

## STATE-OF-THE-ART PAPERS

# Low-Flow, Low-Gradient Aortic Stenosis With Normal and Depressed Left Ventricular Ejection Fraction

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Low-flow, low-gradient (LF-LG) aortic stenosis (AS) may occur with depressed or preserved left ventricular ejection fraction (LVEF), and both situations are among the most challenging encountered in patients with valvular heart disease. In both cases, the decrease in gradient relative to AS severity is due to a reduction in transvalvular flow. The main challenge in patients with depressed LVEF is to distinguish between true severe versus pseudosevere stenosis and to accurately assess the severity of myocardial impairment. Paradoxical LF-LG severe AS despite a normal LVEF is a recently described entity that is characterized by pronounced LV concentric remodeling, small LV cavity size, and a restrictive physiology leading to impaired LV filling, altered myocardial function, and worse prognosis. Until recently, this entity was often misdiagnosed, thereby causing underestimation of AS severity and inappropriate delays for surgery. Hence, the main challenge in these patients is proper diagnosis, often requiring diagnostic tests other than Doppler echocardiography. The present paper proposes to review the diagnostic and therapeutic management specificities of LF-LG AS with and without depressed LV function. (J Am Coll Cardiol 2012;60:1845–53) © 2012 by the American College of Cardiology Foundation

Severe aortic stenosis (AS) is usually defined on the basis of both an aortic valve effective orifice area (EOA)  $\leq 1.0$  cm<sup>2</sup> and a mean transvalvular gradient  $\geq 40$  mm Hg (1,2). Nonetheless, given that gradients are a squared function of flow, even a modest decrease in flow may lead to an important reduction in gradient, even if the stenosis is very severe. A low-flow, low-gradient (LF-LG) severe AS in relation to a decrease in left ventricular ejection fraction (LVEF) may be observed in approximately 5% to 10% of patients with severe AS (3,4). Such patients are classically characterized by a dilated LV with markedly decreased LV systolic function, most often due to ischemic heart disease and/or to afterload mismatch (Fig. 1) (5–8). Prognosis is usually poor (survival rates  $< 50\%$  at 3-year follow-up) if treated medically, but operative risk is high (6% to 33%) if treated surgically (3,6–16). Precise assessment of both the severity of valve stenosis and the degree of myocardial impairment is thus crucial for good therapeutic management.

Recent studies also showed that a “paradoxical” LF-LG state might nonetheless be observed despite a preserved

LVEF in 10% to 25% of patients with severe AS (17–25). This LF state bears analogy with normal LVEF heart failure and is, in large part, due to a restrictive physiology whereby there is pronounced and/or exaggerated myocardial concentric remodeling, small LV cavity size, and reductions in LV compliance and filling (Fig. 1) (17,18). Proper recognition of this entity is important because the presence of LG in conjunction with a normal LVEF may easily lead to an underestimation of AS severity. The present paper thus proposes to review the most recent concepts with regards to the diagnosis and treatment of these 2 challenging entities (i.e., LF-LG AS with or without preserved LVEF).

For the purpose of this state-of-the-art review, a PubMed search of the literature was performed using the terms “aortic stenosis” and “low flow or low gradient or dobutamine.” The search was limited to the title and abstract of full-length articles written in English and published from 1995 to the present. The last update of the search was in April 2012. This search resulted in 309 articles, 133 of which were excluded because they were not related to the targeted topic. Among the remaining 176 articles, 132 were original articles and 44 were review articles, editorials, letters, or case reports. To ensure that no potentially important studies were missed, the reference lists from these articles were also checked. We then primarily focused on original studies and multicenter prospective trials that provided the most robust evidence with regard to diagnosis and treatment.

From the Québec Heart & Lung Institute, Department of Medicine, Laval University, Québec City, Québec, Canada. Part of the work presented in this paper was funded by a CIHR Operating Grant (#MOP 57745). Dr. Pibarot holds the Canada Research Chair in Valvular Heart Diseases, Canadian Institutes of Health Research (CIHR), Ottawa, Canada. Drs. Pibarot and Dumesnil have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 30, 2011; revised manuscript received May 8, 2012, accepted June 5, 2012.

**Abbreviations  
and Acronyms**

- ACC** = American College of Cardiology
- AHA** = American Heart Association
- AS** = aortic stenosis
- AVR** = aortic valve replacement
- BNP** = B-type natriuretic peptide
- CAD** = coronary artery disease
- CT** = computed tomography
- DSE** = dobutamine stress echocardiography
- EACT** = European Association for Cardio-Thoracic Surgery
- EOA** = aortic valve effective orifice area
- ESC** = European Society of Cardiology
- LF-LG** = low-flow, low-gradient
- LVEF** = left ventricular ejection fraction
- SAVR** = surgical aortic valve replacement
- TAVR** = transcatheter aortic valve replacement
- Z<sub>va</sub>** = valvulo-arterial impedance

**Low-Flow, Low-Gradient AS  
With Low LVEF**

Low LVEF, LF-LG severe AS is generally characterized by the combination of an EOA  $\leq 1.0$  cm<sup>2</sup> or  $\leq 0.6$  cm<sup>2</sup>/m<sup>2</sup> when indexed for body surface area, a low mean transvalvular gradient (i.e.,  $< 40$  mm Hg) and a low LVEF ( $\leq 40\%$ ), causing an LF state. Several criteria have been proposed in the literature to define the LF state in AS, including a cardiac index  $< 3.0$  l/min/m<sup>2</sup> and a stroke volume index  $< 35$  ml/m<sup>2</sup> (2,7,17,26,27). Given that the gradient essentially depends on the flow per beat (i.e., the stroke volume) rather than on the flow per minute (i.e., the cardiac output), the former is the most frequently used parameter in this context (2,6,17,28,29). The stroke volume is usually measured in the LV outflow tract by Doppler echocardiography (5–7,16,17,28,29), although it has also been validated using the biplane Simpson method and the thermodilution or green-dye dilution methods during cardiac catheterization (30).

