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

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Introduction

Patient-Prosthesis Mismatch (PPM) represent a controversial issue in current clinical practice. The negative impact of PPM on patient prognosis after aortic valve replacement has been reported in several studies showing increased all-cause and cardiac mortality. Moreover, it has been recently described the relationship between PPM and structural valve deterioration of biological prostheses. In patient at risk for PPM several issues should be considered, and in the current era cardiac surgery the preoperative planning should consider the different type of valve available and the different surgical technique that could be used to prevent it. The present editorial analyse the state of the art in term of PPM.

Definition of PPM

The prosthesis EOA indexed to patient's BSA represent the only right parameter for a good definition of PPM [1-4]. Indexed EOA, i.e. the EOA of the prosthesis divided by patient's BSA, has consistently been reported to strongly correlate with postoperative trans-prosthetic 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]. Of note, moderate PPM is defined when indexed EOA is equal to or less than 0.85 cm^2/m^2, severe PPM in presence of an indexed EOA is equal to or less than 0.65 cm^2/m^2 [2,6-9]. Moderate PPM after AVR is not negligible, ranging from 20% and 70%, whereas the incidence of severe PPM occurs more rarely, from 2% and 10% [7-9]. As compared with mechanical valves, PPM appears to be more likely with stented biological prosthetic valves, because of the stented tissue valves are associated with a smaller EOA due to the space occupied by the supporting stents.

Clinical Impact of PPM

PPM is the concept that too small prosthesis in too large patient may determine abnormal high gradients leading to potentially negative consequences such as might occur in presence of a native aortic valve stenosis. Several studies using the indexed EOA have shown the negative impact of PPM on clinical outcomes. In fact, it seems to be related with less improvement in symptoms, i.e. functional class, lesser regression of left ventricular mass and with an higher rate of early mortality in particular when left ventricular low ejection fraction is associated, i.e. left ventricular ejection fraction <40%, and adverse events during long-term follow-up [10-11]. Although some studies [12-13] suggest that an increased mortality can occur only in presence of a critical level of obstruction, i.e. PPM < 0.4 cm^2/m^2, numerous recent studies showed a negative outcome also in presence of a less degree of PPM.

The impact of PPM on in hospital mortality after aortic valve replacement may be particularly important: the left ventricle is more vulnerable to increased stress and may be more sensitive to increase after load associated with PPM in the postoperative course. Rao and co-workers [7] in 2,154 patients undergone AVR found a 30-day mortality significantly higher in patients with evidence of PPM in comparison with patients without PPM (7.9% *vs* 4.6%, p<0.05). Blais et al. [5] in a study performed on 1,266 patients, with a PPM prevalence of 38% (36% moderate, 2% severe), reported a 3% in-hospital mortality in patients without PPM, 6% in those with moderate PPM, 26% in patients with severe PPM (p<0.001); the relative risk of mortality was increased 2.1-fold in presence of moderate PPM, 11.4-fold in presence of severe PPM. In this series, the risk of mortality for every category of PPM was higher low EF (<40%) as compared with EF > 40% (not significant PPM 2.7 *vs* 1.0; moderate PPM, 7.1 *vs* 1.8, severe PPM, 77.1 *vs* 11.3). Del Rizzo et al. [14] published a study on 1,103 patients with porcine bioprosthetic valve and they reported a strong relationship

