Low-Flow Aortic Stenosis and Reduced Ejection Fraction: New Insights

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With the aging of the population, the incidence of degenerative cardiovascular diseases has steadily increased, especially aortic stenosis (AS), present in 3%-5% of the population older than 75 years[1,2]. In the last decade, severe AS is characterized taking into account several functional aspects between the left ventricle and the aorta, especially by echocardiography, such as mean transvalvular gradient > 40 mmHg, transvalvular jet velocity > 4 m/s and aortic valve area < 1 cm², as well as anatomical aspects such as the degree of the aortic valve calcification. Studies carried out in the 70s [3-5] describing the hemodynamic parameters and ventricular function characterized the diagnosis of severe AS only by aortic valve gradient peak > 50 mmHg by hemodynamic analysis and > 70 mmHg by echocardiography. At that time, they questioned the real benefit of surgery in the correction of severe AS and left ventricular dysfunction due to the fact that these exams showed difficulties identifying patients that could benefit from such treatment. In the 80s and 90s, still with limitations in ventricular function assessment, the intervention indication was only feasible in patients with severe AS (aortic transvalvular gradient peak > 70 mmHg by echocardiography), regardless of the degree of left ventricular dysfunction[6,7].

It is noteworthy that in the last two decades, with the incessant search for answers to these questions and the advent of pharmacological stress echocardiography, emphasis has been given to these peculiar forms of AS, particularly to severe AS with low-flow low-gradient and reduced ejection fraction, with or without contractile reserve. The latter has been the subject of great scientific interest due to the difficulty in diagnosing it and evaluating the real benefits of surgical intervention.

The low-flow low-gradient AS and reduced ejection fraction is found in approximately 5%-10% of these patients with severe AS, and diagnosis occurs in the presence of classic symptoms of AS, such as dyspnea, chest pain and/or syncope, associated with aortic valve area ≤ 1.0 cm² (or ≤ 0.6 cm²/m²), mean LV-Ao gradient ≤ 40 mmHg and reduced ejection fraction (≤ 40%)[8-10]. The ventricular dysfunction, in these cases, may be secondary to ventricular maladjustment caused by afterload mismatch – truly severe AS – or secondary to a myocardial phenomenon concomitant to the mild/moderate valvular disease – anatomically non-severe AS. In the latter, the reduction in ventricular strength would lead to incomplete valve opening, justifying the low transvalvular aortic gradient[10,11]. The differentiation between these two groups is of utmost importance, as patients with anatomically severe AS benefit from the valvular defect correction, whereas treatment for those with anatomically non-severe AS should be directed to the cause of the myocardial disease[10,11]. Therefore, the first question that arises for the clinical cardiologist is: how must one monitor and investigate the patient with a diagnostic hypothesis of low-flow low-gradient AS and reduced ejection fraction?

The initial assessment should be performed by dobutamine stress echocardiography (up to a dose of 20 mcg/kg/min), analyzing myocardial contractile reserve which, when present, allows us to define the anatomical severity of AS[10-12]. If the valve area increase after stress is ≤ 0.3 cm² and/or remains < 1.0 cm² and/or mean LV-Ao gradient is ≥ 40 mm Hg, the anatomically severe AS diagnosis is attained. On the other hand, further increases in the valvular area establish the diagnosis of anatomically non-severe AS. Among the measures described to define contractile reserve during dobutamine stress, Systolic Volume is the most often used index[11]. The absence of contractile reserve is defined by an increase in Systolic Volume after pharmacological stress < 20%[10,11], and this situation creates a new question for the clinical cardiologist: Is there any benefit in the interventional treatment of those who do not have myocardial contractile reserve?

These patients have high surgical mortality (22%-33%); however, this rate is still lower than the mortality observed in patients with AS that remain in clinical treatment[10,11,13]. Therefore, alternative procedures such as Transcatheter Aortic Valve Implantation (TAVI) can be indicated with lower morbimortality[13,14]. However, as stress echocardiography may have major limitations in identifying patients with truly severe AS in the absence of contractile reserve, how should we evaluate and what methods can help by providing information about the anatomical severity and prognosis, aiding in the indication of valve surgery for the symptomatic patient?

Valve calcification is the primary marker of anatomic severity in AS. The echocardiographic assessment using the Rosenhek score[15] defines as significant calcification those with grade 3 (multiple calcium deposits) and grade 4 (extensive calcification of all cusps)[16]. In the assessment through CT, a calcium score > 1650 Agatston units (AU) also indicates severe calcification[16]. However, ongoing studies suggest that the hemodynamic impact of AS may depend not

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only on the amount of calcium in the aortic valve, but also the topography of valve calcifications, demonstrating that significantly lower calcium score values can generate high gradients if the calcification is predominantly found in the valve commissure, with such data helping in the diagnosis of anatomically severe AS[17]. It must be emphasized that, although infrequent, aortic valve calcification may extend to the mitral valve annulus, impairing its function and resulting in moderate to severe mitral regurgitation, which can hinder the assessment of AS severity by reducing left intraventricular pressure. Additionally, in our experience, when severe AS is identified, the isolated treatment of the aortic valve can minimize the effect on the mitral apparatus.

