ASWAN HEART CENTRE
SCIENCE & PRACTICE SERIES
A Qatar Foundation Academic Journal

OPEN ACCESS

Review Article

Prosthesis-patient mismatch

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ABSTRACT

Prosthesis-patient mismatch (PPM) is present when the effective orifice area of the inserted prosthetic valve is too small in relation to body size. Its main hemodynamic consequence is to generate higher than expected gradients through normally functioning prosthetic valves. The purpose of this review is to present an update on the present state of knowledge with regards to diagnosis, prognosis and prevention of PPM. PPM is a frequent occurrence (20%–70% of aortic valve replacements) that has been shown to be associated with worse hemodynamics, less regression of left ventricular hypertrophy, more cardiac events, and lower survival. Moreover, as opposed to most other risk factors, PPM can largely be prevented by using a prospective strategy at the time of operation.

Keywords: heart valve disease, heart valve prosthesis, hemodynamics, Doppler-echocardiography, aortic stenosis

DOI: 10.5339/ahcsps.2011.7

Published: 14 April 2011

QSCIENCE.com
Member of Qatar Foundation

Cite this article as: Pibarot P, Dumesnil JG. Prosthesis-patient mismatch, *Aswan Heart Centre Science & Practice Series* 2011:7 doi: 10.5339/ahcsps.2011.7

INTRODUCTION

Valve prosthesis-patient mismatch (PPM) was first described in 1978 by Rahimtoola as follows: "Mismatch can be considered to be present when the effective prosthetic valve area, after insertion into the patient, is less than that of a normal human valve" [1]. However, for all practical purposes, almost all types of valve replacement have an have a effective valve area that is less than that of a normal human valve and nowadays, the term PPM is more appropriately applied to situations where the effective orifice area (EOA) of the prosthesis is too small in relation to the patient's body size resulting in an abnormally high postoperative gradient [1–4]. The rationale behind this definition is that the EOA must be proportionate to flow requirement for gradients to remain low. At rest, the transvalvular flow, Q, is largely related to cardiac output, which in turn is determined by the patient's body surface area (BSA). The unique relation between gradient and flow is best exemplified by the following hydraulic equation:

$$TPG = \frac{Q^2}{k \times EOA^2} \quad (1)$$

whereby it can be seen that the transvalvular pressure gradient (TPG) is directly related to the square of transvalvular flow (Q) and inversely related to the square of the valve EOA, k being a constant. It should be emphasized that the EOA, is a physiological parameter that represents the minimal cross-sectional area occupied by the transprosthetic flow jet and its size in relation to the geometric orifice area (GOA) of the prosthesis may vary considerably, depending on flow conditions and valve prosthesis morphology (Fig. 1).

For instance, based on the aforementioned equation and assuming a normal cardiac index of 3 litres/min/m^2, the implantation of a prosthesis with an EOA of 1.3 cm^2 in a patient with a BSA of 1.5 m^2 will theoretically result in a mean TPG of approximately 13 mmHg, whereas the mean TPG will theoretically be 28 mmHg if the same prosthesis is implanted in a patient with a BSA of 2.25 m^2 (Table 1). Moreover, this difference in TPGs between these two patients would even be more important during exercise, given that gradients are a square function of flow.

IDENTIFICATION OF PPM

Consistent with the aforementioned definition, the parameter that has been used to characterize PPM is the indexed EOA, i.e. the EOA of the prosthesis divided by the patient's BSA. It should be emphasized that, for all practical purposes, the indexed EOA as measured *in vivo* postoperatively, is the only parameter that can consistently be correlated with postoperative gradients as well as clinical outcomes. It should be emphasized that, in contrast to EOA, the GOA is a static manufacturing specification based on the *ex vivo* measurement of the diameter of the prosthesis and that the criteria used for its measurement may differ from one type of prosthesis to the other. Hence, by definition, the GOA always overestimates the EOA but, for instance, to a much larger extent in the case of a bioprosthesis than in the case of a mechanical prosthesis (Fig. 1) [5,6]. It follows that the relation between GOA and EOA may vary extensively depending on the type and size of prosthesis as well as on flow conditions and, based on these considerations as well as on Eq. (1), it is not surprising that the indexed GOA bears little or no relation to postoperative gradients [7–9]. Also, although homografts and pericardial valves may have similar values for indexed GOA, the observed values for peak and mean gradients are more or less two-fold in the pericardial valves as compared to the homografts [8]. Likewise, because of different flow conditions, the indexed EOAs calculated based on the manufacturer's *in vitro* data are generally too optimistic and correlate poorly with postoperative

Table 1. Theoretical comparison of mean transvalvular pressure gradient in five hypothetical patients receiving the same prosthetic valve but having different body surface areas

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5
Body surface area (m^2)	1.5	1.75	2.0	2.25	2.5
Cardiac Output (L/min)	4.5	5.25	6.0	6.75	7.5
Valve effective orifice area (m^2)	1.3	1.3	1.3	1.3	1.3
Mean pressure gradient (mmHg)	13	17	22	28	35

For the purpose of this simulation, mean pressure gradient was calculated assuming a cardiac index of 3 L/min/m^2, a heart rate of 65 bpm, and a systolic ejection time of 300 ms. (Reproduced and modified with permission from [105]).

gradients [10]. Since GOAs and *in vitro* EOAs bear little relation with postoperative hemodynamics, it should thus be of no surprise that, in contrast to the indexed EOA, most studies using these parameters to identify PPM show that they also bear little or no relation with adverse clinical outcomes [8,11–14]. In this context, it is unfortunate that some authors still do not make the distinction between studies based on the indexed GOA or the indexed EOA calculated with *in vitro* EOAs and those based on the indexed *in vivo* EOA and thus conclude that the clinical implications of PPM still remain unclear and controversial [15]. Indeed, there is now consensus that the indexed *in vivo* EOA is the only valid parameter to predict postoperative gradients or adverse clinical outcomes [16].

In view of the above, the following points need to be emphasized: (1) it is not the size (labeled size or GOA) of the prosthesis that matters but rather its EOA and, also, in whom you implant it; (2) the only parameter yet demonstrated as being valid to define PPM is the indexed EOA and (3) the indexed GOA and labeled valve size cannot be used to identify PPM or characterize its severity.

AORTIC PPM

Fig. 2 shows that the relationship between the TPG and the indexed EOA is curvilinear and that gradients are increased exponentially when the indexed EOA is $\leq 0.8–0.9$ cm^2/m^2 . Based on this relationship, an indexed EOA ≤ 0.85 cm^2/m^2 is now widely accepted as the threshold for PPM in the aortic position [2,3,17–19] with values between 0.65 and 0.85 cm^2/m^2 being classified as moderate PPM and those below 0.65 cm^2/m^2 as severe PPM. It should be of no surprise that these values are very close to those utilized in the case of native aortic stenosis. Depending on studies, the reported prevalence of moderate PPM varies between 20 and 70% whereas that of severe PPM is between 2 and 11% [9,17–30]. As for native aortic stenosis, the impact of PPM on clinical outcomes increases with severity and the categorisation between moderate and severe PPM is thus essential when studying these phenomena. It should also be noted that the prevalence of severe PPM has had a tendency to decrease substantially over the last decade due to: (i) increased recognition and awareness that, notwithstanding associated conditions, severe PPM is invariably associated with adverse outcomes and that it should thus be avoided as much as possible, (ii) more widespread implementation of preventive strategies designed to avoid PPM (see below) and (iii) improved design and hemodynamic performance of newer generation prostheses.

