Dobutamine Stress Echocardiography in Low-Flow, Low-Gradient Aortic Stenosis: Flow Reserve Does Not Matter Anymore

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Low-flow, low-gradient (LFLG) aortic stenosis (AS) is one of the most challenging cardiovascular conditions in terms of diagnosis and therapeutic management. Because of the low-flow state, the transvalvular peak velocity and pressure gradient may underestimate the stenosis severity, whereas the aortic valve area (AVA) may overestimate the severity.[1] It is thus difficult or impossible to confirm the presence of severe AS and thus the indication of aortic valve replacement (AVR) from the resting echocardiography in such patients. LFLG AS may occur with reduced LV ejection fraction (LVEF; ie, classical LFLG) or with preserved LVEF (ie, paradoxical LFLG). In classical LFLG, it is recommended to perform a low-dose dobutamine stress echocardiography (DSE): (1) To assess the presence of LV flow reserve (FR) and (2) To differentiate true-severe versus pseudo-severe AS.[1] The 2017 European Guidelines[2] recommend AVR (Class I) in classical LFLG AS (LVEF <50%, AVA <1.0 cm^2, and mean gradient <40 mm Hg at resting echocardiography) if the patient demonstrates evidence of FR (percent increase in stroke volume ≥20%) and true-severe AS (stress AVA <1.0 cm^2) with DSE. In the absence of FR, these guidelines recommend AVR (Class IIa) if severe AS can be confirmed with other imaging modalities such as aortic valve calcium scoring by computed tomography (CT). The 2017 American Guidelines update[3] do not account for FR and recommend AVR (Class IIa) if the patient shows evidence of true-severe AS on DSE, defined as stress mean gradient ≥40 mm Hg.

In this issue of the *Journal of the American Heart Associaton* (*JAHA*), Sato et al[4] present the results of an elegant study that aimed to examine the prognostic impact of DSE in a series of 235 patients with classical LFLG AS. FR was observed in 59% of the patients and true-severe AS in 37% of the patients. Within a median follow-up of 2.3 years, AVR was associated with a major survival benefit regardless of the presence or absence of FR or true-severe AS on DSE.

Flow Reserve: Does It Matter?

In the French Multicenter Study conducted in the late 1990s and early 2000s,[5,6] the absence of FR on DSE was associated with extremely high mortality (>75% at 2 years) in patients with classical LFLG treated conservatively and with very high short-term mortality (>20% at 3 months) in those treated with initial surgical AVR (SAVR). However, FR did not predict recovery of LVEF, improvement in functional class, or long-term outcomes following SAVR.[6] On the basis of this study, the previous (before 2017) editions of the European Guidelines gave a class IIb to the indication of AVR in patients with LFLG AS and no FR. The rationale for this recommendation was 2-fold: (1) In the absence of FR, it was difficult or impossible to confirm the stenosis severity with DSE; (2) Patients with no FR had very high surgical risk. However, the outcome and management of classical LFLG AS has changed dramatically over the past 15 years. First, the operative outcome of SAVR has improved substantially in this subset of patients, with much lower operative mortality and less frequent severe prosthesis–patient mismatch, which has been shown to have a major negative impact on short- and long-term outcomes in LFLG AS.[7] Second, transcatheter AVR (TAVR) has emerged as a valuable and much less invasive alternative to SAVR in patients with intermediate, high, or extreme surgical risk. The less invasive nature of transfemoral TAVR may be associated with better outcomes than SAVR in patients with vulnerable LV function, such as those with classical LFLG AS. Third, new diagnostic methods (projected AVA at normal flow rate by DSE, aortic valve calcium scoring by CT) have been developed and validated to confirm the

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presence of severe AS and the risk of adverse outcomes in patients with LFLG AS (Figure). CT is recommended in the 2017 edition of the European Guidelines[2] to confirm stenosis severity in LFLG patients with no FR and indication class for AVR has been raised from IIb to IIa.