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between the indexed EOA and the extent of left ventricular mass regression following aortic valve replacement. There was a mean regression of the left ventricular mass of 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 a 7-year follow-up after AVR, found that cardiac index decreased significantly after 3 years from operation only in patients with PPM (p<0.05), and that the greatest deterioration was seen in presence of a severe PPM, i.e. indexed EOA < 0.65 cm^2/m^2. Moreover, PPM was associated with less postoperative improvement of NYHA functional class (p<0.01). Milano et al. [6] in 229 patients subjected to aortic valve replacement with 19-mm and 21-mm St. Jude Medical standard prostheses reported a 10-year better freedom from cardiac events (mostly congestive heart failure) in patients with not significant PPM (indexed EOA > 0.90 cm^2/m^2) in comparison with those affected by moderate PPM (indexed EOA 0.60 cm^2/m^2 to 0.90 cm^2/m^2) and severe PPM (indexed EOA < 0.60 cm^2/m^2) (p<0.05). All 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 and Co-workers [7] in 2,981 patients who underwent AVR with stented bioprostheses reported a 12-year freedom from valve-related mortality significantly lower in patients with an indexed EOA <0.75 cm^2/m^2 in comparison with those with a larger indexed EOA (75 + 5% *vs* 84 + 2%, p=0.004). Cox Regression analysis identified age (RR:1.06) and preoperative NYHA functional class (RR:1.25) as independent predictors of overall mortality, whereas PPM, i.e. EOA/BSA <0.75 cm^2/m^2 (RR:1.46), as predictor of valve-related mortality. As suggested by the Authors it is possible that PPM can have a negative impact on long-term survival for the fact that bioprosthetic valves progressively deteriorate due to leaflets' calcification. This deterioration becomes more frequent 8 to 10 years after their implant. Patients operated on with a moderate or severe PPM already present a degree of the obstruction of the left ventricular outflow. Any further decrease in EOA during follow-up could lead to a more severe obstruction, with a negative clinical impact or need of re-operation. In contrast, patients without PPM have a substantial valve EOA "reserve" that could permit to better tolerate a progressive reduction of the EOA that may occur as a consequence of leaflets' calcification in case of bioprosthetic valves, or pannus overgrowth in case of mechanical prostheses. Tasca and co-workers [15] in a study performed on 315 consecutive patients subjected to AVR either with biological or mechanical prostheses reported that in presence of PPM, (indexed EOA <0.80 cm^2/m^2), at 5 years survival and cardiac event-free survival were 82 ± 3% and 75 ± 4%, in absence of PPM 93 ± 3% and 87 ± 4% (p<0.01). PPM was associated with 4.2-fold increase of all-cause mortality and 3.2-fold increase of cardiac adverse events. PPM in this study was detected in 47% of patients. The Authors clearly underlined that PPM should be avoided or its severity reduced with a preventive strategy 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 performed on 34 observational studies comprising 27,186 patients. PPM, as universally accepted at a value of indexed EOA less than 0.85 cm^2/m^2, was present in 44% of patients (34.2% presented a moderate PPM, 9.8% severe, i.e. indexed EOA <0.65 cm^2/m^2). Both moderate and severe PPM increased all-cause and cardiac-related mortality. The In other studies a strict relation between PPM and long-term mortality was not found. Ruel et al. [17] in 1,563 patients who underwent AVR and followed up to 15 years, did not find PPM, defined as indexed EOA ≤ 0.80 cm^2/m^2, significantly associated with all-cause mortality (HR:1.4, p=0.15), but, on the contrary, PPM was a significant predictor of congestive heart failure events (HR:1.6, p=0.04). Hanayama et al. [18] in their paper published in 2002, in 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 at 7 years, a great number of patients during follow-up remained with a higher abnormal left ventricular mass index, freedom from III to IV NYHA class at 6 years was less than 80%.

