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Editorial

Importance of Flow in Risk Stratification of Aortic Stenosis

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See article by Alkhalil et al., pages 112-118 of this issue.

Optimal risk stratification and therapeutic decision making in aortic stenosis (AS) require accurate grading of AS severity and proper assessment of the extent of cardiac damage related to AS. The peak aortic jet velocity and mean transvalvular pressure gradient are the main parameters used to grade AS severity, and severe AS is defined as a mean gradient $\geq$ 40 mm Hg or peak jet velocity $\geq$ 4 m/s. However, the main limitation of these parameters is that they are highly flow dependent and may thus underestimate AS severity in the presence of low-flow states. Aortic valve area (AVA) is less flow dependent than the gradient or velocity and is considered severe when $<$ 1.0 cm^2. Whereas high gradient is consistent with severe AS, low-gradient AS, defined as a gradient $<$ 40 mm Hg with an AVA $<$ 1.0 cm^2, is severe in 50% to 70% of cases.[1] It is thus necessary to perform dobutamine stress echocardiography or aortic valve calcium scoring by noncontrast computed tomography (CT) to confirm AS severity. Although low-gradient severe AS is often associated with low flow, it may also occur in patients with normal flow.

Ultimately, it is more the repercussions of the AS on cardiac function than the AS severity *per se* that determines the occurrence of heart failure and clinical outcomes. In this regard, the stroke-volume index provides a robust surrogate marker of the state of left-ventricular (LV) pump function and a powerful predictor of clinical outcomes in AS both before and after aortic valve replacement (AVR).[2-7] A stroke volume index $<$ 35 mL/m^2 is the criteria proposed in the European and American guidelines to define low flow state,[8,9] and values $<$ 30 and 25 mL/m^2 are consistent with moderate and severe low-flow state, respectively (Fig. 1). The reduction in LV stroke volume results from the complex interplay among preload, afterload, and myocardial contractility. The causes and mechanisms leading to low flow in AS are therefore multiple and include LV concentric hypertrophy, myocardial fibrosis, impaired LV filling, depressed LV global or longitudinal systolic function, concomitant mitral or tricuspid regurgitation, atrial fibrillation, and right-ventricular dysfunction.

Impact of Low-Flow State on Outcomes in AS

Several studies have reported an association between low-flow state and increased risk of mortality both before and after AVR.[2-7,10] However, most of these studies focused on low- gradient AS, and relatively few examined the impact of low flow in patients with high-gradient AS. In this issue of the *Canadian Journal of Cardiology*, Alkhalil et al. present the results of an elegant study that included 476 patients with high-gradient AS undergoing transcatheter AVR (TAVR).[11] In this cohort, 45% had a low-flow state, thus reiterating the high prevalence of low-flow state in patients with severe AS. Of note, low-flow state was present in 39% of patients with preserved LV ejection fraction (LVEF: ie, paradoxical low flow), and, conversely, 44% of patients with reduced LVEF had normal flow (ie, paradoxical normal flow). Hence, normal LVEF does not necessarily imply normal flow, and low LVEF does not necessarily imply low flow. In the guidelines,[8,9] patients with low-gradient AS and LVEF $<$ 50% are considered to have "classical" low-flow, low-gradient AS. The results of the current study provide support to the addition of a specific low-flow criteria (eg, stroke-volume index $<$ 35 mL/m^2) in this definition, such as is the case for patients with preserved LVEF (paradoxical low-flow, low-gradient AS).

In the study of Alkhalil et al.,[11] patients with low flow at baseline had a 1.5-fold increased risk of rehospitalization for heart failure or death following TAVR. There was, however, an interaction between stroke volume index and LVEF regarding the impact on outcomes, with low flow being associated with a 3.3-fold increase in the rate of the primary endpoint in patients with reduced LVEF vs no significant effect on outcomes in patients with preserved LVEF. The absence of impact of low flow in the subset of patients with preserved LVEF may be related to the limited statistical power in this study. Several studies and meta-analyses indeed reported a significant association between low flow and reduced survival in patients with preserved LVEF.[2-7,10] The most important finding of the current study[11] is that low flow was independently associated with increased risk of all-cause

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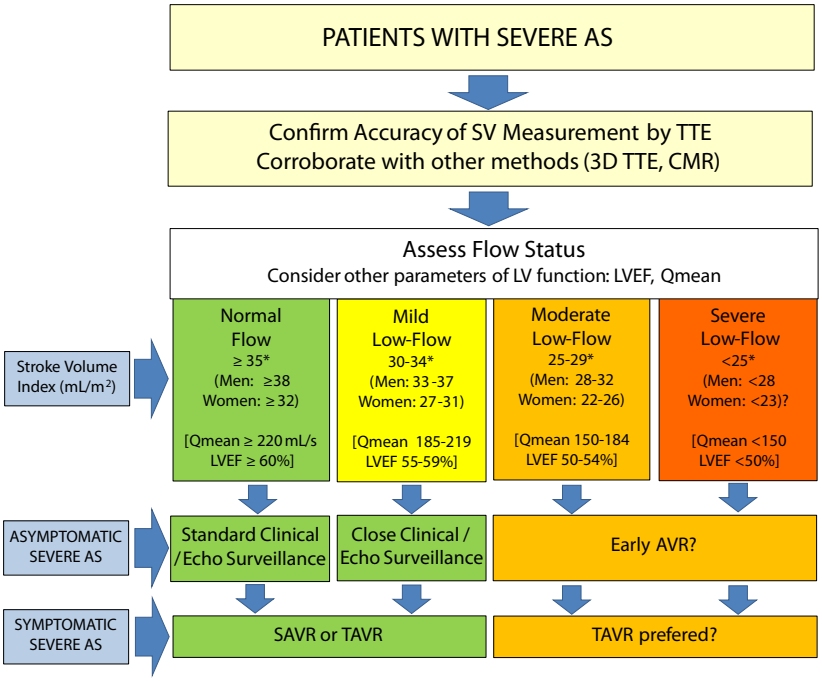