The initial results reported by the French multicenter study[5,6] have not been confirmed or replicated by other studies. In particular, the multicenter TOPAS (True or Pseudo Severe Aortic Stenosis) study,[8,9] which included a larger number of patients treated by SAVR, TAVR, or conservative management, did not report any association between FR and outcomes in classical LFLG AS. In the TOPAS-TAVI (Transcatheter Aortic Vlave Implantation) registry,[10] patients with classical LFLG AS harbored very good outcomes at 1 year (survival: ≈80%) following TAVR, regardless of the presence or absence of FR at preprocedural DSE. Moreover, FR failed to predict recovery of LVEF or improvement in patient's functional capacity. In the present single-center study,[4] FR also showed no association with mortality in both the conservative management group (n=107) and AVR group (42 SAVR and 86 TAVR). The 1-year survival in patients with no FR treated by AVR was ≈85% in this study, which contrasts markedly with the <60% survival rate observed in the French Multicenter study[5,6] for the same subset. It is possible that the utilization of TAVR rather than SAVR in 67% of the patients (versus 0% in the French Multicenter Study) may have contributed to the better survival observed in the patients with no FR included in the present study. However, in the TOPAS study, we also found no association between FR and outcomes even in the subset of patients treated by SAVR.[8,9]

One may wonder why the DSE-induced FR, which is supposed to represent the LV contractile reserve and residual myocardial viability, does not provide any prognostic value in the context of patients with AS. The main reason is probably that the FR is mechanistically flawed and confounded by the presence of AS. Indeed, the LV contractile reserve or FR elicited by DSE has good prognostic value in patients with coronary artery disease and no AS. However, in patients with AS, and especially those with severe AS, a LV with substantial myocardial viability and functional reserve may not be able to