MITRAL PPM

Similarly to native mitral valve stenosis, due to the lower pressure regimen, the threshold values for mitral PPM are higher than for aortic PPM. Hence, mitral PPM is considered moderate when the indexed EOA is $\leq 1.2–1.3$ cm^2/m^2 and severe when it is $\leq 0.9–1.0$ cm^2/m^2 [3,4,31]. Recent studies report that the incidence of mitral PPM is much higher than previously believed: 30–70% and 5–10% for moderate and severe PPM, respectively [32–37]. Awareness with regards to mitral PPM is more recent and preventive strategies more limited. As of yet, it is too early to determine to what extent it can be prevented.

CLINICAL IMPACT OF AORTIC PPM

There is now a strong body of evidence showing that aortic PPM is an important risk factor with regards to clinical outcomes including improvement in symptoms and functional class, regression of left ventricular hypertrophy, improvement in coronary flow reserve, both early and late mortality as well as adverse cardiac events.

LEFT VENTRICULAR (LV) HYPERTROPHY AND FUNCTION

In a study including 1,103 patients with a porcine bioprosthetic valve, Del Rizzo et al. found a strong and independent relation between the indexed EOA and the extent of LV mass regression following aortic valve replacement (AVR) [38]. In a smaller series, Tasca et al. also reported that the normalization of LV mass is negatively and independently influenced by PPM [24]. Whereas some authors have found that the persistence of PPM results in lesser regression of LV hypertrophy, others have reported that patients with PPM and/or small prostheses could exhibit significant reductions in LV mass and, on this basis, have concluded that PPM was not an important an issue [23,39–41]. Interestingly, Tasca et al. found that patients with PPM nonetheless exhibit LV mass regression after operation but that the extent of such regression varies considerably from one patient to the other and

can be largely related to the extent of valve EOA increase after operation [42]. These findings remind us of the following important pathophysiological concepts [42,43]: (1) even in the presence of PPM, surgery normally results in improved hemodynamics, the extent of which can be quite important; (2) a more optimal result can be expected if PPM is completely avoided and (3) In analyzing the results of AVR, it is important to remember that the relationship between gradients and the indexed EOA is curvilinear and that the implications for a given patient will be directly related to his original and final positions on the indexed EOA-gradient curve (Fig. 2). Moreover, it should be emphasized that many patients operated on for aortic stenosis have decreased arterial compliance with concomitant hypertension resulting in an increased overall LV hemodynamic load, which is only partially relieved by the operation [44]. Hence, such patients are likely to have more severe concentric LV hypertrophy that will only partially regress after operation due to the persistence of a partially increased LV load caused by hypertension. Also, for a similar hemodynamic load, patients with hypertension and/or metabolic syndrome will be likely to have more interstitial myocardial fibrosis thus contributing to a

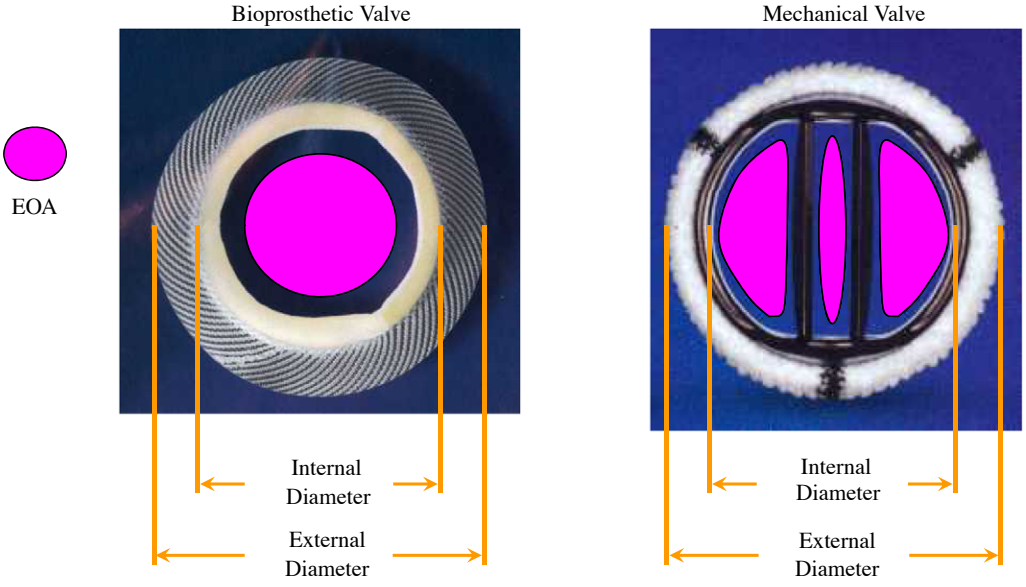

Figure. 1 View of a bioprosthesis and a bileaflet mechanical valve with the leaflets in a fully open position. The area highlighted in green represents the effective orifice area (EOA) (Reproduced and modified from Cardiac Surgery Today with permission from Remedica Publishing [105].

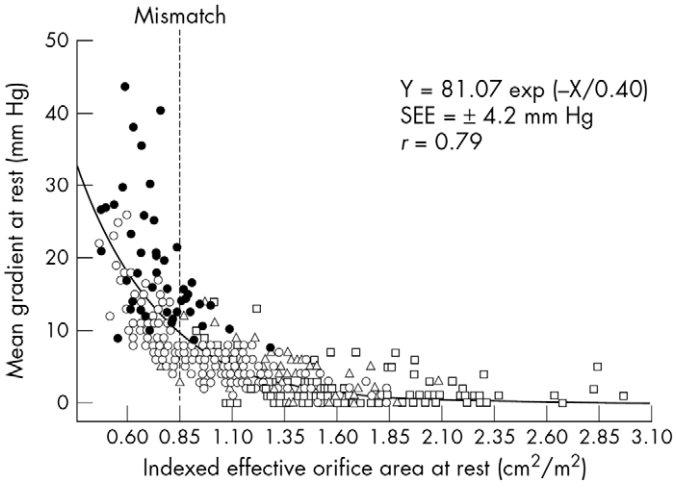

Figure. 2 Correlation between mean transvalvular gradient and indexed effective orifice area in patients with a stented bioprosthesis (n=51; ●), a stentless bioprosthesis (n=194; ◯), an aortic homograft (n=55; △), or a pulmonary autograft (n=96; □). Several points are overlapped (Reproduced with permission from [17].

greater increase in LV mass [45]. In this context, Weidemann et al. [46] found that myocardial fibrosis was frequently an important morphological substrate in patients undergoing AVR (22 of 58 patients in their series) and that, in contrast to myocardial cell hypertrophy, it was not reversible up to nine months after operation. The patients with fibrosis also had a selective decrease in myocardial longitudinal systolic function, as previously described in aortic stenosis (AS) [47,48], which persisted after operation. These patients also had decreased stroke volume and increased BNP (B-type natriuretic peptide) suggesting that they had more extensive and irreversible myocardial damage [49–51]. Hence, the regression of LV hypertrophy and the improvement of LV function after AVR are dependant on many factors and it would be simplistic to think that they can uniquely be related to the improvement of hemodynamics and/or the absence of PPM.

