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REVIEW

Low-flow/low-gradient aortic stenosis—Still a diagnostic and therapeutic challenge

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Aortic stenosis (AS) is the most frequently observed valvular heart disease. During the symptomatic stage, the rate of death increases dramatically, so that a precise diagnostic approach is taken to guide therapeutic options. Of patients with severe AS, 30% to 50% present with low-flow/low-gradient AS (LF/LGAS) status. This review focuses on LF/LGAS and the best diagnostic and therapeutic management in either classic LF/LGAS with reduced left ventricular ejection fraction (LVEF) or paradoxical LF/LGAS with preserved LVEF. Current literature demonstrates that in classic LF/LGAS it is crucial to rule out a pseudo-severe AS, because reduced LVEF may result in an incomplete opening of the valve. This can be done by low-dose dobutamine stress echocardiography. Classic LF/LGAS has poor clinical outcomes when managed conservatively; therefore, surgical or interventional aortic valve replacement should be performed. In paradoxical LF/LGAS, the LVEF is preserved (>50%), but impaired filling of the concentric hypertrophied ventricle leads to reduced stroke volume. Therefore, diagnostic and therapeutic decisions in paradoxical LF/LGAS are even more challenging. It is a heterogeneous disease entity, and it is crucial to rule out any diagnostic errors because numerous potential confounders might lead to misdiagnosis. As in classic stenosis, pseudo-severe stenosis must be ruled out as well. Evaluation via multidetector computed tomography or transesophageal echocardiography can help to evaluate the morphologic alterations of the valve (eg, calcification). Further studies are necessary to understand this disease entity and to evaluate the optimal diagnostic and therapeutic approach for these patients.

KEYWORDS

Valvular Heart Disease, General Clinical Cardiology/Adult, Heart Failure/Cardiac Transplantation/Cardiomyopathy/Myocarditis, Clinical Trials

1 | INTRODUCTION

Valvular aortic stenosis (AS) is the most frequently observed valvular heart disease. In the Western population, prevalence increases exponentially with age, resulting in a prevalence of 9.8% in octogenarians.[1]

When a severe AS becomes symptomatic, the rate of death is >50% at 2 years unless valve replacement is performed.[2] The main symptoms of AS are angina, dyspnea, and dizziness/syncope. Currently there is no medical treatment for the disease, so that valve replacement is the only available treatment option.

AS is routinely diagnosed by echocardiography (Figure 1). Hemodynamic severity can be defined by Doppler echocardiographic measurements of maximum transvalvular velocity and the mean transaortic gradient, as well as with the calculation of valve area by using the continuity equation.[3] Severe AS is defined by an aortic valve area (AVA) <1.0 cm^2, a peak aortic valve velocity >4 m/s, and/or a mean aortic valve gradient >40 mm Hg (Figure 1A).[4] Nevertheless, severe AS can be present in patients with low forward flow, resulting in a peak valve velocity <4 m/s and a mean aortic valve gradient <40 mm Hg. This entity is the so-called low-flow/low-gradient AS (LF/LGAS).

LF/LGAS occurs in 30% to 50% of patients with severe AS.[5] It shows an AVA <1 cm^2 but low gradient (<40 mm Hg) consistent with nonsevere AS. In this population group a reduced left ventricular

