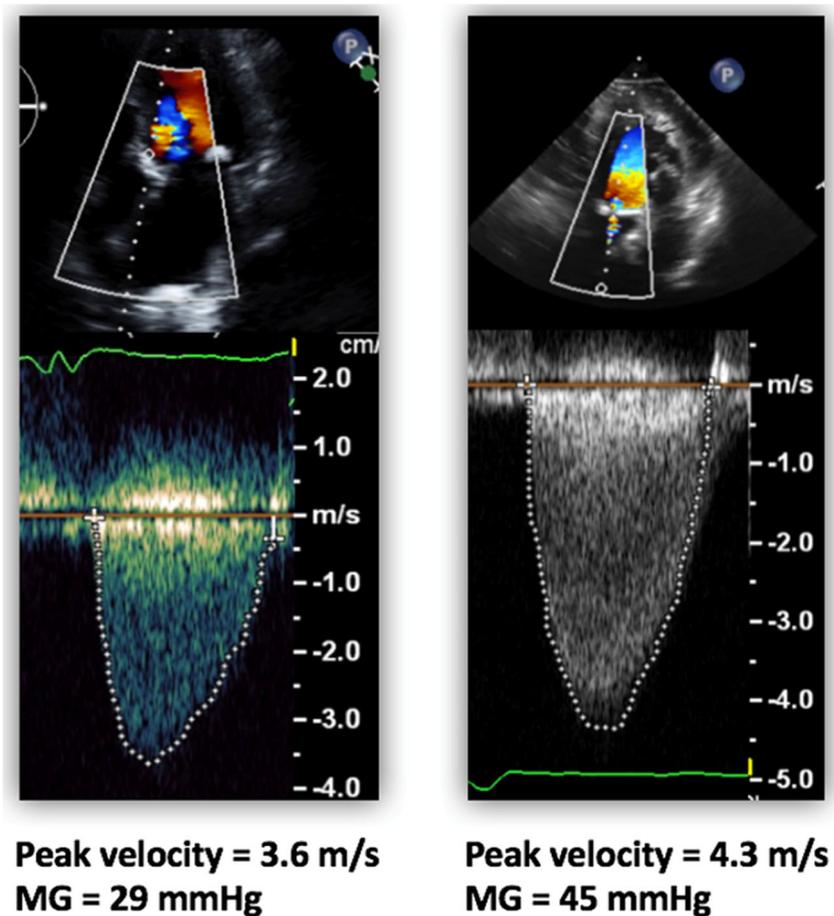
the LVOT is often noncircular as assumed by the continuity equation leading to an underestimation of AVA [19, 20]. When transthoracic images are not adequate for the measurement of LVOT diameter, three-dimensional (3D) echocardiography or cardiac computed tomography (cardiac CT) is recommended if this information is needed for clinical decision-making. Accurate aortic jet velocity by continuous wave Doppler recording mandates use of multiple acoustic windows in order to determine the highest jet velocity which is found outside the apical window in $> 50\%$ of patients, with the right parasternal window being the most common site of higher velocity [21••]. Neglecting nonapical imaging windows results in misclassification of aortic stenosis in up to one fourth of patients [21••]. The more acute the aortic root angulation, the more likely a nonapical window will yield the highest values of peak velocity. In our experience, obtaining the deep transgastric view on transesophageal echocardiography has recorded higher aortic jet velocity compared to transthoracic echocardiography views in a substantial number of patients with resultant change in AS severity classification (Fig. 2).

The dimensionless velocity ratio (DI) is another measure of AS severity which removes cross sectional area from the continuity equation and reduces error related to LVOT diameter measurements. DI is the ratio of LVOT velocity to peak aortic jet velocity, or, the ratio of time-velocity integrals can also be used instead of peak velocity. In the absence of valve stenosis, the DI velocity ratio approaches 1, with smaller numbers indicating more severe stenosis. Severe stenosis is present when the DI ratio is 0.25 or less, corresponding to a valve area 25% of normal [17, 22]. In low-flow situations, DI has an advantage over individual measurements of peak velocity and gradient due to partial incorporation of flow in assessment of AS severity. However, DI is partially flow dependent and is therefore affected by low flow, resulting in smaller values for the same valve area compared to normal flow [23].