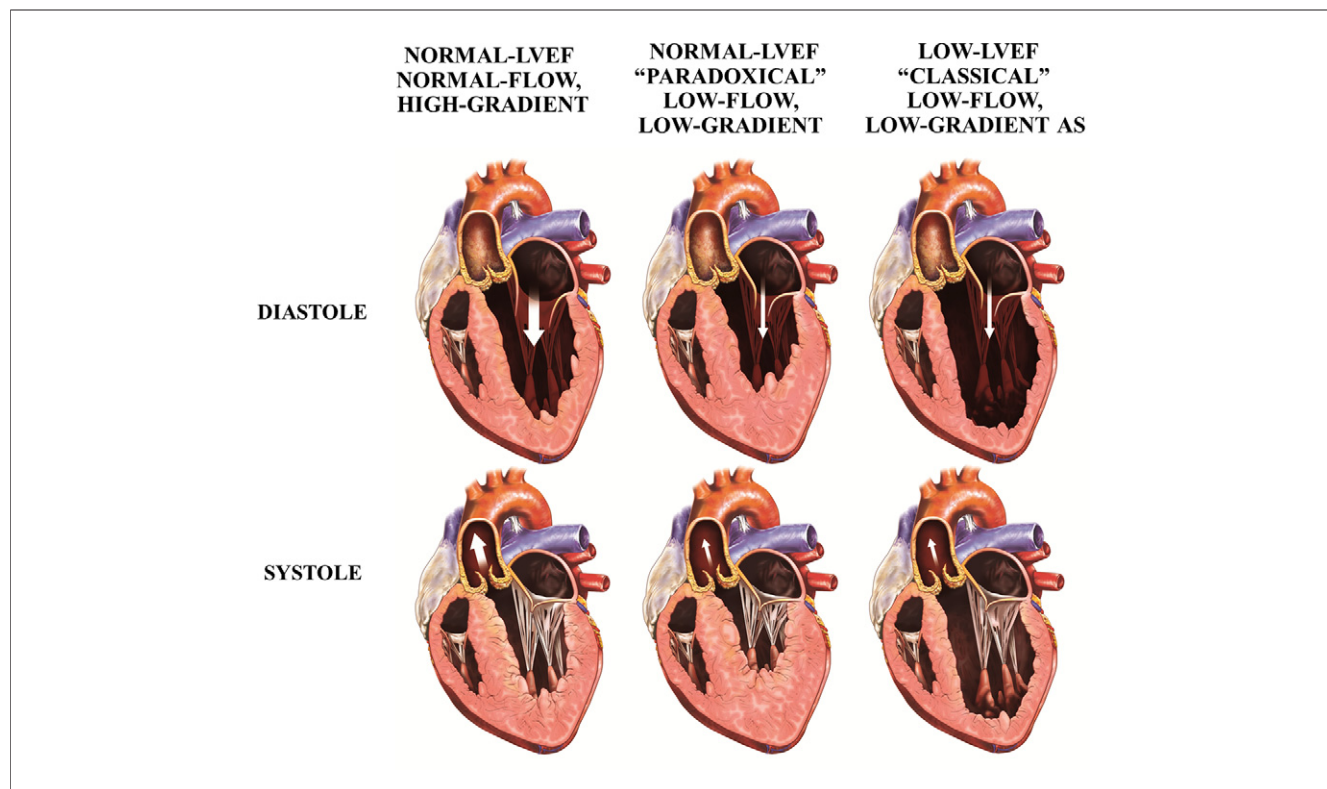
The main diagnostic challenge in LF-LG AS with low LVEF is to distinguish true severe from pseudosevere AS. In the former, the primary culprit is deemed to be the valve disease, and the LV dysfunction is a secondary or concomitant phenomenon. Conversely, the predominant factor in pseudosevere AS is deemed to be myocardial disease, and AS severity is overestimated due to incomplete opening of the valve in relation to the LF state. Distinction between these two entities is essential because patients with true severe AS generally benefit from aortic valve replacement (AVR), whereas those with pseudosevere AS may not benefit. Notwithstanding this distinction, operative mortality remains high, ranging between 6% and 33% depending on the presence and/or absence of myocardial contractile reserve and other comorbidities (3,6–16). In particular, a high proportion (46% to 79%) of patients with low LVEF, LF-LG AS have concomitant coronary artery disease (CAD) that may negatively impact their prognosis independently of AS severity (3,7,16). Hence, identifying which patients may benefit from surgery is challenging because many variables must be taken into account.

**Assessment of disease severity and operative risk.** DeFilippi et al. (5) were the first to demonstrate that low-dose (up to 20  $\mu$ g/kg/min) dobutamine stress echocardiography (DSE) may be used in these patients to assess the presence of LV flow reserve and to distinguish true versus pseudosevere stenosis (Fig. 2). The use of DSE for this purpose has received a Class IIa (Level of Evidence: B) recommendation in the American College of Cardiology/American Heart Association-European Society of Cardiology (ACC/AHA-ESC/EACTS) guidelines (1,2,31), and a similar protocol has also been used in the catheterization laboratory (30).