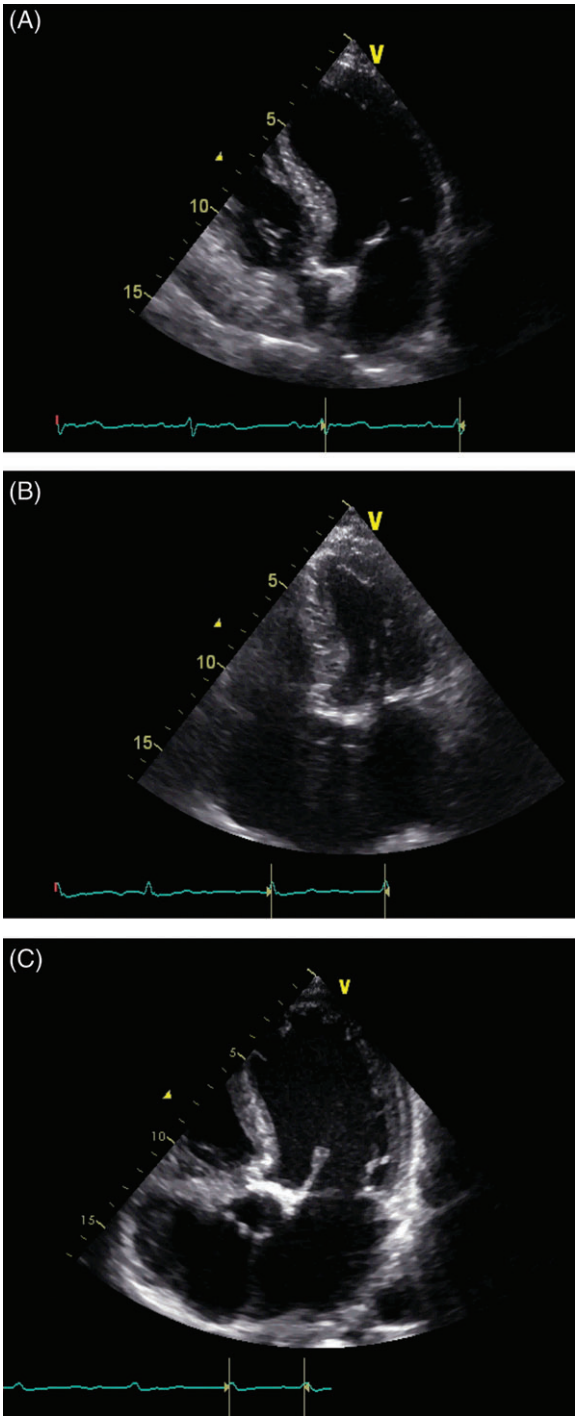

FIGURE 1 Echocardiographic 5-chamber view. (A) Normal flow/HG AS (normal LVEF, mean gradient >40 mm Hg, AVA <1.0 cm^2). (B) Paradoxical LF/LGAS (LVEF >50 mm Hg, mean gradient <40 mm Hg, AVA <1.0 cm^2, concentric hypertrophy with SVI <35 mL/m^2). (C) Classic LF/LGAS (LVEF <50 mm Hg, mean gradient <40 mm Hg, AVA <1.0 cm^2, LV dilation). Abbreviations: AS, aortic stenosis; AVA, aortic valve area; HG, high-gradient; LF/LGAS, low-flow/low-gradient aortic stenosis; LV, left ventricular; LVEF, left ventricular ejection fraction; SVI, stroke volume index.

ejection fraction (LVEF; <50%) is most frequently seen, resulting in a classic LF/LGAS (Figure 1C). Nevertheless, low flow can appear combined with preserved LVEF as well. In this case, the left ventricular cavum is small due to concentric hypertrophy so that the stroke volume is reduced, resulting in a so-called paradoxical LF/LGAS (Figure 1B).

Low-flow conditions are defined in the guidelines[4] by a stroke volume index (SVI) <35 mL/m^2. Management of these patients is difficult because of the uncertainty of whether the discrepancy between AVA and gradient is real or not. Low flow and AS appearing as severe may also occur in pseudo-severe stenosis because of incomplete opening of the valve, so that stenosis severity may be overestimated. In pseudo-severe AS, the underlying valve is only mildly to moderately stenotic, but it appears severe because of a left ventricular dysfunction that leads to an incomplete opening of the valve.[6]

First, it is important to rule out measurement errors. Echocardiographic findings might be incongruent because of underestimation of left ventricular outflow tract (LVOT) diameters in echocardiography. With the continuity equation, any error in the LVOT diameters is squared, which may result in a significantly underestimated AVA.[7] It is recommended to carry out this measurement at the base of the aortic annulus rather than at the mid-LVOT levels. Furthermore, LVOT is often noncircular. The continuity equation assumes a circular geometry, which may result in an underestimation of the LVOT and hence an underestimation of the AVA as well.[8]