With the hemodynamic presentation of classical LF-LG AS, the main diagnostic challenge is to differentiate truly severe AS from pseudo-severe AS as the management may be different. In truly severe AS, there is a mortality benefit with aortic valve replacement (AVR) while pseudo-severe AS is usually managed conservatively with heart failure therapy and close follow up. However, it is conceivable that relief of less than severe AS in patients with severe LV dysfunction could be of benefit, a premise currently under investigation [24]. Low-dose dobutamine stress echocardiography helps in differentiating true from pseudo AS by providing information on the changes in mean gradient and valve area as flow rate increases. It also provides a measure of the myocardial contractile reserve as measured by change in stroke volume or ejection fraction [17].

The protocol for stress echocardiography for evaluation of classical LF-LG AS begins with infusion of dobutamine at a low dose of $5 \mu\text{g/kg/min}$ with an incremental increase

Fig. 2 Example of higher peak velocity and mean gradient obtained through transesophageal echocardiography (TEE). Continuous wave (CW) Doppler in a patient showed a peak velocity of 3.6 m/s and mean gradient (MG) of 29 mmHg using multiple acoustic windows. The transgastric view during TEE in the same patient showed peak velocity of 4.3 m/s and mean gradient of 45 mmHg classifying aortic stenosis severity as severe



in the infusion every 3–5 min to a maximum dose of 20 $\mu\text{g}/\text{kg}/\text{min}$ [17]. Doppler data are recorded at each stage, including LVOT velocity recorded from the apical view. AS jet velocity optimally is recorded from the window that yields the highest velocity signal. The LVOT diameter is measured at baseline and the same diameter is used to calculate the continuity equation valve area at each stage. Measurement of biplane ejection fraction at each stage is helpful to assess the improvement in LV contractile function.

Dobutamine stress echocardiography for evaluation of classical LF-LG AS can have one of the three possible outcomes (Fig. 3):

- a) An increase in AVA to $> 1.0 \text{ cm}^2$ while mean gradient remains $< 40 \text{ mmHg}$, suggesting that stenosis is not severe (pseudo-severe aortic stenosis) [25] (Fig. 4).
- b) An increase in mean gradient to $> 40 \text{ mmHg}$ but AVA does not exceed 1.0 cm^2 at any flow rate suggesting true severe aortic stenosis (Fig. 5).
- c) Absence of contractile reserve (failure to increase SV or ejection fraction by $> 20\%$) with resultant AVA $< 1.0 \text{ cm}^2$ and mean gradient $< 40 \text{ mmHg}$ is a predictor of a high peri-operative mortality and poor long-term

outcome [18, 26]. However, surgical valve replacement can improve LV function and outcome even in this subgroup [27, 28] as does transcatheter AVR (TAVR) [29, 30] which is likely to become the treatment of choice in most of these patients.

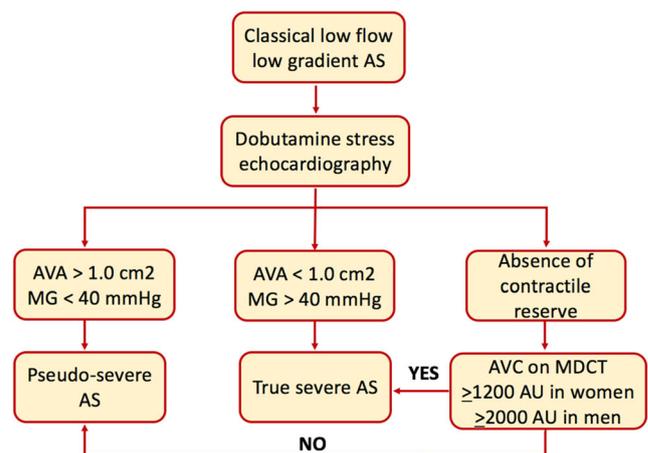


Fig. 3 Evaluation of patients with classical low-flow low-gradient aortic stenosis. AS aortic stenosis, AVA aortic valve area, MG mean gradient, AVC aortic valve calcium, MDCT multidetector computed tomography, AU Agatston units