**ASSESSING LV CONTRACTILE AND/OR FLOW RESERVE.** Patients with no LV flow reserve are defined by a percent increase in stroke volume  $< 20\%$  during DSE (2,7,12,15,16,32) or catheterization (30), and have higher operative mortality (22% to 33%) than those with flow reserve (5% to 8%) (Figs. 2 and 3). They represent approximately 30% to 40% of patients with low LVEF, LF-LG AS (5,7,29–31), and have also been shown to have a higher prevalence of multivessel CAD (7).

The term “flow reserve” is utilized rather than “contractile reserve” because several mechanisms not necessarily related to intrinsic contractility may contribute to the lack of stroke volume increase during DSE, including: 1) afterload mismatch due to an imbalance between the severity of the stenosis and myocardial reserve (33); 2) inadequate increase of myocardial blood flow due to associated CAD; and/or 3) irreversible myocardial damage due to previous myocardial infarction or extensive myocardial fibrosis. The French Multicenter Study of LF-LG AS reported that, in patients with no LV flow reserve who survived operation, the post-operative improvement in LVEF and the late survival rate were as good as in the patients with flow reserve (12) and much better than in those with no flow reserve treated medically (16) (Fig. 3). Comorbidities such as CAD may contribute to the difference between types of treatment, but analysis in propensity score-matched cohorts nonetheless show an independent benefit for AVR (16). When analyzed collectively, these findings suggest that the assessment of LV flow reserve by DSE is useful to estimate operative risk but does not permit prediction of recovery of LV function, improvement in symptomatic status, and late survival after operation (7,8,12,13,30). Hence, the absence of LV flow reserve should not preclude consideration of AVR in these patients (7,16).

**DISTINGUISHING BETWEEN TRUE SEVERE AND PSEUDO-SEVERE AS.** The evaluation of the changes in EOA and gradient during dobutamine infusion are also helpful in differentiating true severe from pseudosevere AS. Typically, pseudosevere AS shows an increase in EOA and relatively little increase in gradient in response to increasing flow, whereas true severe AS is characterized by little or no increase in EOA and an increase in gradient that is congruent with the relative increase in flow (Fig. 2). Several



**Figure 1** Different Patterns of Severe AS According to Flow, Gradient, and LV Geometry

The majority (50% to 70%) of patients with severe aortic stenosis (AS) develop left ventricular (LV) hypertrophy with normal LV cavity size and ejection fraction (EF), which allows maintenance of normal LV pump function. These patients with severe AS and normal transvalvular flow rate exhibit a high gradient. Patients with low LVEF, “classical” low-flow, low-gradient (LF-LG) AS (5% to 10% of the AS population) generally have a dilated LV cavity with markedly depressed myocardial systolic function and reduced LV outflow. Normal LVEF, “paradoxical” LF-LG AS (10% to 25% of AS population) is characterized by pronounced LV concentric remodeling, small LV cavity size and a restrictive physiology leading to impaired LV filling, altered myocardial function, and reduced LV outflow. Because of the LF state, patients with classical or paradoxical LF may present with a LG despite presence of severe stenosis. AVA = aortic valve area (in square centimeters); AVA<sub>Proj</sub> = projected aortic valve area at normal flow rate (in square centimeters); Ca = calcium score (in Agatston units); CABG = coronary artery bypass graft; CT = computed tomography; Op. = operative;  $\delta P$  = mean transvalvular gradient (in mm Hg); SAVR = surgical aortic valve replacement; SV = stroke volume; TAVR = transcatheter aortic valve replacement. Figure illustration by Craig Skaggs.

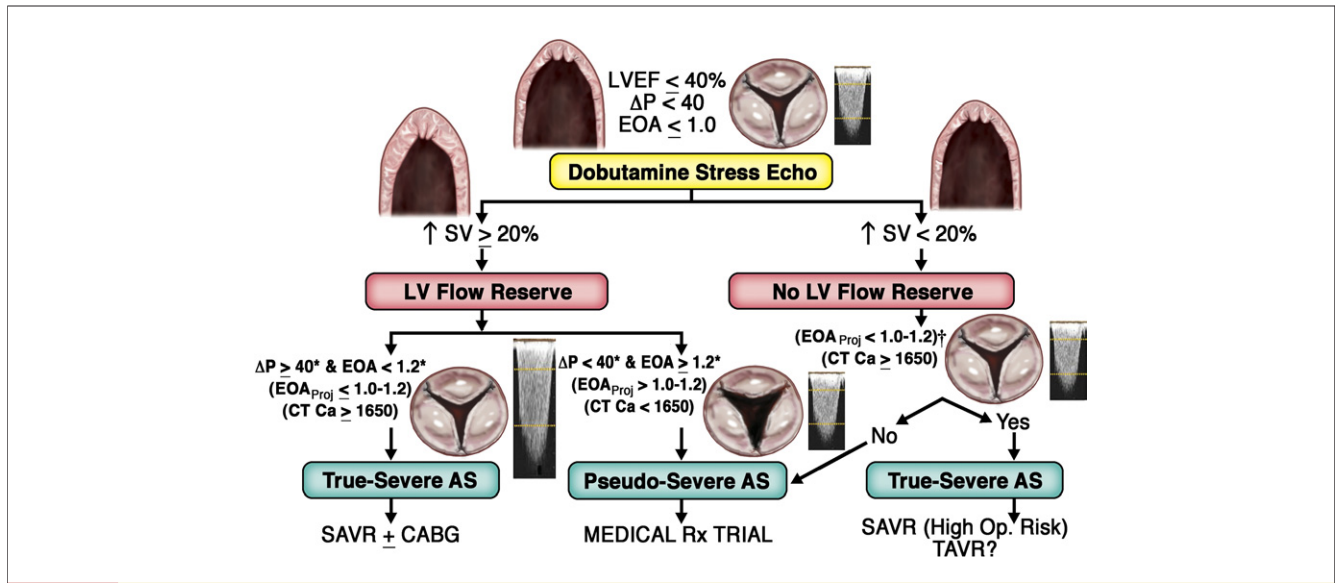
parameters and criteria have been proposed in the literature to identify patients with pseudosevere AS during DSE, including a peak stress mean gradient  $\leq 30$  or  $< 40$  mm Hg depending on studies, a peak stress EOA  $> 1.0$  or  $1.2$  cm<sup>2</sup>, and/or an absolute increase in EOA  $\geq 0.3$  cm<sup>2</sup> (2,5–7,30,34) (Fig. 2); thus, the optimal cutoff values remain to be determined. The prevalence of pseudosevere AS is reported to be between 20% and 30% (5,28–30,35).

