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GUEST EDITORIAL

Valvuloarterial impedance in aortic stenosis: look at the load, but do not forget the flow

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This editorial refers to 'Valvuloarterial impedance does not improve risk stratification in low-ejection fraction, low-gradient aortic stenosis: results from a multicentre study' by F. Levy *et al.*, on page 358.

The vast majority of patients with severe calcified aortic stenosis (AS) have normal left ventricular (LV) ejection fraction, even in the presence of symptoms.[1] Nevertheless, ≈20% of patients with AS and undergoing valve surgery were found with reduced LV ejection fraction (<50%)[1] in the last Euro Heart Survey. This characteristic is often the result of a concomitant coronary artery disease. In some patients, however, LV hypertrophy, due to the chronic pressure overload, is inadequate to normalize systolic wall stress, resulting in an afterload mismatch and a decrease in LV ejection fraction.[2] Reduced LV function may lead to low-flow state and thus to low-gradient, despite the presence of severe AS. In fact, three main types of patients with severe AS, according to LV function and flow, are generally observed: (i) normal LV ejection fraction and normal flow, (ii) reduced LV ejection fraction and reduced flow, and (iii) normal LV ejection fraction and reduced flow.

Low-ejection fraction/low-gradient severe AS represents a challenging clinical entity. The classification of patient in the so-called low-flow/low-gradient (LF/LG) severe AS subset may considerably vary from different studies and is generally based on the presence of the three following haemodynamic criteria: (i) an aortic valve area (AVA) <1 cm^2, (ii) a LV ejection fraction <30–45%, and (iii) a mean transvalvular pressure gradient (MPG) <30–40 mmHg.[3–12] LF/LG severe AS is associated with a poor outcome under conservative management[13] and a high operative mortality risk.[14] Moreover, even after aortic valve replacement (AVR), the prognosis of such patients is worse than those with preserved LV function, and the improvement of symptoms remains limited.

True-severe or pseudo-severe aortic stenosis

The reduced survival reported in LF/LG severe AS, when compared with 'classic' severe AS, is obviously related to both the LV disease and the inappropriate timing of surgery generally reported in such patients. Indeed, due to the low-flow state, the apparent discrepancy between AVA and MPG may be considered as an artefact or a measurement error, which, in turn, could underestimate the severity of symptom and delay intervention. In this regard, the cornerstone of the evaluation of LF/LG AS is the distinction between true- and pseudo-severe AS. In the former, the aortic valve is really severely stenotic, the afterload mismatch is the main cause of LV dysfunction, the symptoms are essentially valve-related, and AVR is recommended and beneficial. In the latter, the aortic valve could be only mildly or moderately stenotic and the small reported AVA is due to an inability of the impaired LV to generate enough forces to open the calcified aortic cups. In this context, low-dose dobutamine stress echocardiography (DSE) is strongly recommended for the assessment of such patients. The DSE is crucial in the management of LF/LG AS[15] and allows (i) as to distinguish true-severe from pseudo-severe AS[3,12] and (ii) to evaluate the presence of LV contractile reserve, which is a marker of better peri-operative outcome.[6,7] During dobutamine infusion, a pseudo-severe AS may increase its AVA and only exhibits small changes in MPG. In contrast, true-severe AS had no or minimal augmentation in AVA during DSE and had a marked increase in MPG.

Nevertheless, in the presence of an excessive LV afterload, with no or few LV contractile reserve (≈one-third of patients), the normalization of flow rate is not possible and, unmasking pseudo-severe AS is challenging. In this regard, the calculation of the projected AVA at a normal transvalvular flow rate (Q_{mean} > 250 mL/s) may be very useful and more accurate than the traditional echocardiographic indices (e.g. valvular resistance, dobutamine-induced increase in AVA, or MPG) to differentiate true from pseudo-severe AS.[5]

Global left ventricular afterload

Concomitantly to the progressive aging of the general population, AS is nowadays becoming a part of the general atherosclerotic disease process, which progressively decreases the compliance of the vascular bed downstream the aortic valve. Besides the LV dysfunction, LF/LG AS is often associated with concomitant systemic hypertension.[5,16,17] This may induce a low-flow state despite

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normal LV ejection fraction. As a result, the LV faces a double afterload: (i) a valvular load, due to the AS and (ii) an arterial load, as a consequence of reduced arterial compliance.

The valvuloarterial impedance (Zva) is a new index proposed by the group of Pibarot and coworkers,[18] assessing the global LV haemodynamic load (i.e. total load) that can be measured by Doppler echocardiography. The Zva is defined as the ratio of the estimated LV systolic pressure [i.e. the sum of systolic arterial pressure (SAP) and MPG] to the stroke volume indexed (SVi) for body surface area: Zva = (SAP + MPG)/SVi. This index in fact represents the valvular and arterial factors that oppose ventricular ejection by absorbing the mechanical energy (transformed in heat) developed by the LV.