Figure 1. Algorithm for risk stratification and management in patients with aortic stenosis according to flow status. The cutoff values of stroke volume index (SVi) that we proposed to define the different strata of low-flow state are not supported by the guidelines and will need to be validated in further studies. (**Asterisk**) In obese patients (body mass index $\geq$ 30 kg/m^2), the cutoff value of SVi should be lowered by 5 mL/m^2. **Question mark** indicates that the proposed strategy is not supported by the guidelines and will need to be validated. Criteria between **brackets** are additional parameters of flow and LV systolic function that may be considered to enhance risk stratification and therapeutic decision making. AS, aortic stenosis; AVR, aortic valve replacement; CMR, cardiac magnetic resonance; LVEF, left-ventricular ejection fraction; Qmean, mean transvalvular flow rate (stroke volume/LV ejection time); SAVR, surgical AVR; TAVR, transcatheter AVR; TTE, transthoracic echocardiography.

mortality and hospitalization for heart failure in patients with high-gradient AS undergoing TAVR.

Echocardiographic Measures of Flow

Besides stroke-volume index, other surrogate markers of LV outflow have been used and have shown association with outcomes, including mean transvalvular flow rate (stroke-volume/LV ejection time) and cardiac index.[12] These 3 echocardiographic parameters include stroke volume in their calculation. There are, however, several technical pitfalls in the measurement of the LV stroke volume by transthoracic echocardiography, and, in most of the cases, these pitfalls lead to an underestimation of stroke volume and thus an overestimation of low-flow state. Particular attention should be paid to obtain, in the parasternal long-axis zoomed view, the imaging plane that bisects the right coronary cusp anteriorly and the commissure between the left and noncoronary cups posteriorly to maximize the size of the LV outflow tract (LVOT). Furthermore, the LVOT diameter should be measured at the level of—or very close to (within 5 mm)—the aortic annulus.[13] In this study,[11] the LVOT was measured below the annulus, which may have led to underestimation of stroke volume in some patients. One limitation of estimates of the stroke-volume index (as well as of the cardiac index) is the risk of overindexation of the stroke volume and thus overestimation of low flow state in obese patients. One approach to overcoming this limitation would be to use lower cutoff values (eg. 30 mL/m^2) to define low-flow state in patients with body mass indexes $\geq$ 30 kg/m^2 (Fig. 1). Further studies are needed to determine whether different cutoff values of stroke-volume index should be used to define low-flow state and predict prognosis in women vs men and in Asian vs Caucasian vs African-American patients.

Cardiac Damage Staging in AS

Previously, we proposed and validated a new scheme for staging the extent of cardiac damage associated with AS.[14,15] Stage 1 corresponds to damage at the level of the left ventricle; Stage 2: left atrium and mitral valve; Stage 3: pulmonary arterial circulation and tricuspid valve; and Stage 4: right ventricular level. Several echocardiographic parameters and criteria have been proposed for each stage to classify patients with respect to the extent of cardiac damage. This staging approach has the potential to improve risk stratification before AVR and also to determine the optimal timing for intervention in patients with asymptomatic severe AS.[14,15] Given that a low-flow state may result from damage at any of the 4 cardiac chambers and constitutes a marker of cardiac decompensation, we recently proposed to add, in Stage 4, the presence of moderate/severe low-flow state (stroke-volume index $<$ 30 mL/m^2).[14] The results of the current study by Alkhalil et al.[11] provide an argument in favour of earlier intervention before deterioration of LV pump function. Some recent studies also suggest that the current cutoff value of LVEF ($<$ 50%) proposed in the guidelines to identify subclinical LV dysfunction in AS is too low and that early AVR

should be considered in asymptomatic patients with LVEF $< 60\%$.[16]

Conclusions

The results of the study by Alkhalil et al. provide further support to the systematic integration of stroke-volume index in the staging of cardiac damage and risk stratification of patients with AS. Indeed, this simple echocardiographic parameter is a powerful risk marker that shows incremental prognostic value beyond other parameters including LVEF. Further studies are now needed to determine whether earlier AVR should be considered in asymptomatic patients with severe AS and low flow and whether TAVR, rather than SAVR, should be considered in symptomatic patients with severe AS and low flow (Fig. 1).

Disclosures

Dr Pibarot has a research contract with Edwards Lifesciences for echocardiography core laboratory analyses and with Medtronic for *in vitro* studies, with no personal compensation. Dr Clavel has a research contract with Edwards Lifesciences for CT core laboratory analyses and with Medtronic for *in vitro* studies, with no personal compensation.

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