2 | CLASSIC LF/LGAS

The definition of classic LF/LGAS applies when echocardiographically a mean gradient <40 mm Hg and a LVEF <50% is seen (Figure 1C).[4] In this case, low gradient might be explained by a low cardiac output (low stroke volume) because of a low LVEF. Nevertheless, AS might be overestimated because of an incomplete valve opening, resulting in a pseudo-severe AS. To distinguish these 2 disease entities, low-dose dobutamine stress echocardiography (DSE) is recommended to assess LV flow reserve.[9] A dobutamine infusion is used that is progressively increased, starting with 5 μg/kg/min. Dosage is increased every 5 to 8 minutes by 5 μg/kg/min to a maximum dosage of 20 μg/kg/min. At each stage, measurements of AVA, stroke volume, and gradient are performed.[10] According to the European Association of Echocardiography/American Society of Echocardiography recommendations, a true severe AS is defined by a maximum velocity >4 m/s with a valve area <1.0 cm^2 at any time point of the protocol.[3] In contrast, patients having a pseudo-severe AS will show an increase in AVA >1.0 cm^2 without a significant increase in the mean gradient, which is primarily a result of a reduced flow rate (Figure 2). Among patients with classic LF/LGAS there is one group that has no LV flow reserve, not even in stress echocardiography. Stroke volume increases <20%, and because there is no increase, DSE is inconclusive and stenosis severity remains unclear.[9] Hence, in this group of patients differentiation between true and pseudo-severe AS via DSE is challenging.

Aortic valve calcification is the leading process to aortic valve stenosis and, hence, an evaluation of calcification may be helpful in evaluating stenosis severity. This can be done by performing transesophageal echocardiography (TEE). It has been shown that there is a high correlation between the grading of calcification determined by TEE and visual evaluation of aortic valve calcification.[11]

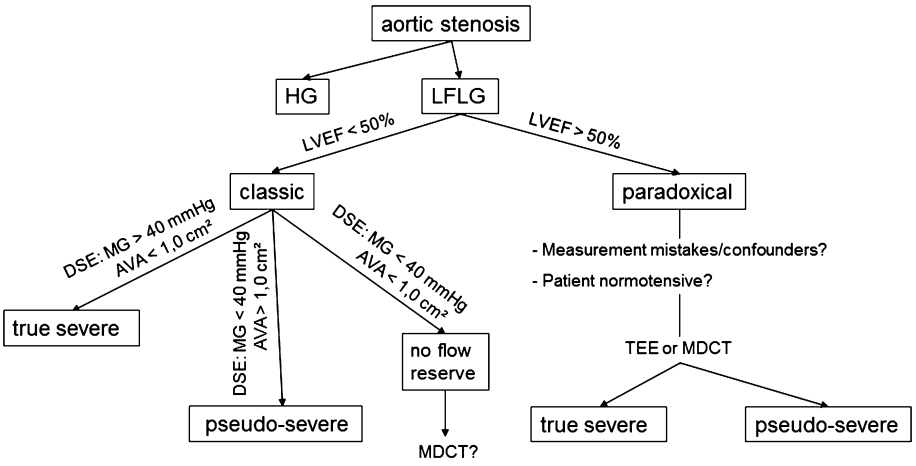

FIGURE 2 Algorithm for the diagnosis of LF/LGAS. Abbreviations: AVA, aortic valve area; DSE, dobutamine stress echocardiography; HG, high gradient; LFLG, low-flow/low-gradient; LF/LGAS, low-flow/low-gradient aortic stenosis; LVEF, left ventricular ejection fraction; MDCT, multidetector computed tomography; MG, mean gradient; TEE, transesophageal echocardiography.