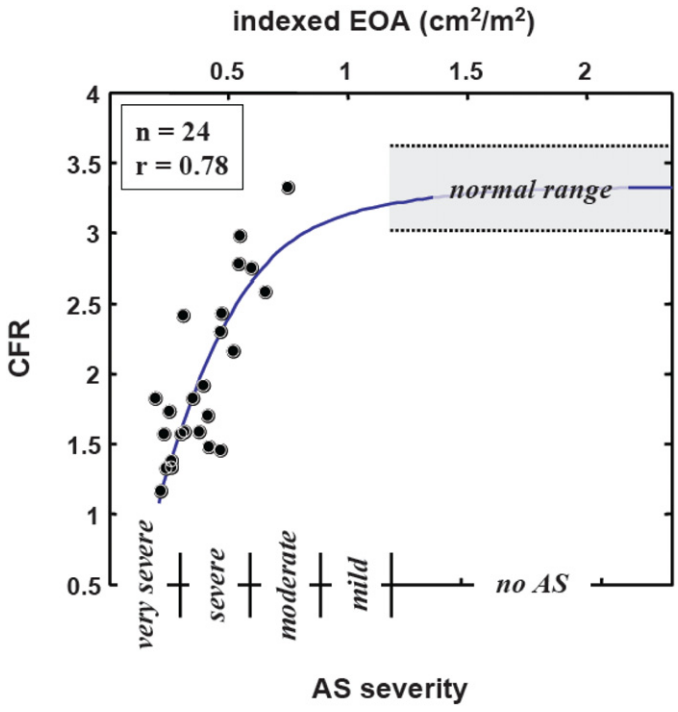

Figure. 3 Coronary flow reserve (CFR) as a function of indexed valve effective orifice area (EOA). The blue line represents the curve fitted over the data generated by 1,000 Monte-Carlo simulations performed over a large range of input physiological conditions. The black circles illustrate the data of CFR measured by positron emission tomography in 24 patients with aortic valve stenosis and no coronary artery stenosis. (Reproduced and modified with permission from [54].

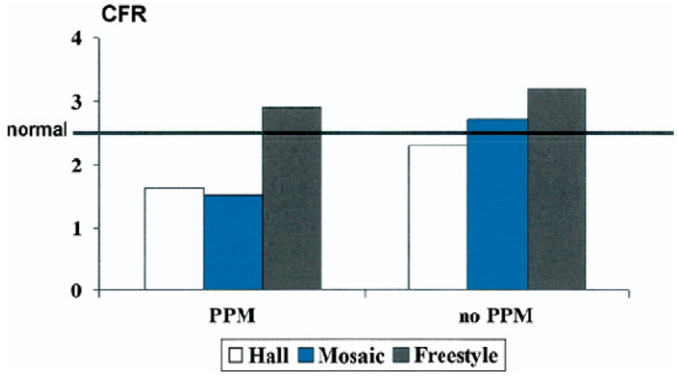

Figure. 4 Reduced coronary flow reserve (CFR) in patients with prosthesis-patient mismatch (PPM) for Medtronic Hall Tilting Disc, Mosaic Stented, and Freestyle Stentless Valves. There were few patients with PPM in the stentless valve group and the results of CFR remained within normal ranges in this group. (Reproduced and modified with permission from [111].

Also noteworthy in this context are the changes in coronary flow reserve (CFR) occurring before and after AVR. Indeed, reduction in CFR is a key factor responsible for myocardial ischemia in AS patients and may contribute to the development of LV dysfunction, symptoms, and adverse outcomes [52]. Hence, in a study of 20 AS patients with angiographically normal coronary arteries, Rajappan et al. demonstrated that the severity of impairment of CFR measured by positron emission tomography was related to the severity of valve stenosis (valve EOA, gradient, LV systolic pressure) rather than to LV mass [52] and the same team subsequently reported that changes in CFR after AVR were not directly related to regression of LV mass but were rather dependent on the magnitude of the change in valve EOA achieved with AVR [53]. Garcia et al. reported that when the aortic valve indexed EOA is larger than 0.8–0.9 cm^2/m^2, there is no significant impact on CFR (Fig. 3). However, the CFR decreases sharply when the indexed EOA is lower than this threshold and becomes almost completely exhausted when the it is below 0.5 cm^2/m^2 [54]. The same principles also apply to patients with prosthetic valves. Bakhtiary et al. have consistently shown that PPM is associated with worse coronary reserve after AVR (Fig. 4) [24]. These findings suggest that beyond LV mass, PPM might also contribute in this manner to a negative impact on LV function after AVR.

Consistent with these findings, recent studies also reported that, in patients with severe aortic stenosis and depressed LV systolic function, the postoperative improvement in LV ejection fraction and a patient's functional capacity depends, in large part, on the extent of the valve EOA augmentation achieved by AVR [55,56]. Hence, the residual LV afterload imposed by PPM negatively impacts on recovery of LV function in these high risk patients. A recent multicenter study revealed that transcatheter aortic valve implantation was associated with better and faster postoperative improvement in LV ejection fraction compared to surgical AVR [56]. This beneficial effect was attributed, in large part, to the superior valve hemodynamic performance and the much lower incidence of PPM associated with transcatheter valve implantation (Fig. 5) [56–58].

EARLY MORTALITY

The impact of PPM is more important on early rather than late mortality given that the left ventricle is more vulnerable during the early postoperative period and that it may thus be more sensitive to the increased hemodynamic burden imposed by PPM. In this regard, there is general agreement that early mortality is significantly increased in patients with PPM [21,23,30,59–61]. Rao et al. first reported in a series of 2,154 patients, that 30-day mortality was significantly higher (7.9% vs. 4.6%, p=0.03) in patients with PPM [21]. We also demonstrated that PPM has a profound impact on early mortality in a series of 1,265 consecutive patients undergoing AVR [30]. In-hospital mortality was 4.6% in this series and moderate PPM had a risk ratio of 2.1 (95% confidence interval: 1.2–3.7) whereas severe PPM had a risk ratio of 11.4 (4.4–29.5). Moreover, the adverse impact of PPM was

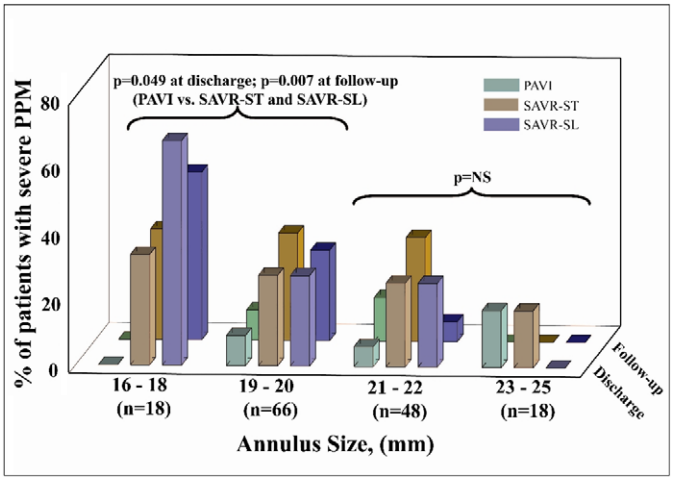

Figure. 5 Incidence of severe prosthesis-patient mismatch (PPM) in the three aortic bioprosthesis groups at hospital discharge and at follow-up according to the aortic annulus size: percutaneous aortic valve implantation (PAVI) (green bars); surgical aortic valve replacement-stentless valve (SAVR-SL) (blue bars); and surgical aortic valve replacement-stented valve (SAVR-ST) (brown bars). (Reproduced and modified with permission from [57].

