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The Prognostic Significance of Patient-Prosthesis Mismatch after Aortic Valve Replacement

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Patient-prosthesis mismatch (PPM) is a controversial issue in current clinical practice. PPM has been reported to have a negative impact on patients' prognosis after aortic valve replacement in several studies, showing increased all-cause and cardiac mortality. Moreover, a close relationship has recently been described between PPM and structural valve deterioration in biological prostheses. In patients at risk for PPM, several issues should be considered, and in the current era of cardiac surgery, preoperative planning should consider the different types of valves available and the various surgical techniques that can be used to prevent PPM. The present paper analyses the state of the art of the PPM issue.

Key words: 1. Aortic valve replacement
2. Patient-prosthesis mismatch
3. Prognostic significance

Introduction

Patient-prosthesis mismatch (PPM) was first reported by Rahimtoola [1] in 1978; it occurs when the effective orifice area (EOA) indexed for the body surface area (BSA) is less than that of a normal human valve. In patients undergoing aortic valve replacement (AVR), PPM is not a negligible issue, and its main consequence is to create high transvalvular gradients through a normally functioning prosthetic heart valve [2]. PPM has been reported to have a negative impact on patients' prognosis after AVR in several studies in terms of increased all-cause and cardiac mortality.

Definition of PPM

The EOA of the prosthesis indexed to the patient's BSA represents the only correct parameter for defining PPM [3,4]. The indexed EOA, or the EOA of the prosthesis divided by the patient's BSA, has consistently been reported to strongly correlate with postoperative transprosthetic gradients, as well as to predict adverse postoperative outcomes [5,6]. An indexed EOA ≤ 0.85 cm^2/m^2 is considered the threshold for PPM [2]. PPM is defined as moderate when the indexed EOA is ≤ 0.85 cm^2/m^2, and severe when the indexed EOA is ≤ 0.65 cm^2/m^2 [2,6-9]. Moderate PPM after AVR is not infrequent, occurring in 20%–70% of cases, whereas severe PPM occurs more rarely, in 2%–10% of cases [7-9]. As compared with mechanical valves, PPM appears to be more likely to occur with stented bioprosthetic valves because stented tissue valves are associated with a smaller EOA due to the space occupied by the supporting stents.

The clinical impact of PPM

PPM refers to the concept that too small of a pros-

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thesis in too large of a patient may cause abnormally high gradients, leading to potentially negative consequences similar to those that might occur in the presence of native aortic valve stenosis. Several studies using the indexed EOA have shown negative impacts of PPM on clinical outcomes. In fact, it seems to be associated with less improvement in symptoms (i.e., functional New York Heart Association [NYHA] class), less regression of the left ventricular mass, a higher rate of early mortality (in particular, when a low left ventricular ejection fraction is concomitantly present), and adverse events during long-term follow-up [10,11]. Although some studies have found increased mortality to occur only in the presence of a critical level of obstruction, such as a PPM ≤ 0.4 cm^2/m^2 [12,13], numerous recent studies also showed negative outcomes to be associated with lesser degrees of PPM.

The impact of PPM on in-hospital mortality after AVR may be particularly important, as the left ventricle is more vulnerable to increased stress and may be more sensitive to the increased afterload associated with PPM in the postoperative course. Rao et al. [7], in a study of 2,154 patients who underwent AVR, found that the 30-day mortality rate was significantly higher in patients with evidence of PPM than in patients without PPM (7.9% versus 4.6%, $p < 0.05$). Blais et al. [5], in a study performed on 1,266 patients that found a PPM prevalence of 38% (36% moderate, 2% severe), reported a 3% in-hospital mortality rate in patients without PPM, compared to rates of 6% in those with moderate PPM and 26% in patients with severe PPM ($p < 0.001$). The relative risk of mortality increased 2.1-fold in the presence of moderate PPM and 11.4-fold in the presence of severe PPM. In that series, the risk of mortality for every category of PPM was higher in the presence of a low left ventricular ejection fraction (<40%) than in the presence of a left ventricular ejection fraction ≥ 40%.