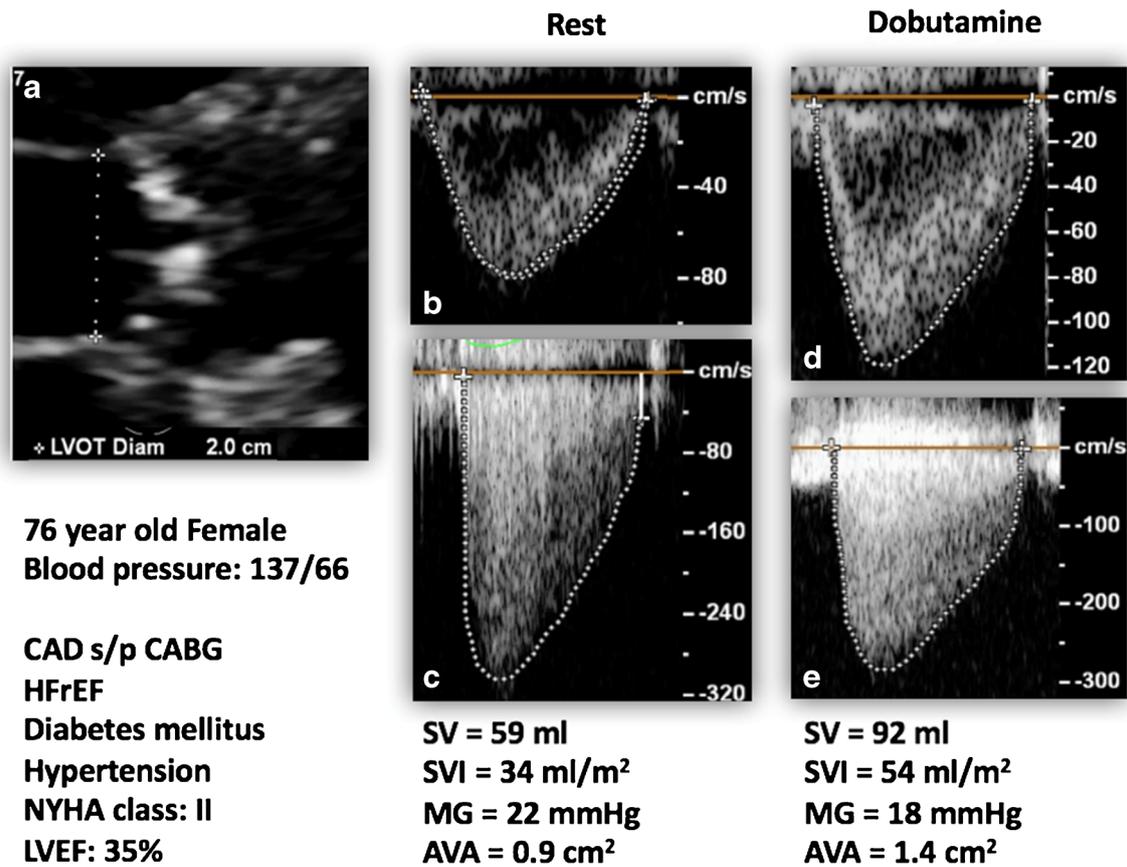


Fig. 4 Example of dobutamine echo in a patient with pseudo-severe LF-LG AS with reduced LVEF. A 76-year-old female with past history of coronary artery disease (CAD) status post-coronary artery bypass graft (CABG), diabetes mellitus, hypertension with left ventricular ejection fraction (LVEF) of 35%, and NYHA class II dyspnea. **a** Parasternal long-axis view showing left ventricular outflow tract (LVOT) diameter

of 2 cm. **b, c** Baseline pulse wave (PW) and continuous wave (CW) Doppler with calculated stroke volume (SV) 59 ml, mean gradient (MG) 22 mmHg, and aortic valve area (AVA) 0.9 cm². **d, e** PW and CW Doppler during dobutamine infusion at 5 μg/kg/min. With improvement in stroke volume, mean gradient decreased to 18 mmHg with increase in AVA to 1.4 cm², suggesting pseudo-severe aortic stenosis