much more pronounced in patients having an impaired LV ejection fraction (≤40%). As shown in Fig. 6, the risk of mortality was relatively low (mortality: 2–5%) in the case of patients with a preserved LV function who had non-significant or moderate PPM. On the other hand, the mortality risk was dramatically increased (mortality: 67%) in patients having poor LV function and, concomitantly, severe PPM and mortality was also definitely high in patients with the combination of moderate PPM and depressed LV function (mortality: 16%). Subsequent studies have indeed confirmed that there is a strong interaction between PPM and depressed LV function not only with regards to early mortality but also to the occurrence of heart failure as well as late mortality (Fig. 7) [61–64]. These findings are consistent with the concept that a failing ventricle is much more sensitive to an increase in afterload than a normal ventricle. In light of these results, avoidance of potential PPM should become a particularly mandatory consideration in the patients with LV dysfunction. From the standpoint of pathophysiology, it would also make sense to consider that these high-risk patients have a decreased ventricular reserve and are thus more vulnerable to the different degrees of PPM particularly in the critical perioperative period.

LATE MORTALITY

Results with regards to late mortality have varied considerably depending on series and have therefore generated much controversy. Several studies have reported that PPM is independently associated with reduced late survival [9,21,27,28,60,62–68], whereas other studies did not find such association [12,14,23,69–74]. In this context, it has become increasingly clear that the analysis of patients' characteristics were of paramount importance when analyzing such data and in this sense, the findings of a recent study from our laboratory [28] may provide some insight into the discrepancies observed in previous studies (Figs. 8 and 9). Hence, our results with regards to late mortality in a series of 2,576 patients having survived AVR showed that moderate PPM was detrimental only in patients with pre-existing LV dysfunction but not in those with preserved LV function, whereas severe PPM increase mortality only in patients <70 years old and/or with a BMI <30 kg/m^2 and/or an LV ejection fraction <50% but not in patients without these characteristics (Fig. 9). Other studies have also reported that the impact of PPM on late survival is more pronounced in patients with depressed LV systolic function as well as in the younger patients [63,64,66,75]. The negative results reported, for instance, in studies not having considered LV function [69,76], having a large predominance of elderly patients in their series [73,77], or having a high prevalence of obesity in their patients with PPM [72] can probably be explained to a large extent on this basis. The lack of significant impact of PPM on survival in the obese population does not mean that obesity protects the patient against the adverse effects of PPM (Fig. 9) [28]. This finding is most likely related to the fact that the utilization of the body surface area for the normalization of EOA may overestimate the prevalence and severity of PPM in obese patients. Future studies will be necessary to determine if the indexation of EOA cannot be improved or refined in the case of obese patients.

When analyzed collectively, these previous studies suggest that the greatest impact of PPM with regards to survival is in the early postoperative period when the left ventricle is most vulnerable. They also suggest that PPM has a significant impact on late mortality in selected groups of patients.

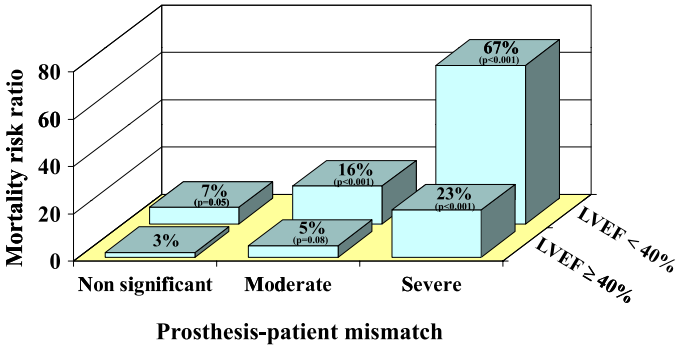

Figure. 6 In-hospital mortality according to patient-prosthesis mismatch and preoperative left ventricular ejection fraction (LVEF). The p values above the bars correspond to the comparison with the group with non-significant mismatch and normal LVEF. (Reproduced and modified with permission from [30]).

Furthermore, regardless of the type of outcome that is considered, the impact of PPM on these outcomes highly depends on its degree of severity. It is unfortunate that some studies reporting negative results in selected populations, or in populations with very low prevalence of severe PPM, have nonetheless interpreted their findings as being a justification for a blanket recommendation to consider PPM as being a myth or a non relevant entity (e.g., the 'size does not matter' or 'valve

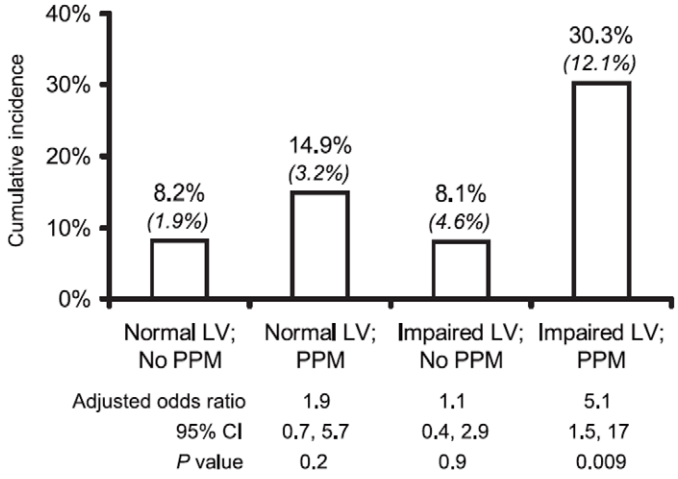

Figure. 7 Effect of preoperative left ventricular function and prosthesis-patient mismatch (PPM) on the cumulative incidence of heart failure symptoms or death related to heart failure at three years after aortic valve replacement. Nonitalic percentages, bars, and odds ratios refer to the occurrence of either heart failure symptoms or death. Italic percentages in parentheses indicate heart failure death. Odds ratios are in comparison to the 'Normal LV; No PPM' group and are adjusted for risk factors of decreased freedom from heart failure after aortic valve replacement and for baseline patient characteristics. Patients with the combination of impaired preoperative left ventricular function and postoperative PPM had a lower freedom from heart failure despite adjustment for confounding factors. CI, Confidence interval; LV, left ventricle. (Reproduced and modified with permission from [63]).

