Editorial

Outcome in Aortic Stenosis: When the Flow Makes the Difference

Evolución clínica de la estenosis aórtica: cuando el flujo marca la diferencia

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Aortic stenosis (AS) was first described as an isolated disease involving the aortic valve leaflets. However, in the past years, the concept has evolved with noteworthy changes, and now, AS is looked upon as a complex, "systemic" disease.[1] Much of our current understanding regarding AS comes from past studies showing that patients with degenerative AS do not have a normal arterial function; they have a higher prevalence of atherosclerosis, isolated systolic hypertension, coronary artery disease and; the left ventricle (LV) in these patients has to overcome not only the valvular obstruction, but also the resulting high arterial hemodynamic load.[2–5] Ultimately, the severity of AS, as a systemic disease, is reflected by the way in which the LV is successful in overcoming both the valvular as well as the arterial hemodynamic load. In response to the increased global LV hemodynamic load, it has to generate more pressure per milliliter of blood to be able to eject during systole. However, when the adaptive mechanisms are exhausted, the LV is unable to maintain adequate flow through the aortic valve. As a result, the tissue metabolic requirements can no longer be satisfied and symptoms may ensue thereafter.

This theory has several implications. First, it can explain why a patient with only moderate AS but concomitant hypertension and low systemic arterial compliance could show symptoms similar to severe AS (exertional dyspnea, syncope, or angina) or present a depressed LV ejection fraction (LVEF) ($<$50%). Second, it draws attention to the fact that the flow across the aortic valve is important in stratifying the severity of AS. In fact, it roughly reflects the complex interplay between the LV pump function, the degree of aortic valve dysfunction, and the arterial function. Hence, in patients with AS, looking at the flow across the aortic valve is considered to be very crucial.

The decision on the mode of treatment is based on the symptomatic status and the severity of the disease in patients with AS. Current guidelines recommend aortic valve replacement, as a class I indication, only for symptomatic patients judged as having severe AS.[6,7] Moderate AS receives a class IIa indication for aortic valve replacement subject to the patient undergoing coronary artery bypass grafting, surgery of the ascending aorta, or surgery of another valve. Hence, an accurate grading of AS severity is mandatory for clinical decision-making. Severe AS is usually defined as follows: aortic valve area (AVA)$<$1 cm^2, mean trans-aortic pressure gradient$>$40 mmHg, and peak aortic jet velocity$>$4 m/s. To date, none of the parameters defined to grade AS can be applied as a single criterion to establish its severity; each having its own limitations. Infact, discrepancies are frequently observed between the mean trans-aortic pressure gradient and AVA in a single patient. These discrepancies are easy to understand in patients with low cardiac output coupled with reduced LVEF, but may also occur in patients with apparently preserved LV function.[1,8] In daily practice, these discrepancies may potentially lead to an underestimation of stenosis and symptom severity and thus, to inappropriate delay of aortic valve replacement in patients with AS.

Transvalvular gradients are highly dependent on flow variation, as they are a square function of the flow across the valve.[4,9–11] Only a modest decrease of flow may lead to a significant reduction in the mean or peak pressure gradient. A low gradient, especially in the presence of a reduced flow across the valve, does not completely rule out severe AS. On the contrary, if measurement errors have been carefully excluded, a low gradient might assist in identifying groups of patients with severe AS, who are at a higher risk of future cardiovascular events.[11–14] Hence, a crucial step in the evaluation of the severity of AS is the analysis of the flow across the valve. AVA is considered a less flow dependent parameter for assessing the severity of AS; although AVA alone cannot be the only parameter applied to judge the severity of AS. AVA is highly dependent on the accurate measurement of the LV outflow tract area, which represents the main source of error. In addition, the cut-off value of AVA that designates severe AS remains a matter of debate; some authors suggest a cut-off value of 0,8 cm^2 to be more adequate, as it could reconcile the discordance with the mean trans-aortic pressure gradient.[8] However, several studies in the past that have graded severe AS as per the cut-off value of AVA$<$1 cm^2, irrespective of the mean trans-aortic pressure gradient, have shown that this particular value holds a predictive power for detecting excess mortality and morbidity.[4,12] Hence, an AVA$<$1 cm^2 is equally conclusive in grading the severity of AS in patients.

Recently, several authors have emphasized that under the same characterization of severe AS (AVA$<$1 cm^2), several conditions may be identified, differing in terms of transvalvular flow rates and pressure gradients developed.[4,9–11] The first group to underline the importance of integrating the valve-gradient relationship to the flow pattern was Pibarot et al.[4]; whereas, Miners et al.[8] was the first group to clearly show the inconsistencies involved in

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grading the severity of AS and to propose with Lancellotti et al.,[14] the new classification of AS. In patients with an AVA<1 cm^2, 4 flow-gradient AS categories can be identified: normal flow/low gradient (NF/LG), normal flow/high gradient (NF/HG), low flow/low gradient (LF/LG), and low flow/high gradient (LF/HG). LF is defined as an indexed LV stroke volume of <5 mL/m^2; LG is defined as a mean trans-aortic pressure gradient of <40 mmHg.[7]

The NF/LG pattern is observed in 31%-38% of patients and seems to represent the group of patients with a less severe degree of AS (an inherent inconsistency contained in the guidelines) or patients who have been exposed to the disease for a shorter period of time. This entity is characterized by a preserved LV longitudinal myocardial function, resulting in lower brain natriuretic peptide (BNP) levels and lower Monin's risk score.[14,15] The prognosis of these patients seems to be relatively preserved as compared to the other categories of patients.