Another diagnostic tool that can be helpful for further differentiation is multidetector computed tomography (MDCT). Measurement of aortic valve calcification by MDCT has shown to correlate with stenosis severity, and therefore may help in patients without flow reserve (Figure 3).[12,13] However, the relationship between aortic valve calcification and AS hemodynamic severity is sex-dependent. Females reach severe AS with lower aortic valve calcification levels in comparison with men. Therefore, it is important to use sex-adjusted cutoff values of aortic valve calcification to define severe AS.[14] MDCT may also be used when DSE is somehow not feasible or contraindicated.

It is known that severe LF/LGAS with low LVEF has poor outcomes when managed conservatively. Studies have shown that 2- and 5-year mortality is dramatically high in medically managed patients once they are symptomatic (Herrmann et al, 2-year mortality 76%; Tribouilloy et al, 5-year mortality 87%), so that interventional or surgical management is needed.[15,16]

After surgical aortic valve replacement (SAVR), perioperative mortality is high. In a study by Tribouilloy et al, 12 out of 55 patients died within 30 days after SAVR or before hospital discharge (perioperative mortality 22%), mainly because of cardiogenic shock (n = 10).[15] Nevertheless, it is important to recognize that this study has been conducted in a small group of patients (n = 81). DSE in all those patients revealed no contractile reserve, so that it is possible that patients with only moderate AS but reduced LVEF had been included in this study. A larger study population had been investigated by Levy et al: 217 patients who got SAVR between 1990 and 2005 were included. In this study, total perioperative mortality after

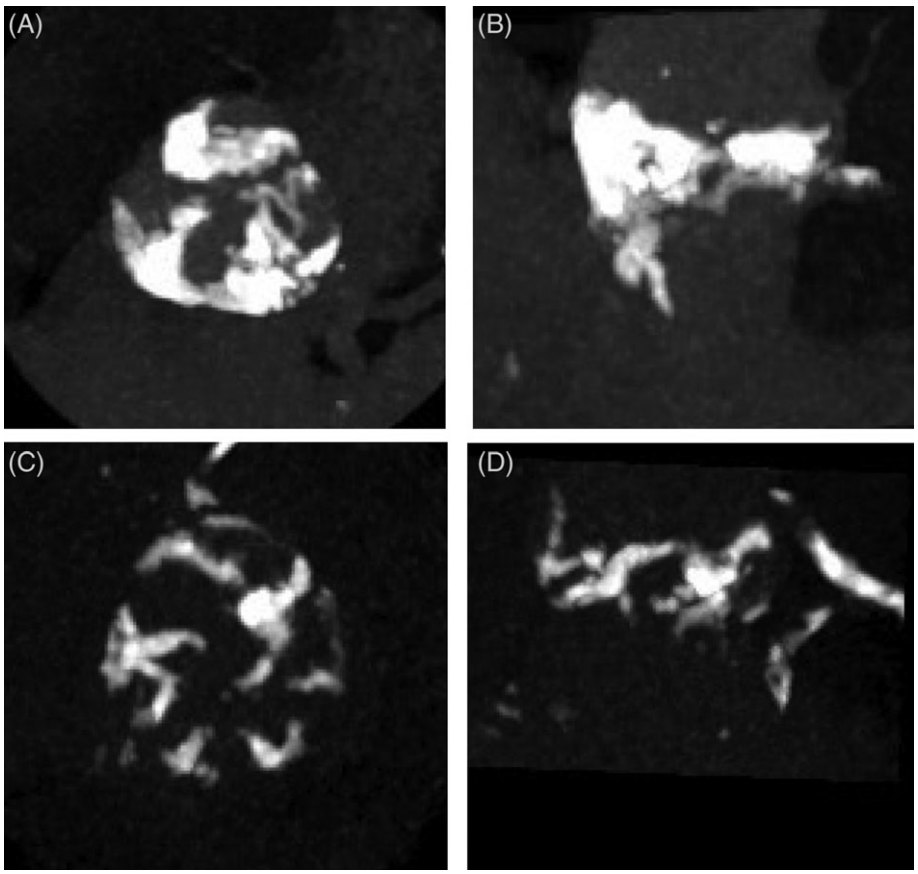

FIGURE 3 MDCT scan to detect the grade of calcification in patients with AS. (A,B) A severely calcified AS, in (A) short-axis view and (B) side view. (C,D) Mild to moderately calcified AS, in (C) short-axis view and (D) side view. Abbreviations: AS, aortic stenosis; MDCT, multidetector computed tomography.