Some patients may nonetheless have an ambiguous response to DSE (e.g., a peak gradient of 29 mm Hg and an EOA of 0.8 cm<sup>2</sup>) due to variable increases in flow (5,28,29), and interpreting the changes in EOA and gradients without considering the relative changes in flow may often be problematic. Hence, to overcome this limitation, the investigators of the TOPAS (Truly or Pseudo-Severe Aortic Stenosis) study proposed to calculate the projected EOA that would have occurred at a standardized flow rate of 250 ml/s (EOA<sub>Proj</sub>) (28,29) (Fig. 4), and this new parameter has been shown to be more closely related to actual AS severity, impairment of myocardial blood flow, LV flow reserve, and survival than

the traditional DSE parameters (8,28,29,36). The full potential of the EOA<sub>Proj</sub> remains to be determined by future studies (Fig. 2).

Patients with no increase in stroke volume may nonetheless have an increase in mean flow rate sufficient to allow a reliable measurement of EOA<sub>Proj</sub>; this is due to shortening of LV ejection time in relation to an increase in heart rate (Fig. 2) (28,29). However, there are 10% to 20% of patients in whom the increase in flow rate is insufficient to allow calculation of EOA<sub>Proj</sub> (28,29). In such cases or those with ambiguous results during DSE, quantification of valve calcification by multislice computed tomography may also be useful (Fig. 2). Cueff et al. (37) suggested that a score  $> 1,650$  Agatston units provides good accuracy to distinguish true severe from pseudosevere AS.

**ASSESSING PROGNOSIS AND OPERATIVE RISK.** In the subset of low LVEF, LF-LG AS patients treated medically, morbidity and mortality risk factors identified in previous studies were reduced functional capacity as assessed by Duke Activity Score Index ( $< 20$ ) or by 6-min walk test



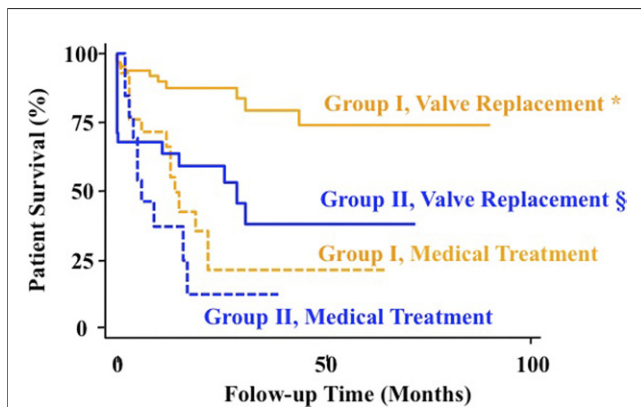
**Figure 2** Clinical Decision Making Process in Low LVEF, LF-LG Severe AS

Dobutamine stress echocardiography (DSE) is useful to assess LV flow reserve and to distinguish between the true severe and pseudosevere AS. Quantification of valve calcification by multislice computed tomography (CT) may also be used to corroborate stenosis severity. Text between parentheses represents new emerging parameters that need to be further validated. EOA = effective orifice area. (in square centimeters); EOA<sub>Proj</sub> = projected EOA at normal flow rate (in square centimeters); ΔP = mean transvalvular gradient (in mm Hg); Ca = calcium score (in Agatston Unit); SV = stroke volume; Op.= operative; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; other abbreviations as in Figure 1. \*Cutoffpoints may vary depending on studies. † See text for explanation and references. Figure illustration by Craig Skaggs.

(<320 m), presence of CAD, more severe stenosis as assessed by EOA<sub>Proj</sub> ≤1.2 cm<sup>2</sup>, and reduced peak stress LVEF (<35%) (8,16,29,35). A high plasma B-type natriuretic peptide (BNP) level (>550 pg/ml) would also appear to be a powerful predictor of mortality in patients with

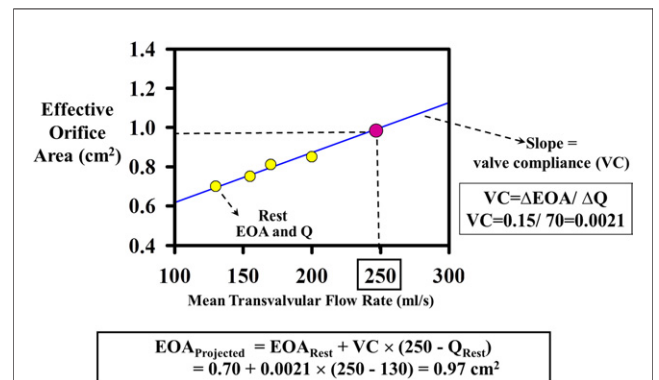
LF-LG AS regardless of treatment (medical vs. surgical) or the presence and/or absence of flow reserve (13).

