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SCIENTIFIC EDITORIAL

Aortic prosthesis-patient mismatch in patients with paradoxical low flow severe aortic stenosis: A dreadful combination



Le *mismatch* patient-prothèse aortique chez les patients avec sténose aortique à bas débit paradoxal : une combinaison tragique?

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The existence of low flow in patients with severe aortic stenosis and normal left ventricular ejection fraction (LVEF), commonly called "paradoxical low flow" (PLF-AS), was first described in 1997 by Hachicha et al. [1] in a group of patients with severe aortic stenosis on the basis of aortic valve area (AVA) < 1.0 cm² and/or indexed AVA < 0.6 cm²/m². These patients usually have lower trans aortic mean pressure gradients (< 40 mmHg) despite the presence of preserved LVEF (≥ 50%). They also develop a restrictive physiology, resulting in low cardiac output (stroke volume index < 35 mL/m²). PLF-AS is, in fact, present typically in elderly patients, and is characterized by a small, calcified aortic annulus and pronounced concentric remodeling, resulting in a small ventricular cavity and severe diastolic dysfunction with elevated left ventricular (LV) filling pressures. Several studies have also shown a depressed LV systolic longitudinal strain despite a LVEF > 50% [2,3] and advanced myocardial fibrosis (as identified by cardiac magnetic resonance imaging) [4]. However, PLF-AS remains a controversial entity in terms of its prevalence, outcome and management [2,5].

Using echocardiography, PLF-AS was initially found in approximately 30% of patients with severe aortic stenosis [1]. However, Minners et al. [6] reported that echocardiography, when compared with cardiac catheterization, slightly overestimates the prevalence of low flow in patients with aortic stenosis. Following this finding, multiple retrospective or prospective studies in symptomatic or asymptomatic patients found a slightly lower

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prevalence when taking into account patients with aortic stenosis with low flow, and low gradient and preserved LVEF, ranging from approximately 10% to 20% [2,5,6], using either echocardiography or the invasive catheterization method for assessing stroke volume, AVA and trans aortic mean gradients.

The main issue when assessing patients with PLF-AS is to confirm the severity of aortic stenosis and recognize the potential pitfalls that may affect its evaluation, namely:

- potential errors in measurement (left ventricular outflow tract diameter, left ventricular outflow tract, or aortic time-velocity integral);
- the presence of other significant valvular disease;
- the presence of atrial fibrillation during echocardiography.

The other possible pitfall of PLF-AS is a borderline moderate to severe aortic stenosis due to the inconsistencies in guidelines between gradients and AVA cut-offs [6] (i.e. 1 cm^2 corresponds to 30 mmHg gradients instead of the classical 40 mmHg cutoff).

Outcome and therapeutic issues in PLF-AS

Controversy exists regarding the outcome of patients with PLF-AS: some authors found it may increase the risk of short- and long-term overall mortality [3,5,7], whereas others found similar outcomes to those in patients with moderate aortic stenosis [8]. Herrmann et al. [4] reported a post-hoc analysis of the prospective Placement of Aortic Transcatheter Valves (PARTNER) trial, showing that patients with aortic stenosis undergoing transcatheter aortic valve replacement (TAVR) and with low flow have an independent higher risk of mortality, even after adjustment for LVEF and mean pressure gradient.

Overall, several studies have confirmed that patients with low flow and severe aortic stenosis despite a preserved LVEF are at advanced stage of their disease, and surgical or percutaneous aortic valve replacement (AVR) may be beneficial when compared with conservative management [9,10].

In the 2012 European guidelines, this form of severe aortic stenosis was given a class IIa recommendation for surgery in symptomatic patients. Very recently, the 2014 American College of Cardiology/American Heart Association guidelines recommended surgery (class IIa) after careful evaluation of aortic stenosis severity and controlled blood pressure [11].

However, we demonstrated in a previous study [5] that despite surgical management, patients with paradoxical low flow (PLF) exhibit poor survival after AVR compared to those with classic severe aortic stenosis with high flow ($> 35 \text{ mL/m}^2$).

Possible reasons for the poor outcome in patients with PLF after AVR

After surgical AVR, some patients may exhibit moderate or severe aortic prosthesis-patient mismatch (PPM), particularly in those who receive a small prosthesis. A moderate PPM is usually defined as an in-vivo effective orifice area

index between 0.65 and $0.85 \text{ cm}^2/\text{m}^2$, while a severe PPM occurs when the effective orifice area is $< 0.65 \text{ cm}^2/\text{m}^2$.

The presence of moderate or severe PPM is associated with higher gradients across the prosthesis that may lead to worse haemodynamics, especially in young patients and in those with significant LV dysfunction [12,13]. PPM is associated with less regression of LV hypertrophy and of the patient's symptoms [14]. In other words, patients with PPM, who suffered from severe aortic stenosis and chronic pressure overload for many years, may remain symptomatic because the pressure overload superimposed to the left ventricle is not removed completely after AVR. Moreover, in patients with preoperative classic low flow (i.e. associated with low LVEF), low gradient severe aortic stenosis, the presence of PPM is associated with higher mortality [15]. The prevalence and prognostic impact of PPM in patients with preoperative PLF are, however, unclear.

In a recent study from our group [16], we sought to assess for the first time the prevalence and long-term impact of moderate to severe postoperative PPM in patients with preoperative PLF-AS. The hypothesis was that PPM is not rare after AVR, and its occurrence in patients with severe aortic stenosis and low flow despite preserved LVEF is associated with decreased survival. The study involved 677 patients who had surgical aortic valve replacement with or without coronary artery bypass graft (CABG) surgery performed for severe aortic stenosis (aortic valve area measured by the invasive Gorlin method) and preserved LVEF. The patients were divided into four groups according to the presence or absence of PLF and the presence or absence of at least moderate PPM. Almost one-quarter of the patients died over a mean follow-up of more than 4 years. The 30-day postoperative mortality rate (ranging from 3% to 6%) was not significantly different among the four groups but the long-term survival rates were significantly reduced in the PLF-AS group versus the no PLF-AS group ($P=0.004$). Moreover, the long-term survival rate was significantly reduced in patients with PPM versus those without significant PPM ($P=0.01$). The group of patients with both PLF and PPM had a worse overall survival rate at 10 years compared with patients free of PLF and PLM (38% vs 70%, $P=0.002$). These results were confirmed by multivariable analysis when the stroke volume index and effective orifice area were entered either as continuous or categorical variables, with a 2.6-fold increase in long-term mortality versus the reference group. Thus, the main messages of this large catheterization-based study in patients with severe aortic stenosis and preserved LVEF undergoing AVR is that:

- the prevalence of low flow was present in one-quarter of this cohort study, a finding similar to previous studies [2,5,6];
- the prevalence of moderate to severe PPM was similar to that reported in previous studies (almost 50%) [17–19] and did not differ between patients with PLF-AS and those with normal flow;
- fifteen per cent of patients with preoperative low flow had at least moderate PPM following AVR;
- PLF-AS and PPM were independently associated with increased long-term mortality;

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