SAVR was 16%. The main cause of death after surgery was cardiogenic shock as well.[17] Interestingly, mortality differed significantly between the study population operated between 1990 and 1999 (20%) and those operated in the years 2000 to 2005 (10%), although basic characteristics remained the same. Again, Levy et al showed that patients without contractile reserve in DSE showed a higher perioperative mortality than those who had contractile reserve. Despite high surgical risk in these studies, surgical treatment was always clearly superior to conservative treatment in terms of overall survival (5-year overall survival after surgery: Tribouilloy et al, 41%; Levy et al, 49%).[15,17]

In contrast with true severe AS, a conservative management in pseudo-severe AS is preferred. It has been shown that under conservative treatment, the 5-year outcome is better in pseudo-severe AS than in true severe AS.[6] Nevertheless, it is important to continue with frequent follow-ups including echocardiography to observe any progress and, if warranted, to consider AVR.

According to the American Heart Association guidelines, transcatheter aortic valve implantation (TAVI) is recommended in patients with classic severe LF/LGAS when there is a prohibitive risk for SAVR and the predicted survival after TAVI is >1 year.[4] Moreover, TAVI is defined as reasonable when SAVR is related with a high surgical risk (Society of Thoracic Surgeons score >10%). These recommendations are in alignment with the European Society of Cardiology guidelines.[18] Both guidelines emphasize that AVR in LF/LGAS with reduced LVEF is especially recommended when there is evidence of flow reserve in DSE. Nevertheless, AVR should be considered even in patients without flow reserve.

Many studies have shown that a reduced LVEF (<50%), a reduced SVI (<35 mL/m^2), and a low transvalvular gradient (<40 mm Hg) are each associated with an increased overall mortality 1 year after TAVI.[19] These parameters individually have a similar prognostic impact on survival after TAVI. Therefore, it was not surprising that a subgroup analysis of the German Aortic Valve Registry that enrolled 3077 patients revealed higher rates of mortality after TAVI in patients with LF/LGAS and reduced LVEF, compared with high-gradient (HG) AS as well as paradoxical LF/LGAS.[20] In-hospital mortality was higher compared with patients with HG AS (7.8% vs 4.9%), and 1-year mortality even differed in comparison with HG AS and paradoxical LF/LGAS (32.2% vs 19.8% vs 22.3%). Results from several other studies confirm these findings. In a small substudy (n = 68) by Elhmidi et al, patients with LF/LGAS and an LVEF <35% had a higher 6-month and 1-year mortality compared with patients with HG AS (1-year mortality: 37% vs 13%, respectively).[21] Comparing medical treatment, TAVI, and SAVR in patients with LF/LGAS with low LVEF vs HG AS, Ben-Dor et al likewise showed that patients with classic LF/LGAS had a higher risk for a worse outcome regardless of the treatment option.[22]

Comparing TAVI with SAVR, Ben-Dor et al suggested that TAVI may be associated with better and faster LVEF recovery after intervention.[22] The same had been stated by Clavel et al when comparing SAVR and TAVI in LF/LGAS with reduced LVEF. Although at baseline, patients treated with TAVI were older and had more comorbidities, after intervention TAVI was associated with faster and better recovery in LVEF (at discharge and 1 year) compared with patients treated with SAVR.[23] However, both studies enrolled only a small numbers of patients, so further studies are needed to confirm a superiority of TAVI over SAVR in LF/LGAS with reduced LVEF.