In the subset of low LVEF, LF-LG patients who underwent AVR, the most powerful operative mortality risk factors were absence of LV flow reserve, very low pre-operative resting mean gradient (<20 mm Hg), multivessel



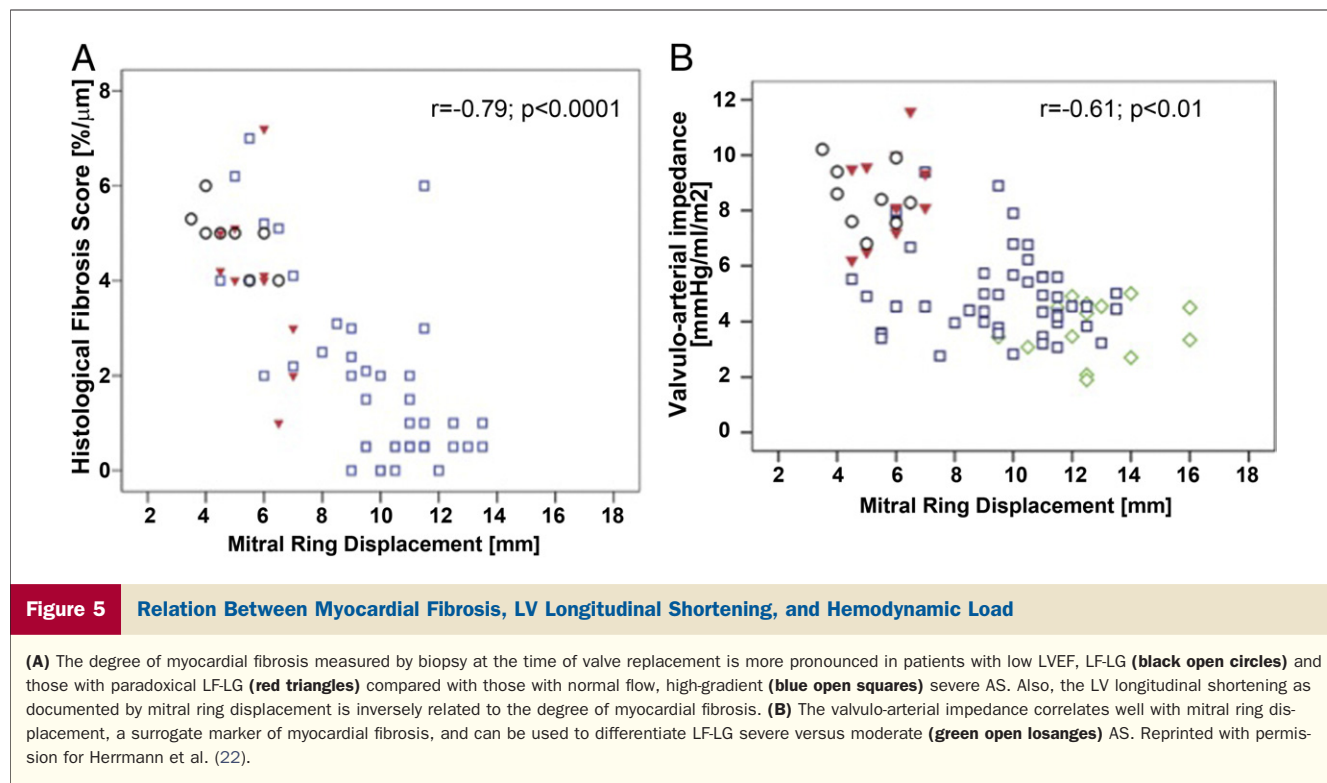
**Figure 3** Survival of Patients With Low LVEF, LF-LG AS According to Presence of LV Flow Reserve and Type of Treatment

Patients with no LV flow (contractile) reserve (Group II) defined as <20% increase in stroke volume during DSE have markedly reduced survival compared with those with LV flow reserve (Group I), regardless of the type of treatment. Aortic valve replacement is associated with dramatic improvement in survival in patients with LV flow reserve and a trend for better survival in those with no flow reserve. \*p = 0.001 versus medical; § p = 0.07 versus medical. Adapted with permission from Monin et al. (7).



**Figure 4** Calculation of Projected EOA at Normal Flow Rate (EOA<sub>Proj</sub>) to Distinguish Between True Severe and Pseudosevere AS

The projected aortic valve area (EOA<sub>Proj</sub>) extrapolates what the EOA would be at a standardized normal flow rate (Q) of 250 ml/s. **Yellow circles** depict the values of EOA as a function of Q at each stage of the DSE. The valve compliance (VC) is the slope of the regression line (**blue line**), which is calculated by dividing the maximal increase in EOA (+0.15 cm<sup>2</sup>) by the maximal increase in Q (+70 ml) during DSE. In this case, there was a discordance between peak stress EOA (0.85 cm<sup>2</sup>) and peak stress gradient (35 mm Hg) during DSE, but the EOA<sub>Proj</sub> (0.97 cm<sup>2</sup>; **pink circle**) confirmed that the stenosis was severe. Abbreviations as in Figures 1 and 2.