Among patients with reduced contractile reserve, it is useful to calculate the projected AVA at normal flow rate when there is minimum of 15% increase in mean transvalvular flow rate (stroke volume/LV ejection time). Here, the baseline flow rate and AVA create the first point on the curve and the augmented flow rate and AVA create the second point on the curve. A line through them is extrapolated to create the AVA that would be expected at a flow rate of 250 ml/s. In the patients with no significant increase in flow rate (<15%) and indeed in most low-flow low-gradient patients, quantitation of the degree of aortic valve calcification by multidetector computed tomography (MDCT) may be used to corroborate stenosis severity (Fig. 6). The aortic valve calcification score has been shown to predict AS hemodynamic severity as well as the rate of stenosis progression and the occurrence of adverse events [31, 32]. Lower cut-point values of aortic valve calcium score that indicate severe AS should be used in women (≥1200 AU) vs. in men (≥2000 AU) to distinguish true-severe from pseudo-severe AS.

Semiquantitative continuous wave Doppler parameters including time to peak velocity (acceleration time) and

acceleration time/LV ejection time ratio were described for evaluation of mechanical prosthetic aortic valvular stenosis [33]. Recently, these variables have been shown to be associated with hemodynamically severe AS in native valves [34, 35] and may be useful in the case of uncertain or discordant echocardiographic results as in case of low gradient AS. However, specific cutoff values are not established in this patient population and should not be used in isolation to make a definitive conclusion about AS severity.

Paradoxical Low-Flow, Low-Gradient Aortic Stenosis

Paradoxical LF-LG AS is defined as an AVA <1.0 cm², indexed AVA <0.6 cm²/m², mean gradient <40 mmHg, LVEF ≥50%, and presence of low flow (stroke volume index <35 mL/m²). Thus, despite normal LVEF, patients with paradoxical LF-LG AS have reduced transvalvular flow rate, usually related to small LV cavities with pronounced LV concentric remodeling [36].