3 | PARADOXICAL LF/LGAS

The phenomenon of paradoxical LF/LGAS was first described by Hachicha et al in 2007. About 30% of patients with AS and preserved LVEF (>50%) have a low-flow state.[24,25] Paradoxical LF/LGAS is defined by an AVA <1.0 cm^2, a mean gradient <40 mm Hg, a preserved LVEF >50%, and the presence of low flow (SVI <35 mL/m^2).[4] When compared with patients with classic AS, patients with paradoxical low flow are characterized by a higher prevalence of female sex, older age, and systemic hypertension. The reduced stroke volume is associated with LV concentric remodeling with a smaller ventricle, an increased relative wall thickness, a higher afterload, and a progressive worsening of diastolic function.[24]

A pronounced concentric hypertrophy contributes to a smaller LV cavity, thus lowering the stroke volume despite a preserved LVEF. The reduced stroke volume is related to low transvalvular gradients. Patients have an abnormally reduced systemic arterial compliance. Global LV afterload is increased in the setting of paradoxical LF/LGAS resulting from the combination of a more severe valvular obstruction and a greater reduction in systemic vascular resistance.[24] Longitudinal studies have shown that a unique remodeling pathway seems to take place in paradoxical AS because LV afterload increases more rapidly in this pattern.[26]

Nevertheless, a systematic stepwise and accurate diagnosis is necessary if discrepancy in AVA and transvalvular gradient appears, because numerous potential confounders might influence these findings. First, an AVA <1.0 cm^2 is considered severe, independent from the body size of the patient. Indexing AVA to body surface area may help find adequate relations. For AVA indexed to body surface area, the cutoff value for a severe AS is 0.6 cm^2/m^2. This might be crucial, especially in extraordinarily small or large people.[18] Another important factor is the presence of arterial hypertension. Arterial hypertension increases the arterial afterload, thus lowering the stroke volume, leading to decreased flow and, thus, to a decreased gradient. This may contribute to symptoms and adverse events. Treatment of hypertension with medical therapy reduces LV filling pressures and pulmonary artery pressures.[27] AS may be overestimated in patients with systemic hypertension so that echocardiographic evaluation of AS should be repeated after optimization of antihypertensive therapy.

Just as in classic LF/LGAS, in paradoxical LF/LGAS it is important to differentiate between true severe and pseudo-severe stenosis (Figure 2). It has been shown that about one-third of patients with paradoxical LF/LGAS had only pseudo-severe stenosis, thus requiring a different therapeutic approach.[28] Distinguishing true from pseudo-severe LF/LGAS is much more challenging than in classic LF/LGAS. It must be taken into account that DSE should not be used in patients with restrictive LV physiology, which is common in patients with paradoxical LF/LGAS. Therefore, DSE is not the preferred tool for further diagnostics.

As in classic LF/LGAS, in paradoxical LF/LGAS, TEE and MDCT may be helpful to further differentiate and detect a severe AS by calculating the grade of calcification (Figures 2 and 3).[14]

Dayan et al showed that patients with paradoxical LF/LGAS seem to have an increased risk of mortality compared with other subtypes of AS with preserved LVEF (normal-flow/low-gradient AS and HG AS).[29] Nevertheless, results differ in studies, with some showing an increased mortality risk,[24,30] whereas others show an outcome similar to that of other subtypes of AS with preserved LVEF.[31] Maes et al even showed that spontaneous outcome at 4 years is significantly better in paradoxical LF/LGAS compared with HG AS with preserved EF.[32] All in all, determination of the outcome of LF/LGAS without treatment seems to differ significantly. Nevertheless, a recent meta-analysis showed that patients with LF/LGAS had a higher risk of mortality than did those with HG AS.[29] The discrepancy in results probably occurred because of a heterogeneous patient population. Patients have a lot of comorbidities, and as discussed before, many confounders might cause a misdiagnosed severe AS (eg, arterial hypertension, small body surface area) or confound the results in general.

