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EDITORIAL COMMENT

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Management of Paradoxical Low-Flow, Low-Gradient Aortic Stenosis

Need for an Integrated Approach, Including Assessment of Symptoms, Hypertension, and Stenosis Severity*

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In 2007, we reported that a substantial proportion of patients with severe aortic stenosis may have a low flow (LF) (i.e., reduced stroke volume), and thus, often have a low transvalvular pressure gradient (LG), despite a preserved left ventricular ejection fraction (LVEF) (1). The 2014 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (2) classified this "paradoxical" LF/LG entity as a D3 stage of aortic stenosis, which is defined as an aortic valve area (AVA) of <1.0 cm^2, an indexed AVA of <0.6 cm^2/m^2, a mean gradient of <40 mm Hg, a LVEF of >50%, and a stroke volume index (SVi) of <35 ml/m^2. Previous studies (3-13) reported that patients with paradoxical LF/LG aortic stenosis have worse outcomes than patients with moderate aortic stenosis or with severe aortic stenosis and a high-gradient (HG) and that their outcomes improve with aortic valve replacement (AVR). Accordingly, the 2014 ACC/AHA guidelines included a Class IIa (Level of Evidence: C) recommendation for AVR in these patients: "AVR is reasonable in symptomatic patients who have low-flow, low-gradient severe AS who are normotensive and have a LVEF ≥50% if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms" (2). The main findings of the retrospective study by Tribouilloy et al. (14) published in this issue of the *Journal* were: 1) patients with LF/LG and preserved LVEF have similar outcomes as patients with moderate aortic stenosis or with severe aortic stenosis and a HG; and 2) AVR does not improve these patients' outcomes. The investigators should be commended for providing important data on the challenging subset of patients with paradoxical LF/LG aortic stenosis.

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OUTCOMES OF PATIENTS WITH PARADOXICAL LF/LG

Because the gradient is a squared function of flow, LF is often associated with a LG, even with severe stenosis. However, flow and gradient are not synonymous and provide complementary information; flow is of prognostic importance as a marker for reduced cardiac pump function and worse outcomes, whereas gradient is of diagnostic importance because a LG with a small AVA raises uncertainty about stenosis severity, and thus, about the indication for AVR. Consequently, several studies (8,15) and guidelines (2) recommend classifying patients with small AVA and preserved LVEF into 4 groups according to their levels of flow (i.e., SVi <35 or ≥35 ml/m^2) and gradient (i.e., <40 or ≥40 mm Hg), each with different diagnostic, prognostic, and therapeutic implications (**Table 1**): 1) normal-flow, low-gradient (NF/LG); 2) normal-flow, high-gradient (NF/HG); 3) LF/LG; and 4) low-flow, high-gradient (LF/HG).

The heart's primary function is pumping blood into the systemic circulation; thus, it appears logical to measure its efficiency using the SVi, which is

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TABLE 1 Outcome and Impact of Aortic Valve Replacement in Patients With Aortic Stenosis According to the Flow/Gradient Category