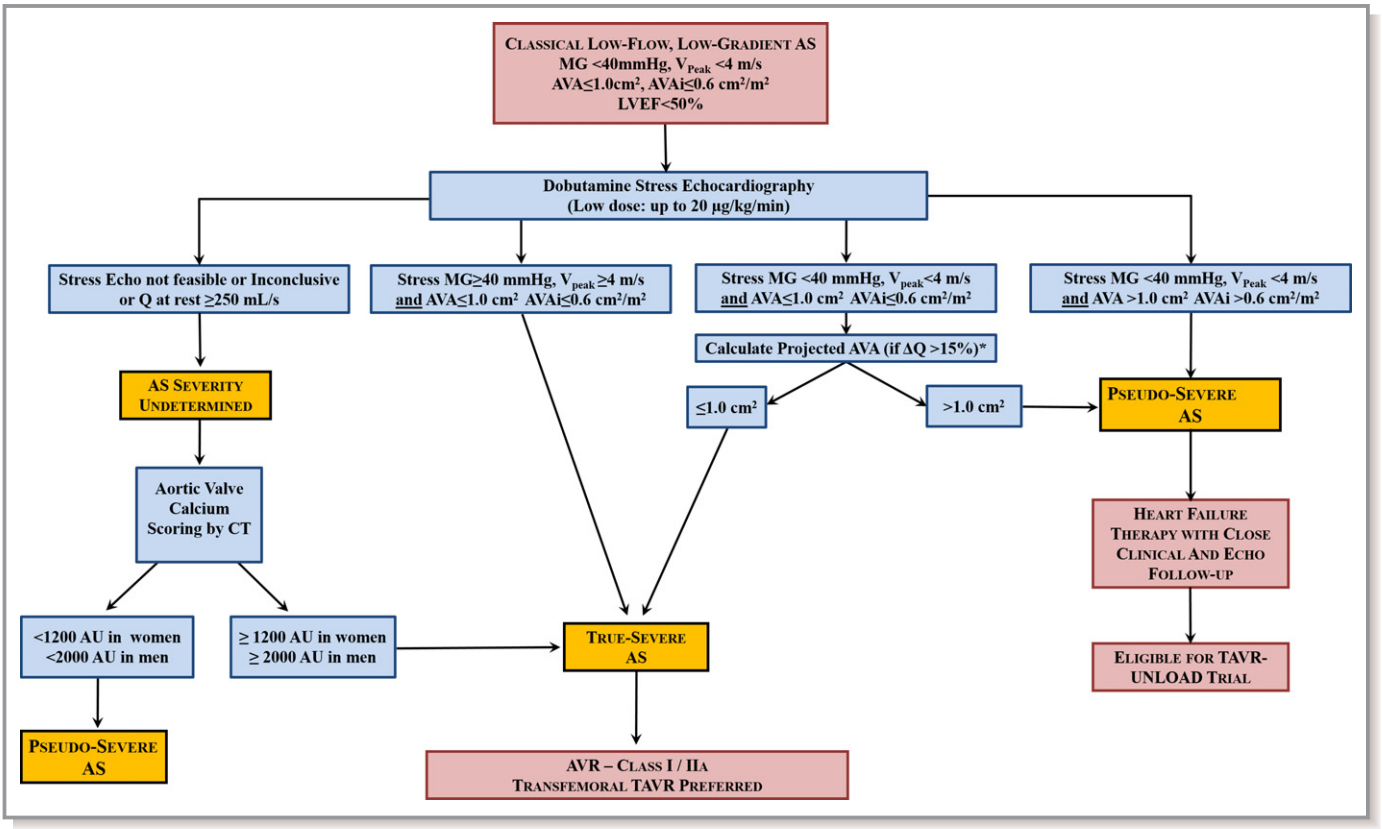

Figure. Algorithm for diagnosis and therapeutic management of low-flow, low-gradient aortic stenosis. *Projected AVA (AVA_{Proj}) at normal flow rate (250 mL/s) can be calculated using the formula: $AVA_{Proj}=AVA_{Rest}+[(\Delta AVA/\Delta Q)\times(250-Q_{Rest})]$, where AVA_{Rest} and Q_{Rest} are the AVA and mean flow rate (Q) at rest and ΔAVA and ΔQ are the absolute increases in AVA and Q during DSE. The value of 250 mL/s included in the formula corresponds to the median value of the normal flow range. An accurate calculation of AVA_{PRoj} requires ΔQ ≥15%. Q is calculated by dividing stroke volume by LV ejection time. AS indicates aortic stenosis; AU, Arbitrary Unit; AVA, aortic valve area; AVAi, indexed AVA; AVR, aortic valve replacement; CT, computed tomography; DSE, dobutamine stress echocardiography; LVEF, left ventricular ejection fraction; MG, mean gradient; TAVR, transcatheter AVR; V_{Peak}, peak aortic jet velocity.

generate any significant FR (ie, increase in stroke volume) with DSE because of LV afterload mismatch. This phenomenon may explain why many patients with no FR have spectacular improvement of LVEF rapidly after the relief of the LV afterload excess by AVR.

AS Severity Grading With DSE: Does It Matter?

DSE is recommended in both American and European Guidelines[2,3] to differentiate true versus pseudo-severe AS and therefore confirm indication of AVR (Class I or IIa) in classical LFLG AS. However, the present study[4] suggests that the grading of AS severity by DSE using a peak velocity ≥4 m/s with an AVA ≤1.0 cm^2 to confirm true-severe stenosis has no association with outcomes, regardless of the type of therapeutic management (AVR or conservative). This counterintuitive finding may be related to the fact that these criteria or the one proposed in the guidelines (mean gradient ≥40 mm Hg during DSE) are far from optimal to confirm AS severity. Indeed, Annabi et al reported that the accuracy (ie, percentage of correct classification) to identify true-severe AS was only 48% for stress mean gradient ≥40 mm Hg and 47% for the combination of stress mean gradient ≥40 mm Hg and stress AVA ≤1.0 cm^2.[9] These disappointing results are related to the fact that a large proportion of patients with LFLG AS have limited increase in stroke volume and mean flow rate (stroke divided by LV ejection time) in response to DSE and they are thus not able to reach the normal flow rate range. In such a situation, the mean gradient may increase but not cross the 40 mm Hg cut point (or peak velocity, the 4 m/s cut point) despite the presence of a true-severe AS. Hence, DSE parameters and criteria proposed in the guidelines may lack sensitivity and underestimate the actual AS severity. In this situation, there is an advantage of using the projected AVA at normal flow rate.[9,11] This parameter, which can be calculated using the formula presented in Figure, provides an estimate of the AVA that would have been reached had the flow rate been fully normalized (ie, reached 250 mL/s) with DSE. Annabi et al reported that the projected AVA has superior accuracy (70%) than other DSE parameters (<50%) to identify true severe AS and is a strong predictor of mortality in the patients with LFLG AS treated conservatively.[9] Interestingly, Sato et al were able to calculate the projected AVA in a subset of 233 patients and the proportion of true-severe AS defined according to AVA_{Pproj} was higher (60%) than with the standard DSE parameters (38%) and was associated with increased risk of mortality in the patients who remained under conservative management.[4]