Del Rizzo et al. [14] published a study of 1,103 patients with porcine bioprosthetic valves. They reported a strong relationship between the indexed EOA and the extent of left ventricular mass regression following AVR. The mean regression of the left ventricular mass was 23% in patients with an indexed EOA >0.80 cm^2/m^2, compared with 4.5% in those with an indexed EOA ≤ 0.80 cm^2/m^2 ($p = 0.0001$). Pibarot et al. [10], following 392 patients during 7 years of follow-up after AVR, found that the cardiac index was significantly lower 3 years postoperatively only in patients with PPM ($p < 0.05$), and that the greatest deterioration was seen in presence of severe PPM, defined as an indexed EOA ≤ 0.65 cm^2/m^2. Moreover, PPM was associated with less postoperative improvement in NYHA functional class ($p < 0.009$).

Milano et al. [6], in 229 patients undergoing AVR with 19-mm and 21-mm St. Jude Medical standard mechanical prostheses, reported better freedom from cardiac events (mostly congestive heart failure) at 10 years in patients with nonsignificant PPM (indexed EOA >0.90 cm^2/m^2) than in those affected by moderate PPM (indexed EOA 0.60–0.90 cm^2/m^2) or severe PPM (indexed EOA ≤ 0.60 cm^2/m^2) ($p < 0.05$). All these results suggest that PPM may have a detrimental impact on the normalization of the left ventricular mass and function during follow-up after AVR. Moreover, Rao et al. [7], in a study of 2,981 patients who underwent AVR with stented bioprostheses, reported that the 12-year freedom from valve-related mortality was significantly lower in patients with an indexed EOA <0.75 cm^2/m^2 than in those with a larger indexed EOA (75%±5% versus 84%±2%, p=0.004). Cox regression analysis identified age (relative risk [RR], 1.06) and preoperative NYHA functional class (RR, 1.25) as independent predictors of overall mortality, whereas an indexed PPM <0.75 cm^2/m^2 was a predictor of valve-related mortality (RR, 1.46). As suggested by the authors, it is possible that PPM can have a negative impact on long-term survival because bioprosthetic valves progressively deteriorate due to the leaflets' calcification. Such deterioration becomes more common 8–10 years after implantation. Patients operated on with moderate or severe PPM already present a degree of obstruction of the left ventricular outflow. Any further decrease in EOA during follow-up could lead to more severe obstruction, with negative clinical impacts and the potential need for re-operation. In contrast, patients without PPM have a substantial valve EOA 'reserve' that could permit them to better tolerate the progressive reduction of the EOA that may occur as a consequence of the leaflets calcifying in case of bioprosthetic valves, or pannus overgrowth in case of mechanical prostheses.

Tasca et al. [15], in a study performed on 315 consecutive patients who underwent AVR either with biological or mechanical prostheses for pure aortic valve stenosis, reported that in the presence of PPM, defined by an indexed EOA <0.80 cm^2/m^2, the 5-year survival and cardiac event-free survival rates were 82%±3% and 75%±4%, in comparison with 93%±3% and 87%±4% if PPM was not present ($p<0.01$). Consequently, PPM was associated with a 4.2-fold increase in all-cause mortality and a 3.2-fold increase in cardiac adverse events. In that study, PPM was detected in 47% of patients. The authors clearly underlined that PPM should be avoided, or its severity reduced, through preventive strategies undertaken at the time of operation. Finally, Head et al. [16] evaluated the impact of PPM after AVR on mid-term and long-term survival in a meta-analysis of 34 observational studies comprising 27,186 patients. PPM, universally defined to be present at an indexed EOA value less than 0.85 cm^2/m^2, was present in 44% of patients (34.2% had moderate PPM and 9.8% severe, as defined by an indexed EOA <0.65 cm^2/m^2). Both moderate and severe PPM increased all-cause and cardiac-related mortality. On the contrary, in other studies, a strong relationship between PPM and long-term mortality was not found. Ruel et al. [17], in a study of 1,563 patients who underwent AVR and were followed for up to 15 years, did not find that PPM, defined as indexed EOA $\leq$ 0.80 cm^2/m^2, was significantly associated with all-cause mortality (hazard ratio [HR], 1.4; p=0.15); however, PPM was a significant predictor of congestive heart failure events (HR, 1.6; p=0.04). Hanayama et al. [18], in their study published in 2002 of 1,037 patients who underwent AVR with mechanical or biological prostheses, found no significant relationship between severe PPM and regression of left ventricular hypertrophy or a negative impact on mid-term survival. However, follow-up data were limited to 7 years, many patients had a higher abnormal left ventricular mass index during follow-up, and freedom from NYHA class III–IV at 6 years was less than 80%.