				Mortality/Event Rates and Benefit of AVR					
					Low-Gradient AS		High-Gradient AS		Group With The Highest Mortality/ Event Rate
First Author, Year (Ref. #)	No. of Patients	Mean Age, yrs	Endpoint	Moderate AS	NF/LG	LF/LG	NF/HG	LF/HG	
Barasch et al., 2008 (3)	Total: 215 HG: 168 LG: 47	77	2-yr mortality 2-yr mortality	—	Medical: 19% Post-AVR: 8.5%		Medical: 9.5%* Post-AVR: 3%		LG
Pai et al., 2008 (4)	LG: 52	76	5-yr mortality 5-yr mortality AVR benefit	—	Medical: 80% Post-AVR: 10% AVR S↑		—		N/A
Belkin et al., 2011 (5)	Total: 248 LG: 181 HG: 67	75	5-yr mortality AVR benefit	—	42% AVR S↑		45% AVR S↑		HG
Tarantini et al., 2011 (6)	LG: 102	77	3.5-yr mortality 3.5-yr mortality AVR benefit	—	Medical: 62% Post-AVR: 26% AVR S↑		—		N/A
Jander et al., 2011 (16)	Total: 619 MAS: 184 LG: 435	68	4-yr CV mortality	4.9%	7.8%		—	—	LG
Clavel et al., 2012 (7)	Total: 561 MAS: 187 LF/LG: 187 NF/HG: 187	69	1-yr mortality 1-yr CV mortality 5-yr mortality 5-yr CV mortality AVR benefit	4%* 2%* 19%* 9%* AVR NS	—	11% 9% 36% 26% AVR S↑	4%* 3%* 18%* 15%* AVR S↑	—	LF/LG
Lancellotti et al., 2012 (8)	Total: 150 NF/LG: 46 LF/LG: 11 NF/HG: 78 LF/HG: 15	70	2-yr cardiac event‡	—	17%†	73%	56%†	70%†	LF/LG
Ozkan et al., 2013 (9)	Total: 1,346 LG: 260	78	2.3-yr mortality AVR benefit	—	Medical: 53%; Post-AVR: 26% AVR S↑	AVR S↑	—		N/A
Mehrotra et al., 2013 (10)	Total: 113 MAS: 70 LF/LG: 38 NF/LG: 75	78	3-yr mortality	15%*	21%†	42%	—	—	LF/LG
Eleid et al., 2013 (12)	Total: 1,704 NF/LG: 352 LF/LG: 53 NF/HG: 1249 LF/HG: 50	77	2-yr mortality 2-yr mortality AVR benefit	—	Overall: 15%† Medical: 18%† AVR NS	Overall: 40% Medical: 56% AVR S↑	Overall: 18%† Medical: 33%† AVR S↑	Overall: 22%† Medical: 19%† AVR NS	LF/LG
Mohty et al., 2013 (11)	Total: 768 NF/LG: 172 LF/LG: 99 NF/HG: 386 LF/HG: 111	74	5-yr mortality 10-yr mortality AVR benefit	—	28%† 45%†	40% 68% AVR S↑	19%† 34%†	30%† 54%†	LF/LG
Maes et al., 2014 (17)	Total: 349 LG: 205 HG: 144	78	4-yr mortality 4-yr mortality AVR benefit	—	52% 52% AVR S↑	52%	68%† 69%* AVR S↑	71%†	LF/HG
Tribouilloy et al., 2014 (14)	Total: 809 MAS: 420 LF/LG: 57 NF/LG: 85 HG: 247	77	2-yr mortality 2-yr mortality 4-yr mortality 4-yr mortality AVR benefit	Overall: 18% Medical: 16% Overall: 28% Medical: 28% AVR NS	Overall: 16% Medical: 17% Overall: 29% Medical: 29% AVR NS	Overall: 31% Medical: 29% Overall: 35% Medical: 34% AVR NS	Overall: 19% Medical: 16% Overall: 29% Medical: 31% AVR S↑		LF/LG

*$p \le 0.05$ from LG group. †$p \le 0.05$ from LF/LG group. ‡Cardiac event: cardiovascular death or need for AVR motivated by the development of symptoms or left ventricular systolic dysfunction.

AS = aortic stenosis; AVR = aortic valve replacement; AVR NS = no significant benefit from AVR; AVR S↑ = significant survival benefit with AVR; CV = cardiovascular; HG = high-gradient; LF = low-flow; LG = low-gradient; MAS = moderate aortic stenosis; N/A = not applicable; NF = normal-flow.

routinely measured in echocardiographic or catheterization laboratories for calculation of cardiac output and AVA. As reported previously (1,3–8,10,11) and corroborated by Tribouilloy et al. (14), 30% to 50% of aortic stenosis patients with preserved LVEF have LF (SVi <35 ml/m^2). This is not necessarily surprising, because the aortic stenosis population is predominantly elderly, with frequent comorbidities (e.g., hypertension, coronary artery disease, atrial fibrillation, pronounced LV concentric hypertrophy, mitral regurgitation, etc.) that may all contribute to reduce SV. Accordingly, in the majority of previous studies (1,3–8,10–13), patients with LF had worse symptomatic status and prognosis. Moreover, compared with patients with moderate aortic stenosis and NF/LG or NF/HG aortic stenosis, those with LF/LG generally have a higher risk of cardiac events, all-cause mortality, and cardiovascular mortality (**Table 1**).