According to the American Heart Association (AHA) guidelines, AVR is reasonable in patients with paradoxical LF/LGAS when they are symptomatic and when the valve is the most likely cause of symptoms.[4] It is emphasized that before therapeutic options are taken, arterial hypertension has to be well managed and that echocardiographic parameters have to be assessed under normotension to ensure optimal results.

Given the older population and higher prevalence of comorbidities, the operative risk of patients with paradoxical LF/LGAS is higher compared with HG AS. Comparing conservative treatment and SAVR, many studies show a superiority of SAVR in terms of the survival benefit.[33,34] It has to be taken into account that these studies have been conducted with very small sample sizes and that most of the patients were age <80 years.

In a study by O'Sullivan et al, after TAVI most paradoxical LF/LGAS patients showed a functional improvement after 1 year, thus improving in their levels of New York Heart Association classification and/or Canadian Cardiovascular Society angina classification.[35] The randomized Placement of Aortic Transcatheter Valves (PARTNER) I trial has shown that in inoperable patients with paradoxical LF/LGAS who were symptomatic, treatment with TAVI reduced the all-cause 2-year mortality significantly compared with medical treatment. In patients with high surgical risk, TAVI was associated with a better survival after 1 year compared with SAVR.[16] In comparison with patients with HG AS, those with paradoxical LF/LGAS have similar overall in-hospital and 1-year mortality after TAVI.[20] Further clinical studies are needed to evaluate the outcome of patients with paradoxical LF/LGAS after SAVR and TAVI. For now, a joint decision by an interdisciplinary heart team, taking into consideration with regard to the clinical status of the patient, the comorbidities and the surgical risk is important to determine the best therapeutic option for each individual patient.

4 | CONCLUSION

AS is the most common valve disease in the older population, and due to our aging population its incidence will only increase in the future.

One of the most challenging entities of AS is LF/LGAS. According to the American Heart Association as well as the European Society of Cardiology (ESC) guidelines, there are 2 subtypes of LF/LGAS: the classic LF/LGAS with reduced LVEF, and the so-called "paradoxical" LF/LGAS with preserved LVEF.

In classic LF/LGAS, differentiation between true severe AS and pseudo-severe AS is crucial to take the correct therapeutic option (Figure 2). For this purpose, DSE is the most important diagnostic instrument. In most cases, differentiation between pseudo-severe and true severe AS can be done using DSE, and hence improve the therapeutic management option. In a small subgroup of patients, differentiation by DSE is not possible because LV flow is not increased under stress so that the severity of stenosis remains unclear. In this case, quantification of valve calcification by TEE or MDCT may further help to differentiate. In pseudo-severe LF/LGAS, optimal conservative management and regular follow-ups are indicated; whereas in true severe LF/LGAS with reduced LVEF, valve replacement is recommended if life expectancy of the patient is >1 year. It has been shown to be always clearly superior compared with medical treatment alone. An AVR via TAVI according to the guidelines is recommended in patients with a prohibitive or high surgical risk. Small studies have shown that TAVI compared with SAVR may lead to faster and better LVEF recovery. Nevertheless, more studies are needed to confirm these results.

Determining correct diagnosis and therapy in paradoxical LF/LGAS is even more challenging because it is a heterogeneous disease entity. First, it is fundamental to rule out any measurement mistakes and confounders. Arterial hypertension must be treated and normalized before any diagnostic approach can be taken, and in extraordinarily small or large people, calculation of the indexed AVA is recommended to avoid any measurement mistakes. Second, pseudo-severe stenosis must be ruled out. Due to an existing restrictive LV physiology, DSE is not preferred. Instead, the evaluation of aortic valve morphology and calcification via TEE and/or MDCT is the preferred diagnostic approach (Figure 1). If the patient is symptomatic, an AVR should be considered in those with severe paradoxical LF/LGAS. It is associated with a significant survival benefit in these patients.

Further investigations are needed to understand the pathogenesis of the different entities of AS and the optimal diagnostic approach and therapy, especially in the LF/LG state.

Conflicts of interest

There are no conflicts of interest.

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