Because PPM is associated with adverse outcomes, it is important to take into consideration preventive strategies to avoid it, such as (1) calculating the BSA from patients' body weight and height; (2) identifying the minimal EOA that the implanted prosthesis must have to avoid PPM (i.e., if the BSA is 1.6 m^2, the minimal EOA of the prosthesis should be calculated on the basis of the cut-off of the PPM, or 1.6 m^2 multiplied by 0.85 cm^2/m^2=1.36 cm^2); and (3) verifying that the published reference value of EOA for the model and size of prosthesis to be implanted meets the criteria to avoid PPM (i.e., >1.36 cm^2 in the example given above).

If the size of a type of prosthesis does not meet the requirements for avoiding PPM, it is necessary to use another prosthesis with a better haemodynamic profile (e.g., mechanical prostheses or different models of biological prostheses) or to perform an aortic root enlargement to implant a larger prosthesis, although with a such surgical strategy, concern remains whether a more complex procedure may increase the operative risk.

Kim et al. [19], in a study performed on 627 patients undergoing AVR, showed that annular enlargement, despite being associated with a prolonged surgical time and an increased risk of operative mortality, was associated with lower aortic valve mean and peak gradients than were observed in patients showing severe PPM (38/25 versus 72/42 mm Hg; p=0.02 and 0.06, respectively). The choice of newer-generation biological prostheses characterized by improved designs and haemodynamic performance (i.e., lower transprosthetic postoperative gradients) can substantially decrease the incidence of moderate or severe PPM at the time of prosthesis valve implantation.

Flameng et al. [20], in a recently published study of 648 patients (mean age, 74±5 years) who underwent AVR with biological valves, analysed the occurrence of structural valve degeneration (SVD) at 10 years of follow-up. SVD was diagnosed in 12.6% of patients; PPM and the absence of antimineralization treatment of the biological valve were found to be independent predictors of SVD. In detail, patients receiving a non-treated valve showed a freedom from SVD at 10 years of follow-up of 70%±4.3% versus 90.9%±3.6% in those receiving a treated valve ($p<0.0001$). Patients with PPM who received a non-treated valve showed a freedom from SVD at 10 years of only 59.8%±7.0% versus 88.7%±3.6% in patients with PPM who received a treated valve ($p<0.0001$). In patients without PPM, the corresponding values were 78.0%±4.3% and 92.7%±3.4% for non-treated versus treated valves, respectively (p=0.01).

The optimization of haemodynamic performance to prevent PPM and improvements in durability have revitalized the use of bioprostheses in the last decade. Newer, third-generation bioprostheses guarantee a much higher performance than previous models, because the fixation process is performed at physiological pressure instead of at high or zero pressure on the valve leaflets and due to the anti-calcification treatment. Examples include the Carpentier-Edwards Perimount Magna (Edwards Life Sciences, Irvine, CA, USA), Crown (Sorin, Saluggia, Italy), and St. Jude Trifecta (St. Jude Medical Inc., St. Paul, MN, USA) valves.