However, a few studies (16,17), including the one by Tribouilloy et al. (14), found similar prognoses for patients with LF/LG and those with moderate, NF/LG, or NF/HG aortic stenosis (**Table 1**). These discrepancies among studies underline the point that LF/LG aortic stenosis is a heterogeneous subset that includes patients with measurement errors, patients with small body size, and patients with bona fide paradoxical LF/LG. In the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) (16), which included only asymptomatic patients with mild-to-moderate aortic stenosis, 70% of patients had LF (vs. <50% in other studies), which suggested a SVi underestimation and LF overestimation in a significant proportion of patients. In the study by Tribouilloy et al. (14), the proportions of LF and LF/LG were similar to previous studies (1,3–13). However, a single group (HG aortic stenosis) included NF/HG and LF/HG patients, making the impact of LF versus LG on outcomes difficult to delineate. In univariable analysis, mortality at 2 years was 2-fold higher in the LF/LG group than in the other 3 groups (**Table 1**), although this was not statistically significant. This was likely related to the lack of statistical power, because the LF/LG group had only 57 patients with approximately 15 deaths. After adjustment for multiple variables, including several causative factors of LF (e.g., age, atrial fibrillation, coronary artery disease), patients with LF/LG had outcomes similar to those with moderate aortic stenosis or NF/LG, and better outcomes than those with HG aortic stenosis. Because individual patients cannot be adjusted for age and other comorbidities, the multivariable models are less clinically relevant than the univariable analysis [Figure 1 of the Tribouilloy et al. paper (14)], which better reflects the patient's actual risk. These results clearly support LF/LG as a marker for increased risk of midterm mortality, as also shown in other studies (1,3–13).

Although Tribouilloy et al. did not report body mass index and obesity data (14), other baseline characteristics (i.e., 35% of patients with type-2 diabetes) suggest that obesity might have been more prevalent in the LF/LG aortic stenosis group. Obesity may lead to underestimation of SVi, and thus to misclassification of patients with NF into the LF group. Moreover, several studies reported an obesity paradox: a protective effect of a larger body mass index in the elderly population with aortic stenosis. Hence, obesity may have an important confounding effect, leading to underestimation of the impact of LF on outcomes.

The similar prognoses observed after multivariable adjustment in the LF/LG group versus the moderate aortic stenosis group (14) may result from a significant proportion of the patients with LF/LG having nonsevere stenosis. With low transvalvular flow, the forces applied against the valve cusps may not be sufficient to completely open an only mildly or moderately stenotic valve. In previous studies, 30% to 40% of patients with paradoxical LF/LG aortic stenosis had pseudosevere aortic stenosis (18–20). Hence, other diagnostic methods, such as low-dose dobutamine stress echocardiography or aortic valve calcium scoring by multidetector computed tomography (MDCT), are essential to confirm stenosis severity and rule out pseudosevere stenosis in patients with LF/LG with preserved LVEF. In the study by Tribouilloy et al. (14) (as in most previous studies), no systematic investigation confirmed stenosis severity in patients with LF/LG or NF/LG aortic stenosis.

IMPACT OF AVR ON OUTCOMES OF PATIENTS WITH PARADOXICAL LF/LG

Does AVR improve outcomes in patients with LF/LG aortic stenosis? The majority of studies have shown that AVR is associated with significant survival benefit in these patients (**Table 1**) (4–7,9,11–13,17), whereas Tribouilloy et al. (14) reported no benefit. However, very few (<10) patients in the LF/LG group underwent AVR, and with such limited statistical power, it is difficult to draw a definitive conclusion. In addition, 61% of the HG severe aortic stenosis group were symptomatic at baseline, and thus, had a class I indication for AVR (14). Furthermore, a large proportion of patients who were asymptomatic at baseline likely became symptomatic during follow-up, thus presenting an indication for AVR. However, only 53% of patients in the HG aortic stenosis group underwent AVR during follow-up. Underutilization of AVR in these symptomatic patients with severe aortic stenosis could result from the inclusion in the study of relatively old patients with several cardiovascular (and probably noncardiovascular) comorbidities. This could also explain the worse outcomes in the HG group.