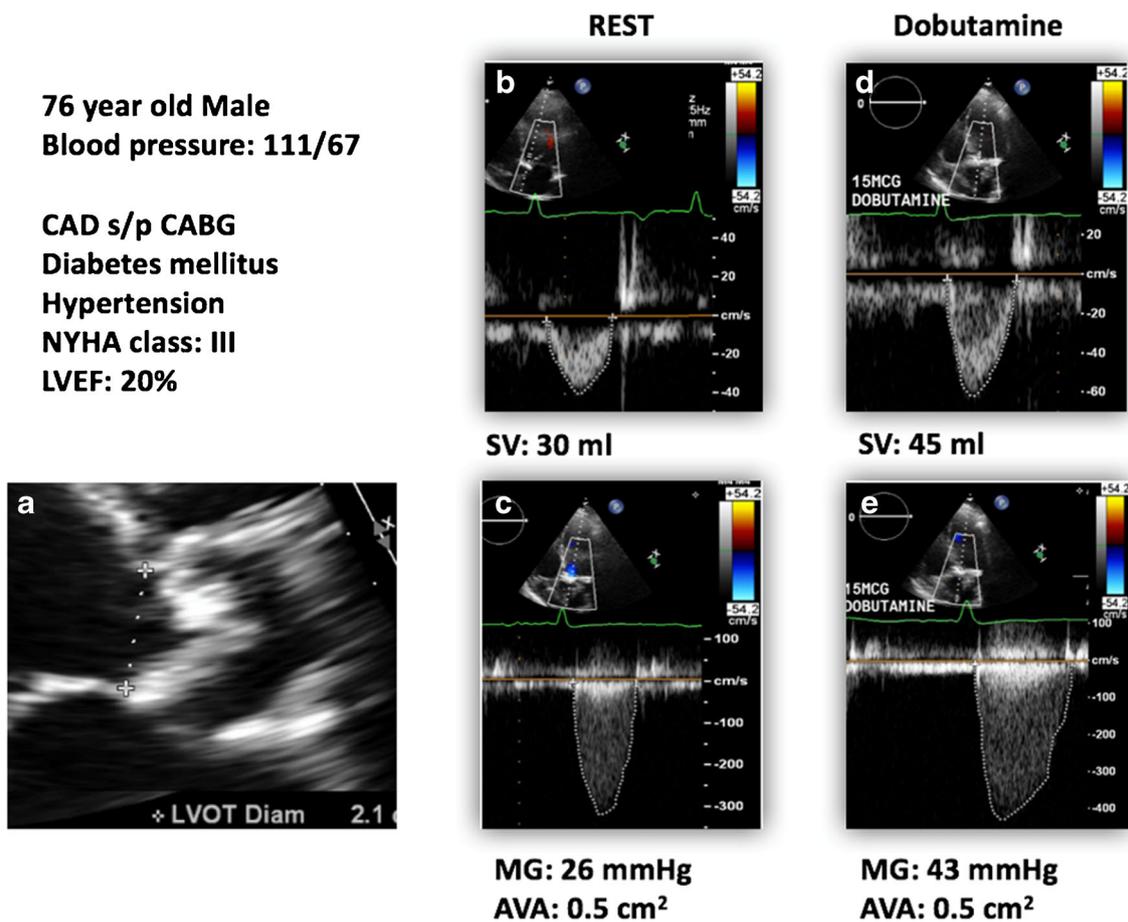


Fig. 5 Example of dobutamine echo in a patient with true classical LFLGAS. A 76-year-old male with past history of coronary artery disease (CAD) status post-coronary artery bypass graft (CABG), diabetes mellitus, hypertension with left ventricular ejection fraction (LVEF) of 20%, and NYHA class III dyspnea. **a** Parasternal long-axis view showing left ventricular outflow tract (LVOT) diameter of 2.1 cm. **b**,

c Baseline pulse wave (PW) and continuous wave (CW) Doppler with calculated stroke volume (SV) 30 ml, mean gradient (MG) 26 mmHg, and aortic valve area (AVA) 0.5 cm². **d**, **e** PW and CW Doppler during dobutamine infusion at 15 µg/kg/min. Mean gradient increased to 43 mmHg and AVA remained at 0.5 cm² with good contractile reserve suggesting true aortic valve stenosis

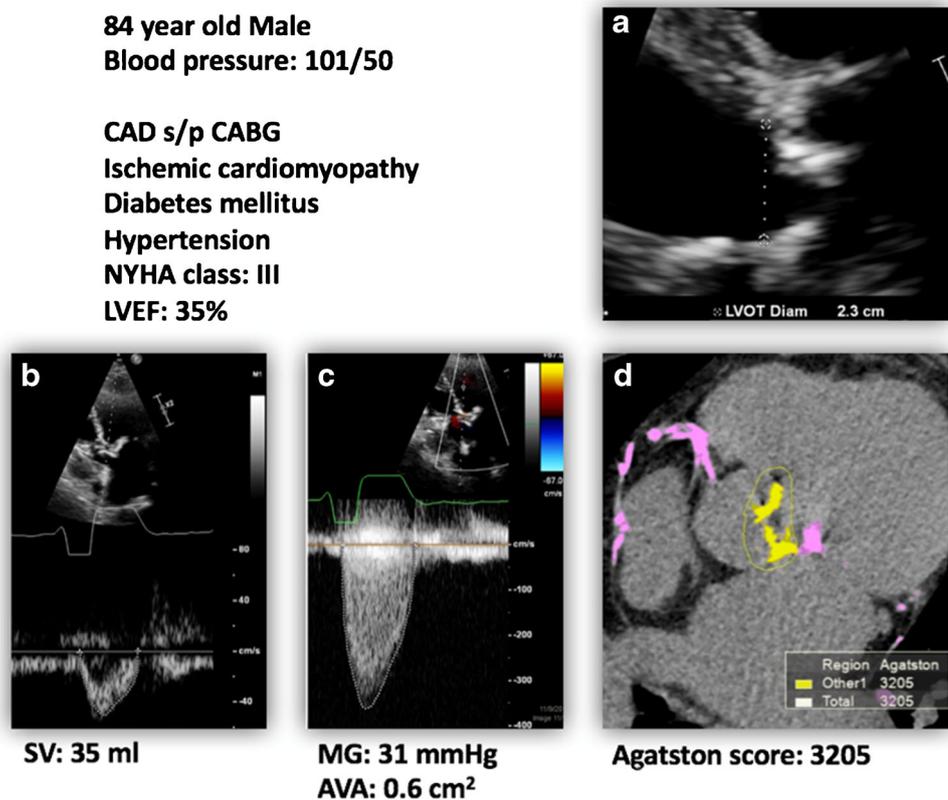
Thus, there is a normal ejection fraction of a small end diastolic volume producing a small stroke volume and hence a low gradient. Other etiologies of low forward flow include significant mitral regurgitation, mitral stenosis, tricuspid regurgitation, and atrial fibrillation. Low stroke volume results in low peak velocity and mean gradient across the aortic valve despite AVA < 1.0 cm². Since transvalvular flow is reduced, the small AVA may reflect underlying true severe AS vs. pseudo-severe AS similar to classical LF-LG AS.