Conclusions and Clinical Implications

In light of the data presented in this issue of *JAHA* by Sato et al[4] as well as in recent previous studies, it is reasonable to conclude that FR does not matter anymore in 2019 for the management of patients with classical LFLG AS. The current evidence indeed suggests that FR assessed by DSE does not provide any incremental prognostic value in contemporary series with LFLG AS. This parameter should thus probably be removed for the next edition of European Guidelines.

On the other hand, grading of AS severity by DSE still matters currently for therapeutic decision making in classical LFLG AS as long as accurate parameters, such as the projected AVA, are used to confirm AS severity.

Figure proposes an algorithm for the management of patients with classical LFLG AS. The definition of classical LFLG AS proposed in the guidelines[2,3] includes LVEF <50% but does not include any criteria for low flow state. Hence, a few patients with mild-to-moderate LV systolic dysfunction (LVEF 40%–50%) and large LV end-diastolic volume may generate a mean flow rate ≥250 mL/s at rest. In these patients, DSE may not be helpful because the flow is already normal at rest and may become supra-normal with dobutamine stress, which may lead to reverse discordant grading (AVA >1.0 cm^2 with mean gradient ≥40 mm Hg). In such case, it is probably preferable to use an aortic valve calcium score measured by CT to confirm AS severity (Figure).

In patients with bona fide LFLG AS, it is recommended to perform a low-dose DSE to increase mean transvalvular flow rate and confirm actual AS severity (Figure). If the mean gradient increases above 40 mm Hg and the AVA remains below 1.0 cm^2, the presence of true severe AS and thus indication of AVR are confirmed. If mean gradient remains <40 mm Hg and AVA increases above 1.0 cm^2 with DSE, this is consistent with pseudo-severe AS and the patient should, a priori, be managed conservatively. However, some studies including the present study by Sato et al[4,9] suggest that patients with pseudo-severe/moderate AS may actually benefit from AVR. This hypothesis is currently being tested in the ongoing TAVR-UNLOAD trial (https://clinicaltrials.gov/ct2/show/NCT02661451), which assesses the effect of TAVR versus medical therapy in patients with moderate AS and systolic heart failure.

If the mean gradient and AVA remain below 40 mm Hg and 1.0 cm^2, respectively, despite significant increase (≥15%) in mean flow rate during DSE, the projected AVA should be calculated and if <1.0 cm^2, the stenosis is considered severe and AVR is indicated. This may also apply to patients with excessively increased mean flow rate in whom mean gradient and AVA are greater than 40 mm Hg and 1.0 cm^2, respectively. In the absence of significant increase (<15%) in flow rate, aortic valve calcium scoring by CT should be performed

to assess the presence of anatomically severe AS and confirm the indication of AVR. CT may also be considered, as the first-line diagnostic modality, for patients with normal resting mean flow rate (≥250 mL/s) and those in whom DSE is contraindicated or is expected to be inaccurate or inconclusive (eg, patients with left bundle branch block, atrial fibrillation, or concomitant ≥ moderate mitral regurgitation).

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