In a recent multicentre study performed by Bavaria et al. [21], the Trifecta valve was shown to be a unique pericardial bioprosthesis that provided excellent haemodynamic performance along with ease of implantation. In that study, the Trifecta bioprosthesis was implanted in 1,014 patients (mean age, of 72.5 years). Early (≤30 days) mortality occurred in 18 patients (1.8%), and there were 23 late (≥31 days) deaths. There were no cases of early valve thrombosis, endocarditis, or clinically significant haemolysis, and 5 late valve explantations were performed, of which only 1 was due to SVD. At the time of discharge, the average mean gradients ranged from 9.3 to 4.1 mm Hg and the EOA ranged from 1.58 to 2.50 cm^2 for valves sized 19 to 29 mm.

Fiegl et al. [22] conducted a matching analysis of the haemodynamic performance of the Trifecta and the Carpentier-Edwards Perimount Magna Ease bioprostheses (Edwards Life Sciences). After AVR, the Trifecta valve showed lower mean pressure gradients in the early postoperative period and at 1 year, as well as a higher EOA and indexed EOA postoperatively. No significant differences were detected between the 2 types of new bioprostheses with regard to left ventricular mass regression and PPM occurrence. These findings were also similar in 2 recent publications by Minardi et al. [23] and Modi et al. [24]. Early haemodynamic performance of the third-generation St. Jude Trifecta aortic prosthesis (St. Jude Medical Inc.) was also investigated in a systematic review performed by Phan et al. [25]. In this meta-analysis, a total of 13 studies and 2,549 patients undergoing AVR with this prosthesis were included. The most frequent valve sizes implanted were 21 and 23 mm (71.3% of patients). The rates of 30-day mortality, cerebrovascular accidents, and acute kidney injury were 2.7%, 1.9%, and 2.6%, respectively. After implantation, the pooled mean gradient decreased to 9.2 mm Hg, whereas discharge EOA increased to +1.8 cm, compared with preoperative parameters. Most patients had satisfactory or nonsignificant PPM, and only 2.7% had severe PPM. That systematic review demonstrated that in a short-term period of follow-up, the St. Jude Trifecta prosthesis (St. Jude Medical Inc.) provided excellent safety and haemodynamic outcomes with satisfactory mean gradient and EOA values. Long-term follow-up and randomized controlled trials are clearly warranted to confirm these early results.

In an elegant study on the fluid-dynamic results obtained by comparing 4 pericardial aortic bioprostheses (Magna Ease, Mitroflow, Trifecta, and Soprano-Armonia) implanted in small porcine aortic roots, Tasca et al. [26] reported that Trifecta implantation, in comparison with the other implanted bioprostheses, led to better EOA (2.3±0.3 versus 1.57±0.2 [Magna Ease], 1.77±0.2 [Mitroflow], and 1.75±0.2 cm^2 [Soprano-Armonia]; $p < 0.001$), lower mean gradients (6.1±2 versus 13.2±3, 10.2±3, and 9.6±2 mm Hg, respectively; $p < 0.001$), and lower valve resistance (33±10 versus 69±16, 55±13, and 51±11 dyn·s/cm5, respectively; $p < 0.001$), showing that the bioprostheses with the pericardium outside the stent (i.e., the Trifecta valve) were more efficient, thus preventing PPM and structural valve deterioration. Clearly, although there may be haemodynamic differences, no studies have conclusively shown that one type of biological valve is superior to others with regard to hard clinical endpoints.

Conclusion

The current knowledge suggests that moderate PPM should be avoided in patients with certain conditions, such as depressed left ventricular function, severe left ventricular hypertrophy, age <70 years, an athletic lifestyle, and concomitant mild or moderate mitral regurgitation not addressed by surgery, as well as in elderly patients seeking an enhanced quality of life. Severe PPM should be avoided in all cases.

The use of newer, better-performing, and easy-to-implant third-generation biological prostheses can significantly decrease the occurrence of PPM, without

any increased operative risk related to the requirement for more demanding and complex surgical techniques for annulus and aortic root enlargement.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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