As with classical low-flow AS, underestimation of LVOT diameter is the most common error in the calculation of AVA. In patients with paradoxical LF-LG AS, systemic hypertension (usually absent in low-EF patients) may cause severity of AS to be overestimated [37] or underestimated [38]. Thus, the assessment of AS severity should be made when the patient is normotensive. Often, such patients present with symptoms that are difficult to attribute solely to AS. In such cases, the clinician is faced with the challenge of adequately characterizing the severity of AS and its contribution to symptoms and determining whether

the patient would benefit from aortic valve replacement. If treatment of hypertension results in resolution of symptoms, continued medical therapy is reasonable although data in this area are inadequate to dictate management.

Projected AVA measured by stress echocardiography was suggested to better predict actual stenosis severity and clinical outcome of patients with paradoxical LF-LG AS in a small study [39]. However, such patients often have pronounced LV concentric remodeling with small cavities and impaired LV filling, and thus, they may be at risk for hemodynamic deterioration during dobutamine stress. Clinical value and risk-benefit ratio of stress echocardiography in this context is not established and is not advocated for routine clinical utilization in patients with paradoxical LF-LG AS. MDCT helps to identify patients with true severe aortic stenosis by calculating the grade of aortic valve calcification [32, 40]. Similar to patients with classical LF-LG AS, an aortic valve calcium score of ≥ 1200 AU in women and ≥ 2000 AU in men can be used to distinguish truly severe from pseudo-severe AS in paradoxical LF-LG AS patients [5].

Fig. 6 Example of aortic valve calcium scoring in a patient with true classical LFLGAS. An 84-year-old male with left ventricular ejection fraction (LVEF) of 35% and NYHA class III dyspnea. **a** Parasternal long-axis view showing left ventricular outflow tract (LVOT) diameter of 2.3 cm. **b, c** Pulse wave (PW) and continuous wave (CW) Doppler with calculated stroke volume (SV) 35 ml, mean gradient (MG) 31 mmHg, and aortic valve area (AVA) 0.6 cm². **d** Cardiac computed tomography showed heavily calcified aortic valve leaflets with a measured Agatston score of 3,205 suggesting true severe aortic valve stenosis. *CAD* coronary artery disease, *CABG* coronary artery bypass graft



Patients with LF-LG AS have increased mortality compared with high-gradient AS but still have improved outcome after aortic valve replacement compared to no therapy [41–43]. Given the older population and higher prevalence of comorbidities, the operative risk in these patients is higher. In the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines, AVR is reasonable (class IIa) in symptomatic patients with paradoxical LF-LG AS if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms and data is recorded when the patient is normotensive (systolic blood pressure < 140 mmHg) [4, 5].

Conclusions

Aortic stenosis is one of the most common valvular heart diseases and the challenging entity of low-flow, low-gradient AS is seen in up to 30–40% of AS patients. LF-LG AS has two subtypes: (a) classical LF-LG AS with reduced LVEF and (b) paradoxical LF-LG AS with preserved LVEF. It is critical to differentiate truly severe AS that benefits from aortic valve replacement compared to pseudo-severe which is currently managed conservatively. Low-dose dobutamine stress echocardiography (DSE) helps to make this differentiation in patients with classical LF-LG AS. Aortic valve calcium scoring with multidetector computed tomography plays a major role in those patients with

paradoxical LF-LG AS and also among classical LF-LG AS patients who have reduced contractile reserve on DSE. Current ACC/AHA guidelines provide class IIa indication for aortic valve replacement in symptomatic patients with low-flow, low-gradient severe aortic stenosis, and transcatheter aortic valve replacement is likely to play a major role in these patients.

Compliance with Ethical Standards

Conflict of Interest Krishna Alluri, Blase A. Carabello, and Rajasekhar Nekkanti declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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