CAD, and valve patient–prosthesis mismatch (3,4,7,15,38). The intriguing inverse relationship between baseline gradient and operative mortality is probably due to the fact that a very LG is a composite marker for a less severe or pseudosevere stenosis and/or a more pronounced impairment of intrinsic myocardial function. Also, these patients are known to be more vulnerable than patients with normal LVEF to the excess in LV load caused by patient–prosthesis mismatch (4,38); therefore, a particular effort should be made to avoid this eventuality.

The predictors of late mortality after AVR are higher EuroSCORE (European System for Cardiac Operative Risk Evaluation), previous atrial fibrillation, multivessel CAD, low pre-operative gradient, high plasma levels of BNP, and patient–prosthesis mismatch (4,7,15). Although data are limited, some studies also reported that AVR and concomitant coronary artery revascularization both had independent beneficial effects on survival (8,14). Other factors reported as also having a significant impact on outcome and response to treatment were the degree of myocardial viability and, conversely, the extent of myocardial fibrosis (22,39,40). Reversibility of myocardial fibrosis following AVR likely depends on its type (reactive interstitial vs. replacement) and extent (mild vs. severe) as well as extent of correction of its causal mechanism (i.e., pressure overload and/or myocardial ischemia) (41). A recent study (22) reported more extensive myocardial fibrosis in patients with both types of LF-LG AS compared with patients with normal flow, high-gradient AS (Fig. 5). Furthermore, longitudinal myocardial shortening was affected to a larger

extent in these patients with LF-LG AS due to more advanced fibrosis in the subendocardial layer, where fibers are oriented longitudinally (42). Better standardization and validation are, however, necessary before quantification of myocardial fibrosis by magnetic resonance imaging can be implemented clinically (41).

**Therapeutic management.** The ACC/AHA guidelines (1) provide no specific recommendation for the treatment of patients with low LVEF, LF-LG AS, whereas the ESC/EACTS guidelines (2) support the utilization of AVR (Class IIa; Level of Evidence: C) in the subset of patients with LV flow reserve. Nonetheless, there presently appears to be a clear consensus that patients with true severe AS and evidence of “LV flow” reserve should be considered for AVR and that coronary artery bypass graft surgery should be performed concomitantly whenever necessary.

The evidence, albeit limited, is however not as clear in patients with LV flow reserve and pseudosevere AS because prognosis appears to be poor, whatever the treatment (7,30,32,35). Hence, such patients should probably be treated medically at first, but nonetheless followed up very closely (i.e., every 2 to 3 months), and the therapeutic options reconsidered in case of lack of improvement or deterioration (Fig. 2) (35). The outcome of these patients is largely determined by the extent of the imbalance between the degree of myocardial impairment and the degree of AS severity. Hence, although moderate AS may be well tolerated by a normally functioning ventricle, it may have the same impact as a severe stenosis in a failing ventricle. This observation may explain why a substantial proportion of

patients with pseudosevere AS have a better prognosis if treated surgically rather than medically (7,29,30,35). To this effect, the cutoff values of EOA  $<1.0 \text{ cm}^2$  or mean gradient  $\geq 40 \text{ mm Hg}$  found in the guidelines were originally derived from series of patients with preserved LVEF, and it is possible that less stringent cutoff values (e.g., EOA or  $\text{EOA}_{\text{Proj}} \leq 1.2 \text{ cm}^2$  and mean gradient  $>30$  to  $35 \text{ mm Hg}$ ) would be more appropriate for patients with decreased LVEF (29,30,35) (Fig. 2). AS severity is only one half of the equation, the other half being the degree of myocardial impairment which, for a given degree of AS severity, may vary considerably from one patient to the other, to the extent that, in selected cases with severe myocardial impairment, heart transplantation might also become an option. Finally, failure of medical therapy could also be due to a worsening of AS severity during follow-up, in which case AVR should be reconsidered.

Patients with no LV flow reserve are an equally challenging group with regard to diagnosis and treatment. AVR can certainly be contemplated in patients with evidence of a true severe AS on DSE or computed tomography (CT) (Fig. 2) (37). As for the DSE parameters, it is possible that the cutoff value of CT valve calcium score used to define severe AS may also have to be adapted (i.e., lowered down from 1,650 to  $\sim 1,200$  Agatston units), because as outlined previously, what is moderate stenosis for a normal ventricle may correspond to a severe stenosis for a diseased ventricle. In the ESC/EACTS guidelines (2), AVR received a Class IIb (Level of Evidence: C) recommendation for patients with low LVEF, LF-LG AS, and no LV flow reserve. Given that operative risk for open heart surgery is generally very high in absence of flow reserve, transcatheter AVR (TAVR) could provide a valuable alternative in these patients, although the rates of morbidity and mortality may be higher than in patients with normal flow (43–45). Recent studies reported a greater and more rapid improvement of LVEF in patients treated by TAVR than those treated by surgical AVR (43,45). This advantage is believed to be related to better myocardial protection as well as to a lesser incidence of patient–prosthesis mismatch. In contrast, TAVR is associated with a higher incidence of paravalvular regurgitation, which may eventually have a negative impact on outcomes. Obviously, further randomized studies comparing surgery versus TAVR in LF-LG AS patients are warranted.