The choice of newer generation biological prostheses characterized by improved design and hemodynamic performance (i.e., lower trans-prosthetic postoperative gradients) can decrease substantially the incidence of moderate or severe PPM at the time of prosthesis valve implantation. Flameng and co-workers [19] in a recently published study on 648 patient (mean age 74 ± 5 years) who underwent AVR with biological valves analyzed the occurrence of Structural Valve Degeneration (SVD) at 10 years of follow-up. SVD was shown in 12.6% of patients. PPM and the absence of anti-mineralization treatment of the biological valve were recognized as independent predictors of SVD. In detail, patients receiving a non-treated valve show a freedom of SVD at 10 years follow-up of 70 ± 4.3% *vs* 90.9 ± 3.6% in those receiving a treated valve (p<0.0001). Patients having PPM and receiving a non-treated valve showed a freedom of SVD at 10 years of only 59.8 ± 7.0% *vs* 88.7 ± 3.6% in patients also having PPM but receiving a treated valve (p<0.0001). In patients not having PPM, the corresponding values were 78.0 ± 4.3% and 92.7 ± 3.4% for non-treated *vs* treated valves, respectively (p=0.01). The optimization of hemodynamic performance to prevent PPM ad the improvement of durability have revitalized the use of the bioprostheses in the last decade. Third-generation newer bioprostheses, i.e. Carpentier-Edwards Perimount Magna Ease (Edwards Life Sciences, Irvine CA) valve, Crown (Sorin, Saluggia, Italy) valve, and St. Jude Trifecta (St. Jude Medical Inc., St. Paul, MN) valve could guarantee a much higher performance than that observed by previous models. In a recent multi-center study performed by Bavaria et al. [20] the Trifecta valve results as an unique pericardial bioprosthesis that provides excellent hemodynamic performance while providing ease of implantation. In this study Trifecta aortic valve prosthesis was implanted in 1,014 patients (mean age of 72.5 years). Early (≤ 30 day) mortality occurred in 18 patients (1.8%), and there were 23 late (≥ 31 days) deaths. There were no early valve thrombosis, endocarditis, or clinically significant hemolysis, and 5 late valve explants, only one due to SVD. At the time of discharge, average mean gradients ranged from 9.3 mmHg to 4.1 mmHg and EOA ranged from 1.58 cm^2 to 2.50 cm^2 for valve sizes 19 mm to 29 mm. Fiegl K et al. [21] matched the hemodynamic performance of the Trifecta and the Carpentier-Edwards Perimount Magna Ease valves. The Trifecta aortic valve showed after AVR lower mean pressure gradients in the early postoperative period and at 1 year, as well as higher EOA and effective orifice area index postoperatively. No significant differences were detected in both types of new bioprostheses with regard to left ventricular mass regression and PPM occurrence. These findings were also similar in two recent publications, from Minardi [22] and from Modi [23]. Early hemodynamic performance of the third-generation St Jude Trifecta aortic prosthesis was also investigated in a systematic review performed by Phan K et al. [24]. 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-mm 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 mmHg, whereas discharge EOA increased to +1.8 cm, compared with preoperative parameters. Most patients had satisfactory not significant PPM, 2.7% only has a severe PPM. This systematic review demonstrated that in a short-term period of follow-up this prosthesis provided excellent safety and hemodynamic outcomes with satisfactory mean gradient and EOA mean values. In a study performed on the fluid-dynamic characteristics obtained comparing four pericardial aortic bioprostheses (Magna Ease, Mitroflow, Trifecta, and Soprano-Armonia) implanted in small porcine aortic roots, Tasca and co-workers [25] reported after Trifecta implantation better EOA (2.3 ± 0.3 *vs* 1.57 ± 0.2 [Magna Ease], 1.77 ± 0.2 [Mitroflow], 1.75 cm^2 ± 0.2 cm^2 [Soprano-Armonia]), lower mean gradients (6.1 ± 2 *vs* 13.2 ± 3, 10.2 ± 3, 9.6 ± 2 mmHg), lower resistance values (33 ± 10 *vs* 69 ± 16, 55 ± 13, 51 ± 11 dyn^*s/cm^5) ($p<0.001$, for all comparisons). The authors showed that a biological aortic valve with the pericardium outside the stent (i.e., the Trifecta valve) is more efficient, thus likely preventing PPM and SVD. In conclusion, the use of a newer better performing and at easy implantation bioprostheses can significantly decrease the occurrence of PPM, without any increased operative risk.

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