The Zva is associated with LV myocardial dysfunction,[19] and with longitudinal, radial, and circumferential LV deformation impairment,[20] especially in low-flow patients. Of note, the LV of patients with moderate AS and concomitant hypertension may face a global haemodynamic load equivalent, or even superior, than patients with severe AS but no hypertension. In this regard, patients may probably develop myocardial dysfunction and symptoms because of the combination of moderate AS and some degrees of hypertension.

The concept of 'global afterload' emerges as appealing and, in a clinical standpoint, may be very useful to reconcile the apparent discordance between moderate AS and the symptomatic status. In the case of a low Zva, the symptoms may be related to another concomitant disease. On the contrary, in high-Zva patients, the symptoms could be the result of the additive effects of a moderate AS and reduced arterial compliance and/or increased vascular resistance.

Furthermore, as expected, high Zva is associated with a poorer outcome.[21] Retrospectively, Hachicha *et al.*[22] found a graded relationship between increased Zva and reduced overall survival. In addition, we recently found that high Zva ($\geq$5 mmHg/mL m^2) was a powerful predictor of reduced cardiac event-free survival in asymptomatic patients with moderate to severe AS.[21]

Impact of valvuloarterial impedance in low-ejection fraction/low-gradient severe aortic stenosis

The study by Levy *et al.*[23] was aimed to evaluate the prognostics value of Zva in patients with low-ejection fraction, low-gradient severe AS. From 1995 to 2005, consecutive symptomatic patients with severe LF/LG AS who underwent DSE were included in this French multicentre registry. The Zva was retrospectively calculated in 184 patients (71 $\pm$ 10 years, 75% of male) and confronted to other demographic or echocardiographic parameters in predicting the outcome. A total of 88 patients (48%) had a high Zva ($\geq$5.5 mmHg/mL/m^2). Compared with the low-Zva group, these patients had more severe AS, significant lower ejection fraction and LV end-diastolic diameter, and had more frequently a contractile reserve. Based on a DSE-induced increase in AVA $\geq$0.3 cm^2 associated with a peak DSE AVA $\geq$1 cm^2, pseudo-severe AS was found in 12% of the cohort. Interestingly, the Zva value was statistically similar between true and pseudo-severe AS and therefore, was not helping to discriminate these patients.

As previously published,[19–21] the authors reported a significant association between reduced LV function and increased Zva. They elegantly found that this relationship seems to be more pronounced in patients with very low LV ejection fraction (<20%).

In the whole cohort, a high Zva was not associated with 5-year reduced survival. In addition, in the subset of patients who were operated on, Zva was not predictive of both operative and 5-year post-operative mortality.

The authors concluded that, by opposition to LV contractile reserve, Zva had no prognostic value and seems to be useless for predicting mid-term survival and both operative and 5-year post-AVR mortality.

However, the lack of relationship between Zva and outcome in LF/LG severe AS might be explained, in part, by fluid mechanics.

Valvuloarterial impedance: a flow-dependent parameter

By nature, Zva is flow-dependent and may considerably vary in a same patient over time and during an echocardiographic examination, more specifically in the presence of low-flow state. Moreover, two patients with similar AVA and degree of hypertension (i.e. similar LV global afterload), may have different Zva values. The MPG (included in the numerator of the equation for the calculation of Zva) is highly flow-dependent and had a square relationship with the Qmean. Because the SVi is the only parameter included in the denominator, the impact of flow on the variability of Zva is more important in low-flow state than in a normal or high-flow situation. Subtle changes in SVi and in heart rate may result in high variation in Zva in LF/LG patients (*Figure 1*). In addition, the impact of minor error in the measurement of SVi on the calculation of Zva may be stronger in low-flow patients. The weak correlation reported by the authors between Zva and MPG confirms that these two parameters are subject to broad variability.

Under dobutamine, a small increase in Qmean may rapidly and noticeably decrease Zva. In patients with low-ejection fraction and low-flow, the Qmean may also markedly vary over patients, from very low (<100 mL/s) to quite normal (>250 mL/s). As emphasized in *Figure 2*, the Zva calculated for a patient with severe AS (AVA = 0.7 cm^2) considerably varies according to the flow. Interestingly, this simulation is obtained with a constant SAP (120 mmHg), as it is often the case in low-flow patients due to the adaptation of vascular resistance, suggesting that the variability of Zva is not only related to the changes in SAP. Furthermore, the extent of the flow dependency is higher in low-flow state (SV <60–50 mL). While Zva rises by only 10% between 120 and 60 mL of SV, the increase in low-flow state is very high (>45%). This observation suggests that the calculation of Zva in LF/LG AS is less accurate for estimating the LV global haemodynamic load. Zva was previously found to be associated with a poor outcome in a large series of patients with AS and preserved LV function.[21,22] Hence, as highlighted by the results of Levy *et al*,[23]