### Low-Flow, Low-Gradient AS With Normal LVEF

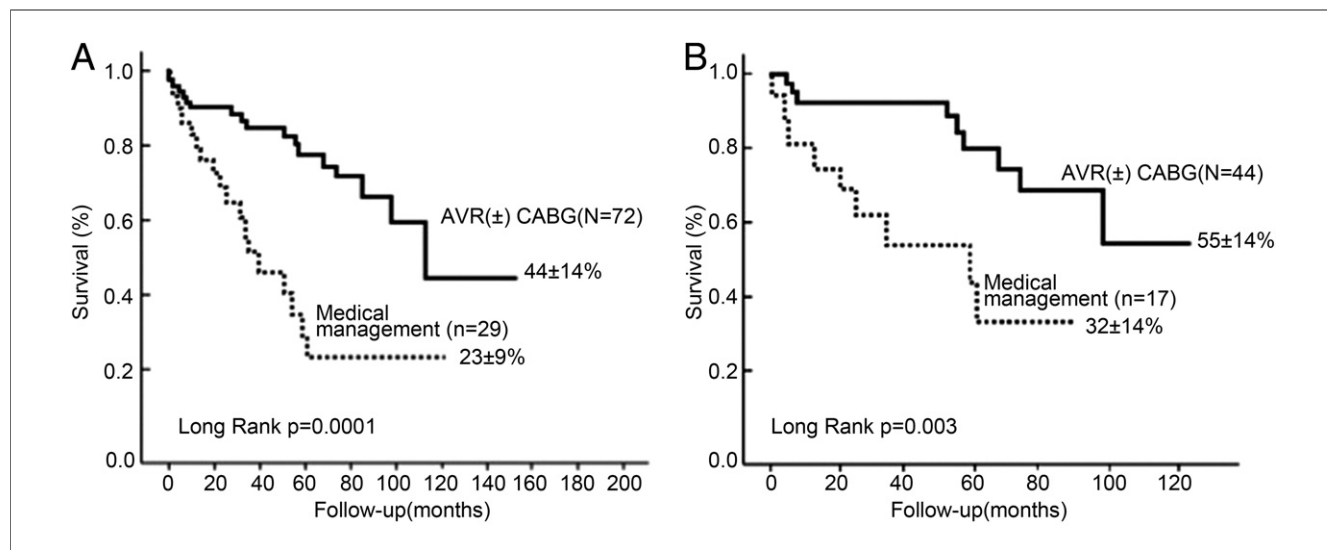
A previous paradigm was that patients with severe AS and preserved LVEF should necessarily have a high transvalvular gradient. However, Hachicha et al. (17) reported that a substantial proportion of patients with severe AS on the basis of EOA  $<1.0 \text{ cm}^2$  and/or indexed EOA  $<0.6 \text{ cm}^2/\text{m}^2$  might develop a restrictive physiology, resulting in low cardiac output (i.e., stroke volume index  $<35 \text{ ml}/\text{m}^2$ ) and lower than expected transvalvular gradients (i.e.,  $<40 \text{ mm Hg}$ )

despite the presence of a preserved LVEF (i.e.,  $\geq 50\%$ ); this clinical entity was labeled “paradoxical” LF-LG AS (Fig. 1) (17,18).

**Pathophysiology and clinical presentation of paradoxical LF-LG AS.** Paradoxical LF-LG AS shares many pathophysiological and clinical similarities with normal LVEF heart failure (17,18,20). The prevalence of these entities increases with older age, female gender, and concomitant presence of systemic arterial hypertension. Both entities are also characterized by a restrictive physiology, whereby LV pump function and thus stroke volume are markedly reduced despite a preserved LVEF. The distinctive features of this entity are: 1) more pronounced LV concentric remodeling and myocardial fibrosis both contributing to reduce the size, compliance, and filling of the LV (Fig. 1); and 2) a marked reduction in intrinsic LV systolic function, not evidenced by the LVEF, but rather by other more sensitive parameters directly measuring LV mid-wall or longitudinal axis shortening. In particular, longitudinal shortening is reduced to a larger extent in these patients due to more advanced fibrosis in the subendocardial layer (Fig. 5) (17,20–22,24,25,39,46). These findings are consistent with more advanced stages of both valvular and ventricular diseases despite the normal LVEF. Several studies reported that these patients have a worse prognosis than those with moderate AS or normal flow severe AS (17,24,47).

The distinctive mode of presentation of this entity often complicates the assessment of AS severity and therapeutic decision making. Patients with paradoxical LF-LG are characterized by similar or worse EOA and Doppler velocity index than patients with normal flow, but yet their gradients are lower than what would be expected in these circumstances (17,18). Moreover, the LF state may also cause these patients to have normal blood pressure levels despite a reduced systemic arterial compliance and/or an increased vascular resistance due to a phenomenon of pseudonormalization (17,18). Hence, both the valvular and arterial hemodynamic burdens may appear artificially low, whereas several studies reported that the level of global LV hemodynamic load, as measured by valvulo-arterial impedance ( $Z_{\text{va}}$ ), is consistently much higher than that observed in patients with normal flow severe AS (Fig. 5) (17,20–22,24,25,48,49).

**Pitfalls and differential diagnosis.** Patients with paradoxical LF-LG AS should always be distinguished from patients with severe AS based on EOA  $<1.0 \text{ cm}^2$  and LG (i.e.,  $<40 \text{ mm Hg}$ ) but normal flow (i.e., stroke volume index  $>35 \text{ ml}/\text{m}^2$ ) (18). In the latter, the features of restrictive physiology or of a marked increase in  $Z_{\text{va}}$  are conspicuously absent (18,24,25,50), and the discordance between EOA and gradient may be explained by one or more of the following (18,23): 1) measurement errors: that is, underestimation of stroke volume and AVA and/or underestimation of gradient; 2) small body size: AS severity may be overestimated in a patient with a small body surface area if EOA is not indexed for body surface area; and 3) inherent inconsistencies in the guidelines criteria



**Figure 6** Impact of AVR on Survival in Patients With Paradoxical LF-LG AS

The data for the (A) entire cohort (n = 101) and (B) propensity score matched patients (n = 61). AVR = aortic valve replacement; other abbreviations as in Figure 1. Reprinted from *The Annals of Thoracic Surgery*, Volume 91(6), Tarantini G, Covolo E, Razzolini R, et al. Valve replacement for severe aortic stenosis with low transvalvular gradient and left ventricular ejection fraction exceeding 0.50, 1808–1815, 2011, with permission from Elsevier.