The main limitation of most of the previously published studies was that they were nonrandomized, often retrospective, or ambispective. The only study comparing AVR versus conservative management in patients with paradoxical LF/LG aortic stenosis that used a randomized design was the post-hoc analysis of the PARTNER-I (Placement of Aortic Transcatheter Valve Trial) (21). In PARTNER-I, cohort B (inoperable patients), compared with conservative management, transcatheter AVR was associated with a major survival benefit in patients with LF/LG aortic stenosis and preserved LVEF. Moreover, in cohort A (patients at high operative risk), compared with surgical AVR, transcatheter AVR was associated with significantly better survival during the first year of follow-up. Further studies are needed to determine which patients with paradoxical LF/LG aortic stenosis would benefit from AVR and which type of AVR (surgical vs. transcatheter) should be used.

MANAGEMENT OF PATIENTS WITH PARADOXICAL LF/LG

When confronted with a patient with a small AVA (<1.0 cm^2), small indexed AVA (<0.6 cm^2/m^2), a low gradient (<40 mm Hg), a preserved LVEF (≥50%), and a low SVi (<35 ml/m^2), one should first rule out measurement errors and confirm that this is bona fide paradoxical LF/LG aortic stenosis, and not moderate aortic stenosis with an underestimated SVi and AVA or severe aortic stenosis with an underestimated gradient. The 2014 ACC/AHA guidelines (2) recommend consideration of AVR (Class IIa) in patients with LF/LG and preserved LVEF if they are symptomatic, normotensive, and have evidence of severe stenosis. The following algorithm for clinical decision-making addresses these key criteria.

STEP 1: IS THE PATIENT SYMPTOMATIC? If asymptomatic (confirmed by exercise testing), the patient can likely be managed conservatively. In Tribouilloy et al. (14), 44% of LF/LG patients were asymptomatic. If symptomatic, proceed to the second step.

STEP 2: IS THE PATIENT HYPERTENSIVE? If so, antihypertensive therapy should be initiated or optimized, and symptoms and echocardiographic parameters should be reassessed after normalization of blood pressure. In Tribouilloy et al. (14), 77% of the LF/LG group had a history of hypertension, and >50% had inadequately controlled blood pressure (systolic pressure >140 mm Hg). Hypertension may lead to decreased flow, and thus, to a decreased gradient, and may contribute to symptoms and adverse events. If the LF/LG pattern and symptoms persist after optimization of antihypertensive therapy, proceed to the third step.

STEP 3: IS THE STENOSIS SEVERE? Pseudosevere aortic stenosis, which may be present in 30% to 40% of LF/LG aortic stenosis patients (18–20), must be ruled out. Low-dose dobutamine stress echocardiography may be used (18), but may not be applicable and/or conclusive in a significant proportion of patients with paradoxical LF/LG aortic stenosis, particularly in those with restrictive LV physiology. Alternatively, true-severe versus pseudosevere aortic stenosis may be differentiated using quantification of aortic valve calcification by MDCT, by applying different cutpoints in women (>1,200 AU) versus men (>2,000 AU) (19,20).

The guidelines (2) do not address the situation of patients with small AVA and NF/LG. Several studies (8,10–13) reported better outcomes in these patients than in those with LF/LG or with HG, and that AVR generally did not improve their outcomes (**Table 1**). However, recent studies (19) suggested that a significant proportion of these patients might have hemodynamically severe stenosis. Hence, an approach including optimization of antihypertensive therapy and confirmation of stenosis severity with additional diagnostic tests should probably be considered in a symptomatic patient with NF/LG.

CONCLUSIONS

Paradoxical LF/LG aortic stenosis is a challenging, heterogeneous clinical entity that requires special attention and further studies. Collectively, published studies (**Table 1**) support the guidelines' recommendation (2) that AVR is reasonable in symptomatic and normotensive patients with paradoxical LF/LG if the stenosis is truly severe and the likely cause of symptoms.

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