Regarding the operative prognosis, the presence of a mean LV-Ao gradient ≤ 20 mmHg on echocardiography and high levels of serum brain natriuretic peptide (BNP) are associated with unfavorable outcomes. Patients with low-flow low-gradient AS and reduced ejection fraction with BNP levels < 550 pg/mL, regardless of contractile reserve, have a better surgical prognosis[13,18,19]. The presence of coronary lesions with intervention indication in the coronary angiography, usually performed as part of preoperative tests in patients older than 40 years or with risk factors for atherosclerosis, is also a prognostic factor, as the combined surgery of CABG and TAVI increases mortality when compared to isolated valve replacement (53% vs. 10%, p = 0.007)[13]. Nishimura et al[20] demonstrated the use of hemodynamic study with dobutamine stress for contractile reserve assessment similar to echocardiography; however, they used high doses of dobutamine (40 mcg/kg/min), which may increase the likelihood of complications and side effects during testing, such as severe arrhythmia, hypertension or hypotension and other symptoms of dobutamine intolerance.

In conclusion, dobutamine stress echocardiogram is a crucial test for the assessment of patients with low-flow, low-gradient AS and reduced ejection fraction, by differentiating anatomically severe AS patients from those with anatomically non-severe AS. However, when the test is not diagnostic, that is, the patient has no contractile reserve, other parameters can be useful to assess anatomic severity and prognosis (Figure 1). There are many variables that can contribute to such evaluation in patients with low-flow, low-gradient AS and reduced ejection fraction without contractile reserve; however, none of them alone should contraindicate the surgical procedure. One must, above all, individualize the assessment of this subgroup of patients and, for those in which the operative risk is considered unacceptable, TAVI is mandatory.

Author contributions

Conception and design of the research, Acquisition of data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Rosa VEE, Accorsi TAD, Fernandes JRC, Lopes ASSA, Sampaio RO, Tarasoutchi F.

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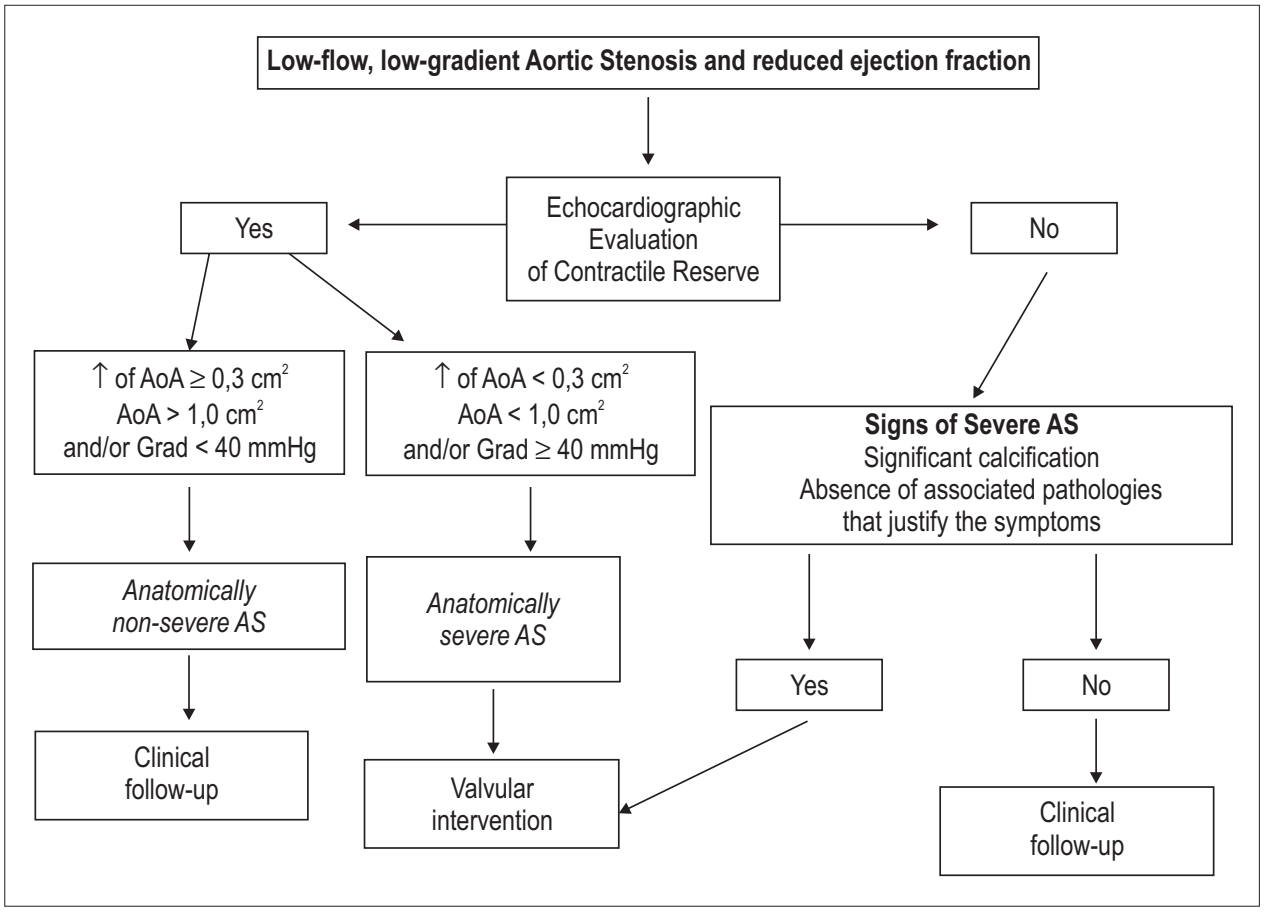

Figure 1 – *Proposed Algorithm for assessment of patients with low-flow, low-gradient Aortic Stenosis and reduced ejection fraction. AS: aortic stenosis; AoA: aortic valve area; Grad: LV-Ao gradient.*

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