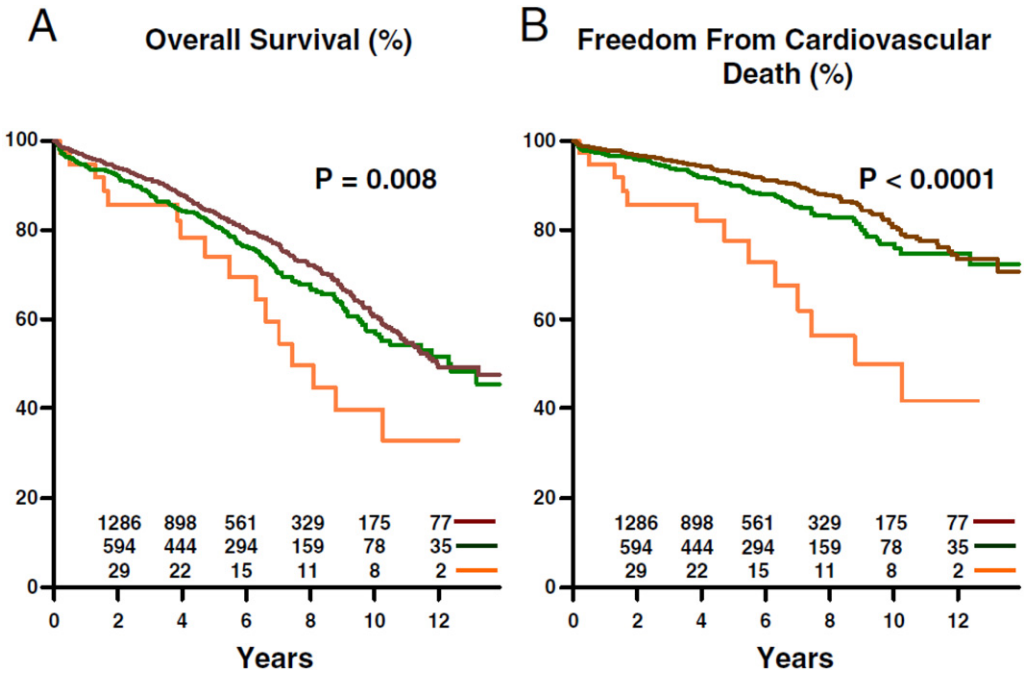

Figure. 8 Late overall survival and freedom from cardiovascular death. Brown line indicates non-significant prosthesis-patient mismatch (PPM); green line indicates moderate PPM; orange line shows severe PPM. (Reproduced and modified with permission from [28]).

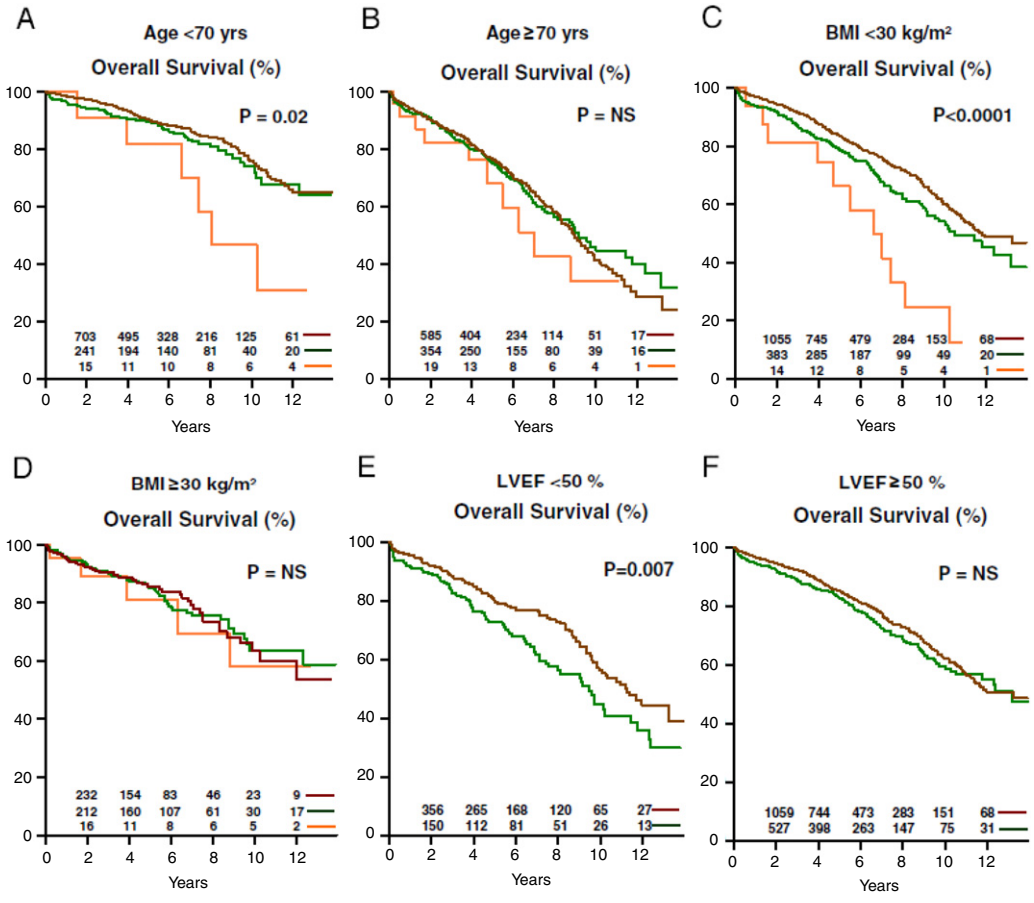

Figure. 9 Impact of prosthesis patient mismatch (PPM) on late overall survival. Panel A: Patients <70 years old; Panel B: ≥70 years old; Panel C: body mass index <30 kg/m^2 ; Panel D: body mass index ≥30 kg/m^2 ; Panel E: preoperative LVEF <50%; Panel F: LVEF >50%. Dark brown line: non-significant PPM; dark green line: moderate PPM in Panels A,B,C,D and moderate-severe PPM in Panels E and F; orange line: severe PPM. (Reproduced and modified with permission from [28]).

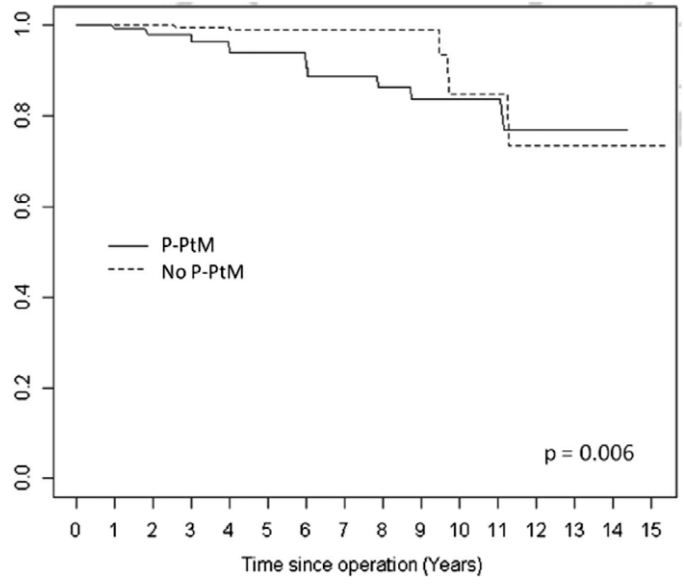

Figure. 10 Freedom from structural valve deterioration (SVD) since for patients with and without prosthesis-patient mismatch (P-PtM). (Reproduced and modified with permission from [29].

hemodynamics do not matter' arguments). Fortunately, important groups have somewhat backtracked from previous positions and now indeed admit that prosthesis size and hemodynamic performance should be considered in the decision making process with regard to AVR.