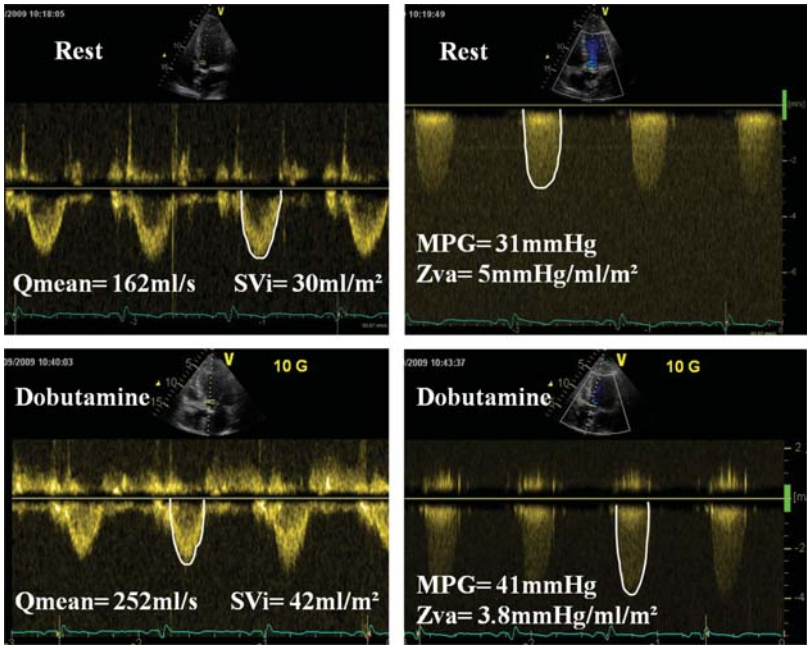

Figure 1 Doppler echocardiographic measurements in a patient with low-flow/low-gradient severe aortic stenosis. Resting indexed aortic valve area was 0.35 cm^2/m^2 and increased up to 0.5 cm^2/m^2 under 10μm/kg/min of dobutamine infusion. Systolic arterial pressure remained unchanged during the test. The normalization of transvalvular flow rate (Qmean) during dobutamine stress echocardiography resulted in a significant decrease in valvuloarterial impedance (Zva). SVi indicates indexed stroke volume and MPG, mean pressure gradient.

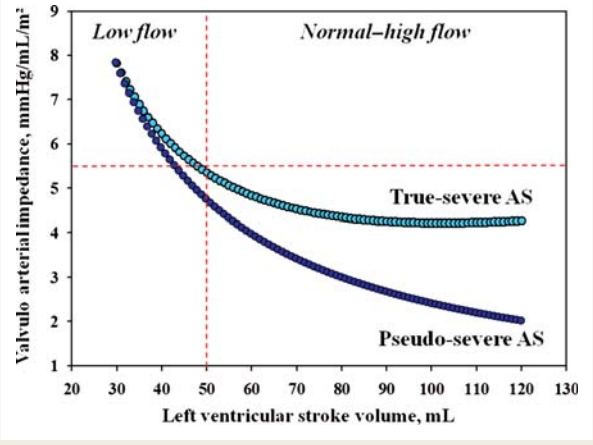

Figure 2 Simulation of the relationship between valvuloarterial impedance and left ventricular stroke volume in patients with true-severe (aortic valve area <0.7 cm^2) and pseudo-severe aortic stenosis. In low-flow state (stroke volume <50 mL), (i) the Zva markedly increased in response to small changes in stroke volume, and (ii) true- and pseudo-severe aortic stenosis exhibited similar Zva. Body surface area was assumed at 1.8 m^2, left ventricular end-diastolic volume at 120 mL, heart rate at 65 b.p.m., and systolic arterial pressure at 120 mmHg.

it might be argued that the presence of poor LV function represents the main determinant of outcome in LF/LG severe AS. The outcome of such patients thus seems to relate more to the intrinsic LV myocardial dysfunction than to the global LV haemodynamic burden.

The authors reported no statistical differences in Zva between pseudo and true-severe AS. *Figure 2* revealed that the Zva is markedly lower in pseudo than in true-severe AS patients when the SV is >60 mL. On the other hand, for a SV <50 mL, Zva are very similar in both groups. This may also explain why Zva is not accurate to distinguish pseudo-severe from true-severe AS. This observation also strengthens the idea that Zva at rest might not be a good parameter to evaluate the global LV haemodynamic burden in LF/LG AS. Thus, the use of peak DSE or DSE-induced changes in Zva might be of more interest.

Conclusion

To improve the risk stratification and the management of AS, which remains challenging in numerous cases, the comprehensive evaluation of the valvular and arterial load is mandatory. In this regard, the calculation of Zva appears as particularly useful. However, in LF/LG AS, the Zva seems to be less precise in the assessment of the LV global afterload, essentially due to its high-flow dependency in this specific subset of patient.

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