(18,23,51): theoretical models have shown that a patient with normal transvalvular flow rate and an EOA of 1.0 cm<sup>2</sup> should be expected to have a mean gradient around 30 to 35 mm Hg rather than the 40 mm Hg cutoff value given in the guidelines (1,2).

Notwithstanding measurement errors, the distinction between the two conditions is important given that, among patients with EOA <1.0 cm<sup>2</sup>, patients with bona fide paradoxical LF-LG AS have the worse prognosis, whereas those with normal flow and LG have the best (18,24,50). Differential diagnosis can be made by indexing the EOA, by confronting measurements of stroke volume and EOA with those obtained by other independent methods (e.g., Teicholz, 2- or 3-dimensional volumetric methods using echocardiography or cardiac magnetic resonance imaging) (52), and by searching for the other typical features usually associated with paradoxical LF-LG AS.

Another caveat is that, as in patients with low-LVEF, LF-LG AS, the LF state may nonetheless conceal a pseudosevere stenosis. As in patients with low LVEF, measurements of EOA and gradient during DSE and of valve calcification by multidetector CT might prove useful in this regard. The clinical relevance of pseudosevere AS in the context of paradoxical LF-LG AS, however, remains to be determined and should be approached with circumspection, given that these patients nonetheless have a restrictive physiology with low cardiac output, high global LV hemodynamic load, and a poor prognosis (18).

**Therapeutic management and outcome. PARADOXICAL LOW-FLOW, LOW-GRADIENT AS.** In the current 2006 ACC/AHA guidelines (1,2), there is no specific recommendation for the management of patients with paradoxical LF-LG AS, given that this is a new entity first described in 2007

(17). A class IIa recommendation for AVR in the patients with paradoxical LF-LG and evidence of severe AS is however included in the recent ESC/EACTS guidelines (2). Nonetheless, the mode of presentation of this entity is most challenging given that the EOA is consistent with severe AS and thus constitutes a Class I indication for AVR when the patient is symptomatic, whereas the LG in association with a normal LVEF would rather suggest a moderate AS warranting conservative therapy. Accordingly, previous studies reported that the referral rate for surgery is 40% to 50% lower in patients with paradoxical LF-LG severe AS than in patients with normal flow severe AS, which is likely due to an underestimation of AS severity in light of the LG (17,19,48,53). However, these patients clearly have a better prognosis if treated surgically (Fig. 6) (14,18,48,53–55), although they could theoretically be at higher operative risk given their myocardial impairment and their increased risk of having patient–prosthesis mismatch due to their small LV cavity (18,22,24,25,48,56). The advantage of surgery is still present when other variables such as CAD are taken into account by performing propensity score–matched analysis (Fig. 6B). It remains to be determined if TAVR could not be a better alternative in these patients.

**NORMAL-FLOW, LOW-GRADIENT AS.** As mentioned previously, patients with preserved LVEF, normal flow, LG but small EOA (often between 0.8 and 1.0 cm<sup>2</sup>) are generally patients with moderate-to-severe AS who have an EOA–gradient discordance due to an inherent inconsistency in the guidelines criteria and/or to a small body size. In a recent substudy of the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial, Jander et al. (50) reported that patients with

preserved LVEF and small EOA but LG had a similar prognosis compared with those with moderate AS. However, these patients were an heterogeneous group, likely comprising without distinction patients with bona fide paradoxical LF AS and patients with normal-flow, LG AS in conjunction with measurement error, small body size, and/or inconsistencies due to the guidelines criteria (57). Moreover, the weighing of each entity within the whole group could have influenced the results given that, among patients with EOA  $<1.0$  cm<sup>2</sup>, the former were found to have the worse prognosis and the latter the best prognosis (24). These observations further underline the importance of making a meticulous differential diagnosis when seeing a patient with LG severe AS despite a preserved LVEF, and in particular, to validate the stroke volume measurements and to search for other features usually associated with paradoxical LF AS (i.e., small LV with restrictive physiology, unequivocally high Z<sub>va</sub>, and so on).

## Conclusions

LF-LG AS with either normal or reduced LVEF is among the most challenging of situations encountered in patients with valvular heart disease. DSE greatly aids risk stratification and clinical decision making in patients with low LVEF, LF-LG AS. Valve calcium quantification by multidetector CT and measurement of plasma BNP may also be helpful for the management of these patients, especially in those with no LV flow reserve in whom DSE is often inconclusive.

Paradoxical LF-LG AS despite normal LVEF is a recently described entity that has been shown to be associated with a more advanced stage of the disease and worse prognosis. Hence, it must be properly identified, and in particular, it must be differentiated from other confounding situations, including measurement errors, small body size, and discrepancies due to the inherent inconsistencies in the guideline criteria.

TAVR may eventually prove to be an attractive alternative to surgical AVR in both types of LF-LG severe AS, but this remains to be confirmed by future randomized studies.

## Acknowledgments

The authors would like to thank Marie-Annick Clavel, Mia Pibarot, and Ian Burwash for their assistance in the preparation of the paper.

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**Key Words:** aortic stenosis ■ flow ■ LV ejection fraction ■ stress echocardiography ■ valvular heart surgery.