Also worth considering in this context are the results of a recent study by Flameng et al. [29] showing that PPM is an important risk factor for early (2-3 years after AVR) stenosis type structural valve deterioration in bioprostheses (Fig. 10). PPM in these patients can even be seen as an evolving process and they should logically develop severe stenosis of their valve more rapidly than the patients without PPM undergoing the same processes. Hence, patients with PPM have less valve EOA 'reserve' at the outset of operation and, moreover, they exhaust this limited reserve more rapidly during the postoperative course.

EXERCISE CAPACITY AND QUALITY OF LIFE

Besides the extension of longevity of life, the improvement in the quality of life is an essential objective of AVR. Several studies have shown that PPM is associated with reduced functional capacity and quality of life [68,77–79]. In a study where maximum exercise testing was systematically performed at 6 months post AVR in a consecutive series of 312 patients, Bleiziffer et al. found that PPM was a powerful independent predictor of reduced exercise capacity [79]. In the elderly population, several studies have reported that, although moderate PPM does not necessarily alter late survival, it does however impair quality of life [77].

MISCELLANEOUS OUTCOMES

Beyond survival, other negative outcomes associated with aortic PPM include decreased quality of life, decreased exercise tolerance and a higher rate of late cardiac events (most of them being congestive heart failure) [9,22,65,68,80]. For instance, Ruel et al. analyzed the factors associated with persistent or recurrent heart failure in 1,563 patients having undergone AVR [68] and found that PPM defined as an indexed EOA $\leq 0.80\ cm^2/m^2$ was an independent risk factor associated with a 60% increase in the risk of recurrent heart failure, a finding confirmed by other subsequent studies [9,65]. Interestingly, Vincentelli et al. reported that abnormalities of Von Willebrand factor and associated bleeding complications are common in patients with severe aortic stenosis [81]. They also demonstrated that Von Willebrand abnormalities are directly related to the transvalvular pressure gradient and the stenosis-induced shear stress. Interestingly, these abnormalities were generally improved by AVR in patients with no PPM but persisted in those with PPM (Fig. 11). Yoshida et al. subsequently confirmed this adverse effect of PPM on Von Willebrand factor and reported that patients with PPM have a significantly longer bleeding time after operation [82]. Finally, Mannacio et al. [83] reported that exercise induced arrhythmias were more frequent in patients with PPM and Unger et al. [84] noted that there was more residual mitral regurgitation after AVR in patients with PPM. Hence, the residual LV pressure overload imposed by PPM could predispose patients to the persistence of mitral regurgitation and LV dysfunction and to the occurrence of arrhythmias and bleeding complications, which could, in turn, contribute to explain the increased risk of mortality associated with PPM.

CLINICAL IMPACT OF MITRAL PPM

For a long time, mitral PPM remained quite unexplored and might have been thought to be a relatively rare phenomenon with minimal impact on postoperative outcomes. However, recent studies demonstrate that this is not the case and that mitral PPM is not uncommon and is independently associated with worse hemodynamic and clinical outcomes following mitral valve replacement (MVR). PPM has been shown to be associated with persisting pulmonary hypertension [32], increased incidence of congestive heart failure and reduced survival after MVR (Fig. 12) [34,35,37]. As for aortic PPM, early and late mortality would seem to be affected only by severe PPM but further studies are necessary to determine if, as for aortic prosthesis, moderate mitral valve PPM could not be detrimental in some specific subgroups of patients. For instance, a recent study has suggested a possible interaction between preoperative pulmonary hypertension and either moderate or severe PPM [36].

PREVENTION OF PPM

Aortic valve replacement

As opposed to most other risk factors associated with adverse clinical outcomes, PPM is modifiable andcan be largely avoided by using a simple strategy at the time of operation [7,17]. Our original description of this strategy was as follows:

Step 1- Calculate patient's BSA from patient's weight and height,

Step 2- Multiply body surface area by 0.85 cm^2/m^2, the result being the minimal EOA that the prosthesis to be implanted should have in order to avoid PPM. For instance, if patient's body surface area is 1.80 m^2, then 1.80 × 0.85 = 1.53 cm^2 = minimal EOA to avoid PPM,

Step 3- Chose the prosthesis in light of the result obtained in step 2 and the reference values for the different types and sizes of prosthesis (Table 2). Hence, the EOA of the prosthesis to be implanted in the example chosen would have to be >1.53 cm^2 in order to completely avoid PPM and if, for instance the surgeon had intended to implant a Carpentier-Edwards Perimount prosthesis, it would have had to be a size 23 or greater. Fortunately, most prosthesis manufacturers have now made this exercise easier by providing charts that give the projected indexed EOAs for the different levels of patient's BSA and prosthesis sizes (Fig. 13). With regards to reference values for EOA and indexed EOA, there are three caveats worth reiterating : *(1)* The values should be derived from *in vivo* rather than the *in vitro* data supplied by the manufacturers since the latter are usually too optimistic,

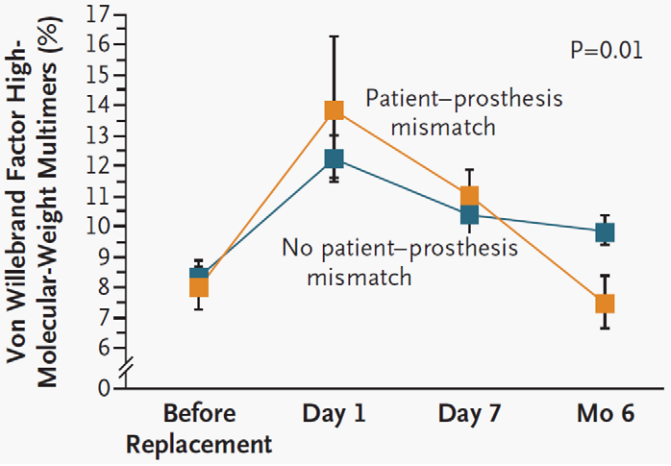

Figure. 11 Evolution of highest-molecular-weight von Willebrand factor multimers after aortic valve replacement in patients with and without prosthesis-patient mismatch (PPM). (Reproduced and modified with permission from [81]).