The NF/HG pattern represents the most prevalent pattern (39%-72%) in patients with AS and is fully consistent with the criteria proposed by the guidelines.[4,14–16] When compared with the NF/LG group, although the LV longitudinal function is preserved in these patients, the BNP levels are higher and the cardiac event-free survival rates are reduced. Furthermore, patients with NF/HG seem to have more severe AS, suggesting a longer exposure to this progressive disease. When symptomatic, these patients are classically referred for aortic valve replacement; whereas when asymptomatic, the management of these patients underlines the need for optimized risk stratification.

The LF/HG pattern accounts for 8% of patients with severe AS.[4,14–16] It is characterized by an indexed LV stroke volume of <35 mL/m^2 in spite of a preserved LVEF, a high BNP level, a high Monin's risk score, and a significant reduction in LV longitudinal function.[14] It is necessary to note that LVEF is a crude estimate of LV systolic function. LVEF is influenced by both intrinsic myocardial function and LV cavity geometry. Hence, for a similar extent of intrinsic myocardial shortening, the LVEF will tend to increase in relation to the extent of LV concentric remodeling. The LVEF may therefore markedly underestimate the extent of myocardial impairment in the presence of LV concentric remodeling, which is generally the case in AS patients. Hence, what is normal, in terms of systolic function for a LV with normal geometry may be abnormal for a LV with concentric remodeling. Moreover, the reduction in LV output (related to intrinsic myocardial dysfunction and significant LV remodeling) may, in turn, result in lower than expected trans-valvular gradients. The disease outcome in these patients is nearly identical to patients with NF/HG. When symptomatic, these patients tend to have a better survival if treated surgically.

The prevalence of LF/LG pattern seems to be lower than what was initially reported. This pattern accounts for 7% of asymptomatic patients and 15%-35% of symptomatic patients.[4,9–11] This pattern, namely paradoxical LF-AS, represents a challenging clinical entity, the importance of which has been recently emphasized. It is associated with more pronounced LV concentric remodeling, smaller LV cavity, increased global LV afterload, intrinsic myocardial dysfunction, myocardial fibrosis, and a dismal prognosis.[9,10] In asymptomatic patients with LF/LG AS, our study showed that the likelihood of remaining alive without aortic valve replacement at 3 years was 5-fold lower than in the NF/LG group of patients and 4-fold higher than in the NF/HG group of patients.[14] This clinical entity is often misdiagnosed, which may lead to an underestimation of AS severity, thereby leading to its under-utilization; or may result in an inappropriate delay in surgery. It is very crucial to recognize this entity and ensure that surgery is not denied to a symptomatic patient with small AVA and LG. In clinical practice, when AVA is <1 cm^2 and mean trans-aortic pressure gradient is <40 mmHg, measurement errors and small body size (indexed AVA) need to be ruled out first. Subsequently, typical paradoxical LF-AS features have to be identified: stroke volume index of ≤35 mL/m^2 associated with reduced LV, end-diastolic diameter of <47 mm and a volume index of <55 mL/m^2, increased relative wall thickness of $>0,45$, and valvulo–arterial impedance of $>4,5$ mmHg/mL^{-1}/m^2.

In the article published in *Revista Española de Cardiología*, Melis et al.; following the new proposed classification for severe AS according to the flow-gradient pattern, performed a retrospective analysis on the outcome of patients with severe AS (AVA<1 cm^2) and preserved LVEF (≥50%).[16] Their main outcome was global mortality. The main finding of this study was that patients with LF severe AS, irrespective of mean trans-aortic pressure gradient, had higher mortality rates as compared to patients with NF AS (26.6% vs 13.6%; *P*=.004). Also, the NF/LG group emerged as the group with the best prognosis, in terms of global mortality. These findings are in concordance with results from our study.[14] Also, the proportion of each group in their studied populations resembled the results shown in our population; approximately half of the population having NF/HG severe AS, about 27% of the population having NF/LG AS, 15% having LF/HG AS, and 12% having LF/LG severe AS. The higher prevalence of LF/LG severe AS in the present study as compared to our data (12% vs 7%) was probably due to the differences in inclusion criteria of the patients (both symptomatic and asymptomatic patients versus truly asymptomatic patients). Aligned with other publications, the present article reinforces the fact that patients with LF/LG severe AS have smaller LV diameters, lower systemic arterial compliance, higher systemic vascular resistance, higher global hemodynamic load (valvular and arterial), and worse outcome.[4,14] There are some limitations of the study that have to be acknowledged: *a)* its retrospective character, and *b)* the fact that the prevalence of coronary artery disease was more frequent in the group of patients with LF/LG severe AS, which may partly account for the higher mortality rate in this group. However, the higher prevalence of coronary artery disease in patients with LF/LG severe AS is a part of the "systemic" character of this disease and cannot be considered as a separate conclusive parameter.

Judging severe asymptomatic AS with the use of the new proposed classification, taking into account AVA and the 4 flow-gradient patterns, might diminish the degree of uncertainty involved in interpreting the severity of this valvular disease in clinical practice. This approach is unifying and allows a better characterization of the clinical outcome in these patients.

CONFLICTS OF INTEREST

None declared.

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