Circulation Topic Review

Low-Flow/Low-Gradient Aortic Stenosis

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Aortic stenosis (AS) is 1 of the most common valve disorders encountered in clinical practice and 1 of the most frequent indications for valve replacement surgery. Decades of research and clinical experience have resulted in the development of guidelines that provide the clinician with an evidence-based approach to the management of patients with valvular disease.[1] Nonetheless, there remain patients with AS for whom management decisions are less clearly defined and who continue to pose significant diagnostic and therapeutic dilemmas.

Severe AS has been defined as that associated with a valve area <1.0 cm^2, a mean transvalvular gradient >40 mm Hg, and a peak flow velocity >4.0 m/s[1]. Patients with severe AS have a significant risk of cardiac morbidity and mortality[2,3] and have improved symptoms and reduced mortality following aortic valve replacement (AVR).[3] Traditionally, the decision to proceed with AVR in patients with AS has been based on the assessment of aortic valve area (AVA) and the presence of associated symptoms. However, as many as 30% of patients who have a calculated AVA in the severe range have other parameters suggesting mild or moderate disease (ie, mean gradient <30 mm Hg).[4] These patients with low-flow/low-gradient AS (LF/LGAS) may truly have severe AS with resultant myocardial failure (true AS) or may have more moderate degrees of AS and unrelated myocardial dysfunction (pseudo-AS). In the latter setting, the aortic valve may appear severely stenotic as a result of the flow-dependent nature of the valve area calculation by either invasive or noninvasive techniques,[5] and the inability of the myopathic ventricle to generate adequate force to fully open the valve. Distinguishing between these possibilities has important clinical implications in regard to prognosis and management options, as patients with true AS will likely benefit from corrective valve surgery, whereas patients with pseudo-AS may not.

Distinguishing True AS From Pseudo-AS

The utility of a dobutamine challenge in the evaluation of LF/LGAS during either cardiac catheterization or stress echocardiography has been well documented.[6,7] The inotropic effect of dobutamine results in an augmentation of stroke volume. In patients with true AS, this increased flow across a fixed valve orifice results in increased transvalvular flow velocity and gradients, without a change in calculated valve area. In contrast, in the setting of pseudo-AS, the augmented flow results in only a mild increase in transvalvular gradient and an increase in valve area by ≥0.2 cm^2. As many as 30% of patients with LF/LGAS fail to augment stroke volume by at least 20% with dobutamine infusion; these patients are denoted as having no contractile reserve.[8] The reported incidence of true AS and pseudo-AS in patients with LF/LGAS varies.[7,8] In 1 multicenter study, 136 patients underwent dobutamine stress echocardiography for the evaluation of LF/LGAS (mean AVA 0.7 cm^2, mean gradient 29 mm Hg, mean left ventricular ejection fraction [LVEF] 30%), and contractile reserve was present in 68%.[9] Only 7 patients (5%) were thought to have pseudo-AS, suggesting that the majority of patients with LF/LGAS have significant valve stenosis.

The differentiation between true and pseudo-AS may be improved by using other noninvasive parameters, such as the projected valve area at a normal flow rate, an echocardiographic method that attempts to control for the variable augmentation of transaortic flow induced by dobutamine.[10] Nonetheless, distinguishing true AS from pseudo-AS in patients with no contractile reserve remains challenging. Other imaging modalities may aid in the diagnosis of severe AS in this setting. Recent studies demonstrate good correlation between an aortic valve calcium score as measured by multislice computed tomography and the severity of AS as assessed by echocardiography.[11,12] When applied to a patient with LF/LGAS, a calcium score of >1651 U was 93% sensitive and 75% specific in the identification of patients with truly severe AS, suggesting that this modality may have a role in the evaluation of patients with LF/LGAS when other modalities are not definitive.[12] Using positron emission tomography imaging, coronary vasodilator reserve has been shown to be impaired in patients with severe AS and left ventricular hypertrophy, and the severity of the impairment is related to AVA, hemodynamic load, and diastolic perfusion. Furthermore, a reversal of the transmyocardial coronary vasodilator reserve pattern occurs in patients with an AVA <0.92 cm^2, with the coronary vasodilator reserve in the subendocardium being significantly lower than that in the subepicardium in patients with severe AS.[13] Nonetheless, the ability of positron emission tomography to prospectively distinguish severe from nonsevere AS has not been documented, and its applicability to patients with LF/LGAS is uncertain.

Prognostic Indicators

Although the surgical mortality of patients with LF/LGAS has decreased significantly over the past several decades,[14] these patients continue to have a high risk of adverse cardiac events and high mortality whether their disease is managed medically or surgically.[15–17] Determining which patients with

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LF/LGAS will benefit from AVR can be challenging. In this regard, the presence of contractile reserve is a powerful predictor both of perioperative mortality after AVR and of long-term survival. In a multicenter study of dobutamine stress echocardiography for risk stratification prior to AVR, patients with contractile reserve had an operative mortality of 5% compared with 32% for patients without an augmented response to dobutamine.[9] Furthermore, patients with contractile reserve had significantly improved long-term survival after AVR, whereas patients without contractile reserve had a dismal prognosis with or without valve replacement surgery, in large part related to the high perioperative mortality.