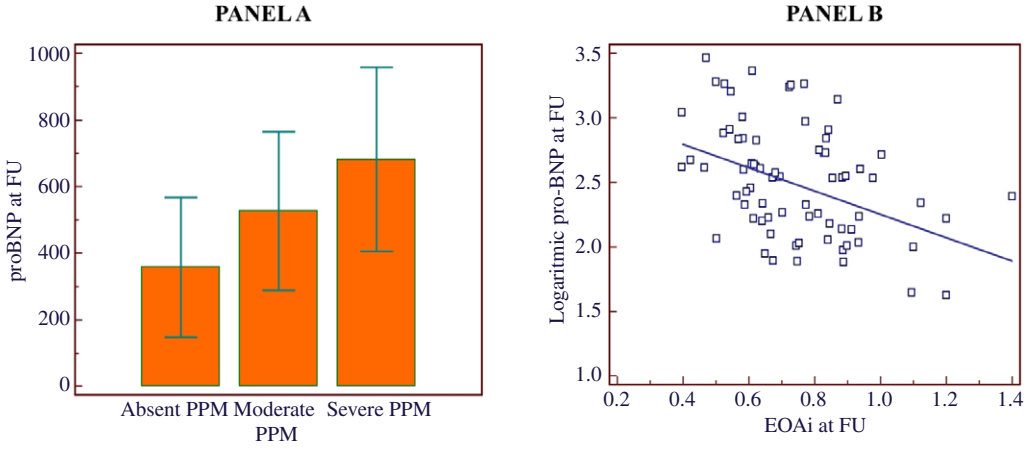

Figure. 12 Overall survival after mitral valve replacement in patients with non-significant, moderate and severe prosthesis-patient mismatch (PPM). (Reproduced and modified with permission from [34]).

particularly in the case of stentless valves [85], Moreover, the *in vivo* reference EOAs should be derived from reliable sources, i.e. from studies that included a sufficient number of patients in each model/size subcategory and used adequate Doppler-echocardiographic methods for EOA measurement [10]. *(2)* Reference values derived from geometric measurements (e.g., internal diameters or geometric areas) are inadequate since they bear no relation to postoperative hemodynamics particularly if different types of valves are being compared (see aforementioned considerations) [7,10,65], *(3)* When using these charts (or Table 2), it is important remember that there are often important discrepancies between the sizes of the different types of prostheses and

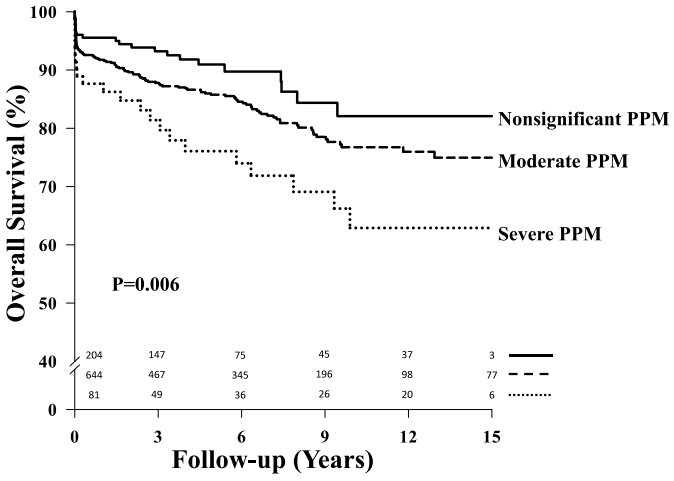

Figure. 13 **Example of a chart provided by the manufacturers for the risk assessment of prosthesis-patient mismatch. The chart gives the projected indexed effective orifice areas (EOA-I) for the different level of patient's body surface area (left-hand side) and the different prosthesis sizes (top of the chart) of a given model of prosthesis (hypothetical model in this example). Green cells indicate that the projected EOA-I is $>0.85\ cm^2/m^2$, yellow cells indicate borderline values and red cells, indicate that there is a risk of mismatch. (Reproduced with permission from [109]).**

	EOAi by Prosthesis size (mm)					
Prosthesis size (mm)	**19**	**21**	**23**	**25**	**27**	**29**
Average EOA (cm^2)	1.1	1.3	1.5	1.8	2.3	2.7
BSA (m^2)						
0.6	1.83	2.17	2.50	3.00	3.83	4.50
0.7	1.57	1.86	2.14	2.57	3.29	3.86
0.8	1.38	1.63	1.88	2.25	2.88	3.38
0.9	1.22	1.44	1.67	2.00	2.56	3.00
1	1.10	1.30	1.50	1.80	2.30	2.70
1.1	1.00	1.18	1.36	1.64	2.09	2.45
1.2	0.92	1.08	1.25	1.50	1.92	2.25
1.3	0.85	1.00	1.15	1.38	1.77	2.08
1.4	0.79	0.93	1.07	1.29	1.64	1.93
1.5	0.73	0.87	1.00	1.20	1.53	1.80
1.6	0.49	0.88	0.88	0.88	0.88	1.69
1.7	0.65	0.76	0.88	1.06	1.35	1.59
1.8	0.61	0.72	0.83	1.00	1.28	1.50
1.9	0.58	0.68	0.79	0.95	1.21	1.42
2	0.55	0.65	0.75	0.90	1.15	1.35
2.1	0.52	0.62	0.71	0.86	1.10	1.29
2.2	0.50	0.59	0.68	0.82	1.05	1.23
2.3	0.48	0.57	0.65	0.78	1.00	1.17
2.4	0.46	0.54	0.63	0.75	0.96	1.13
2.5	0.44	0.52	0.60	0.72	0.92	1.08

Figure. 14 **Comparison of the changes in transvalvular gradient during follow-up in patients with pulmonary autograft versus those with aortic homograft. The transvalvular gradient falls down to an average value of 5 mmHg after operation and remains stable during the whole follow-up in the pulmonary autograft group, whereas it progressively increases in the aortic homograft group. (Reproduced with permission from [96]).**

that for a given patient's annulus, the labeled size that fits may vary from one type of prosthesis to the other.

The validity and feasibility of this strategy is now widely accepted [10,86] and we believe that, given its simplicity and rapidity, this exercise should be performed in every patient undergoing AVR. Depending on the result, if moderate PPM is anticipated in a patient with certain characteristics (e.g., depressed LV function and/or severe LV hypertrophy, young age (<70 years old), athletic lifestyle or an elderly patient seeking enhanced quality of life) or a severe PPM in any given patient, the following strategies can be considered: *i)* the implantation of a prosthesis with a better hemodynamic performance (e.g., a newer generation of stented bioprosthesis or bileaflet mechanical valves implanted in a complete supra-annular position or a stentless bioprosthesis), or *ii)* the performance of an aortic root enlargement, allowing the implantation of a larger size of the same type of prosthesis. Unfortunately, some recent papers have challenged the use of this approach based on the false premise that the first-line strategy, if not the only option, for avoiding PPM is aortic root enlargement, which may carry an increased operative mortality, particularly in the elderly. In reality, given the significant improvements in design leading to the availability of a newer generation of mechanical or biological prostheses, contemporary prevention of PPM can largely be accomplished by the implantation of prosthetic models providing a better hemodynamic performance. Indeed, several studies have shown that PPM can be successfully avoided, or its severity reduced, by using such strategies. The study by Bleiziffer et al. [10] is particularly illustrative in this regard whereby the investigators were able to reduce the incidence of moderate PPM from 44% to 30% and that of severe PPM from 9 to 1% by applying strategy *i)* described above. Botzenhardt et al. also demonstrated the incidence of PPM could be significantly reduced just by using a Perimount Magna rather than a Perimount standard bioprosthesis. Several randomized clinical trials and meta-analyses have also confirmed that the valve's hemodynamic performance may differ substantially depending on the models of prosthesis used for AVR and that, accordingly, the selection of the prosthesis model with superior hemodynamic performance may contribute to reducing the incidence and/or severity of PPM [25,26,87–94]. To this effect, the hemodynamic performance is generally superior in newer versus older generations of prostheses, in mechanical versus stented bioprosthetic valves [66], in stentless versus stented bioprosthetic valves [92,93] and in supra-annular versus intra-annular stented bioprostheses [25,26]. The pulmonary autograft is likely the best valve substitute in terms of hemodynamic performance and avoidance of PPM [95,96]. Furthermore, this performance is well maintained in the long-term (Fig. 14) [96]. However, the Ross operation is more complex and is not applicable in all patients. This operation may be considered in young, athletic patients at risk of PPM.