The dependence of postoperative prognosis on preoperative contractile reserve likely has pathological correlates. A recent study correlated delayed enhancement on preoperative cardiac magnetic resonance (MR) with the presence of myocardial fibrosis on surgical biopsy in patients with severe AS.[18] Patients with no or only mild fibrosis had marked improvement in symptoms postoperatively, whereas patients with severe fibrosis failed to improve. Repeat cardiac MR 9 months after surgery revealed no change in the delayed enhancement pattern, suggesting that AVR does not reverse presurgical myocardial fibrosis. Furthermore, midwall fibrosis on a preoperative cardiac MR is an independent predictor of mortality in patients with severe AS.[19] Although the utility of MR for determining the prognosis of patients with LF/LGAS is unclear, it is likely that the lack of contractile reserve in some patients with LF/LGAS is mediated in part by the presence of irreversible cardiac fibrosis.

Nonetheless, other studies have demonstrated that a majority of patients with LF/LGAS and no contractile reserve on preoperative dobutamine stress echocardiography have significant improvement in left ventricular (LV) function and reduction in congestive symptoms after AVR.[8,16] Futhermore, although surgical therapy in patients with LF/LGAS and no contractile reserve is associated with high perioperative mortality, the 5-year survival is significantly improved after AVR in these patients when compared with medical management (54% versus 13%; $P=0.001$).[16] These data suggest that, although the absence of contractile reserve is an important predictor of adverse outcome, it should not preclude consideration of AVR in these patients.

Other factors may also play a role in risk stratification of AVR in patients with LF/LGAS. The presence of severe coronary artery disease or the performance of coronary artery bypass graft (CABG) at the time of AVR significantly increases the perioperative risk in patients with LF/LGAS.[8,14,16] In 1 series, the operative mortality after combined AVR/CABG in these patients was 53%, compared with 10% for patients in whom CABG was not performed.[16] Similarly, patients with LF/LGAS who have very low mean transaortic gradients (<20 mm Hg) have a significantly higher risk of perioperative death than those with higher gradients (44%–67% versus 10%–16%)[9,16] and have less improvement in LV function after AVR.[8] In patients who do undergo AVR, prosthesis-patient mismatch, defined as an effective valve orifice area ≤ 0.85 cm^2/m^2, is associated with an increased rate of postoperative congestive heart failure, less regression of LV hypertrophy, and a trend toward increased mortality.[2,17] Although brain natriuretic peptide (BNP) is elevated in patients with LF/LGAS and is higher in patients with true AS than in patients with pseudo-AS, it cannot accurately distinguish between these 2 conditions.[20] However, BNP is a strong predictor of mortality in patients with LF/LGAS; a BNP level >550 pg/mL predicts both overall 1-year survival (47% if BNP $\geq$550 versus 97% if BNP <550) and 1-year survival after AVR (53% if BNP $\geq$550 versus 92% if BNP <500).[20]

Paradoxical Low-Flow AS

The majority of patients with LF/LGAS have decreased left ventricular systolic function (ie, LVEF <40%); however, as many as 35% of patients with severe AS (AVA <0.6 cm/m^2) and preserved LVEF (>50%) have paradoxically low flow, defined as a stroke volume index of <35 mL/m^2.[21] These patients have lower peak transaortic velocities (3.5 versus 4.0 m/s) and lower mean gradients (32 versus 40 mm Hg) compared with patients who have normal transaortic flow rates, despite having similar AV area (0.76 versus 0.84 cm^2), similar dimensionless index (0.24 versus 0.23), and similar LVEF (65% versus 69%). These features predispose to a clinical underestimation of the severity of AS in these patients and delays in pursuing appropriate care. The mechanism of the paradoxically low flow in the face of preserved LVEF likely relates to high afterload, and the reduced stroke volume in this setting is likely an early marker of intrinsic myocardial dysfunction.

The prognosis of patients with LF/LGAS with preserved LVEF depends in part on the presence of symptoms.[4,21] In a series of symptomatic patients, those with low transaortic flow had a significantly worse prognosis compared with their counterparts with normal flow (3-year survival 76% versus 86%); however, they obtained similar mortality benefit from AVR.[21] In contrast, in a larger and more contemporary report, asymptomatic patients with LF/LGAS with preserved LVEF had a prognosis similar to that of patients with more moderate AS (92.2% versus 95.1% survival at 46 months).[4]

Clinical Approach to Patients With LF/LGAS

How then should we approach patients with LF/LGAS, and how do we determine which patients will benefit from AVR? The current data suggest that patients with LF/LGAS who have true AS and contractile reserve on dobutamine challenge should proceed to AVR unless comorbid conditions preclude surgical approaches, and patient-prosthesis mismatch should be carefully avoided. The absence of contractile reserve clearly predicts a higher risk of morbidity and mortality with or without AVR; however, AVR should not be systematically denied to these patients, because significant long-term benefit is obtained by patients who survive the surgery. Newer modalities may help to further risk stratify these patients and help to guide therapeutic decision making; however, each patient must be considered individually, as current modalities only incompletely distinguish those patients who will benefit from AVR from those who will not.

Disclosures

None.

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