Opinions with regards to aortic root enlargement for the purpose of avoiding PPM also vary, many groups having reported favourable outcomes using this procedure [86,97–100]. In summary, although there are still questions to be answered, there is nonetheless more than enough evidence to

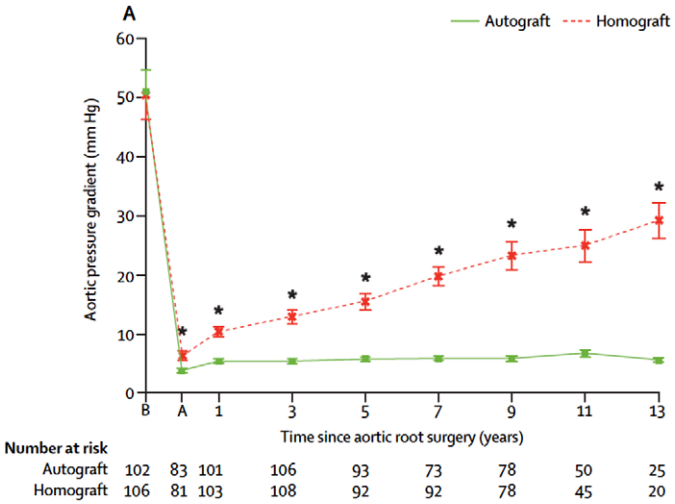

Figure. 15 Algorithm for the interpretation of high transprosthetic gradient. DVI: Doppler velocity index; EOA: effective orifice area; IEOA: indexed EOA; TEE: Transesophageal echocardiography. (Reproduced with permission from [104]).

affirm that the issue of PPM based on the aforementioned algorithm should always be incorporated in the decision making process when considering AVR thus allowing an enlightened decision based on the overall risks confronting the patient. Furthermore, in patients with a small BSA, the preoperative calculation of the projected indexed EOA at the time of operation can be used to validate the use of a small prosthesis and hence avoid more aggressive procedures such as aortic root enlargement [101–103]. Indeed, whereas some might still advocate systematic avoidance of smaller prostheses, several studies demonstrate that such prostheses may be safe and adequate in patients with smaller BSAs, pending calculation of the projected indexed EOA before operation.

Finally, recent studies suggest that valve hemodynamics are superior with transcatheter aortic valve implantation than with surgical AVR, especially in the subset of patients with small aortic root (Fig. 5) [56–58]. Hence, transcatheter valve implantation should provide another valuable alternative to avoid PPM in high risk patients, while minimizing the invasive nature of the procedure.

Table 2. Normal reference values of effective orifice areas for the aortic and mitral prostheses.

Prosthetic valve size (mm)	19	21	23	25	27	29	Reference
Aortic Stented Bioprostheses							
Mosaic	1.1±0.2	1.2±0.3	1.4±0.3	1.7±0.4	1.8±0.4	2.0±0.4	[17]
Hancock II	-	1.2±0.1	1.3±0.2	1.5±0.2	1.6±0.2	1.6±0.2	[17]
Carpentier–Edwards Perimount	1.1±0.3	1.3±0.4	1.5±0.4	1.8±0.4	2.1±0.4	2.2±0.4	[17]
*Carpentier–Edwards Magna	1.3±0.3	1.7±0.3	2.1±0.4	2.3±0.5	-	-	[25,91]
*Biocor (Epic)	-	1.3±0.3	1.6±0.3	1.8±0.4	-	-	[106]
*Mitroflow	1.1±0.1	1.3±0.1	1.5±0.2	1.8±0.2	-	-	[107]
Aortic Stentless Bioprostheses							
Medtronic Freestyle	1.2±0.2	1.4±0.2	1.5±0.3	2.0±0.4	2.3±0.5	-	[17]
St. Jude Medical Toronto SPV	-	1.3±0.3	1.5±0.5	1.7±0.8	2.1±0.7	2.7±1.0	[17]
Aortic Mechanical Prostheses							[17]
Medtronic-Hall	1.2±0.2	1.3±0.2	-	-	-	-	[17]
*Medtronic Advantage	-	1.7±0.2	2.2±0.3	2.8±0.6	3.3±0.7	3.9±0.7	[108]
St. Jude Medical Standard	1.0±0.2	1.4±0.2	1.5±0.5	2.1±0.4	2.7±0.6	3.2±0.3	[17]
St. Jude Medical Regent	1.6±0.4	2.0±0.7	2.2±0.9	2.5±0.9	3.6±1.3	4.4±0.6	[109]
MCRI On-X	1.5±0.2	1.7±0.4	2.0±0.6	2.4±0.8	3.2±0.6	3.2±0.6	[109]
Carbomedics Standard	1.0±0.4	1.5±0.3	1.7±0.3	2.0±0.4	2.5±0.4	2.6±0.4	[17]

Prosthetic valve size (mm)	25	27	29	31	33	Reference
Mitral Stented Bioprostheses						
Medtronic Mosaic	1.5±0.4	1.7±0.5	1.9±0.5	1.9±0.5	-	[34,110]
Hancock II	1.5±0.4	1.8±0.5	1.9±0.5	2.6±0.5	2.6±0.7	[35]
*Carpentier-Edwards Perimount	1.6±0.4	1.8±0.4	2.1±0.5	-	-	[34]
Mitral Mechanical Prostheses						
St. Jude Medical Standard	1.5±0.3	1.7±0.4	1.8±0.4	2.0±0.5	2.0±0.5	[34]
†MCRI On-X	2.2±0.9	2.2±0.9	2.2±0.9	2.2±0.9	2.2±0.9	[34]

Effective orifice area is expressed as mean values available in the literature. * These results are based on a limited number of patients and should thus be interpreted with caution. † The strut and leaflets of the MCRI On-X valve are identical for all sizes (25- to 33-mm). (Reproduced with permission from [104]).

MITRAL VALVE REPLACEMENT

The rationale for the prevention of PPM in the mitral position is the same as for the aortic but it is a much more demanding challenge given that as opposed to the aortic position, the techniques allowing to implant a larger size prosthesis are very complex and as of yet unproven with regards to their risk-benefit ratio [37]. For the time being, the preventive strategy should therefore be focused on the implantation of the prosthesis having the largest EOA for a given size (Table 2). This observation also underlines the need for the development of better performing mitral prostheses and provides further motivation for repairing rather than replacing the valve whenever possible.

PPM IN THE CONTEXT OF THE INTERPRETATION OF HIGH POSTOPERATIVE GRADIENTS

The presence of increased transprosthetic gradient (mean gradient >15 to 20 mmHg for aortic prostheses and >5 to 7 mmHg for mitral prostheses) cannot be equated with intrinsic prosthesis dysfunction [104]. Hence, a high gradient can be due to an associated subvalvular obstruction or a high flow state (e.g., hyperadrenergism, valvular regurgitation); such occurrences can be suspected when the dimensionless velocity index is normal (>0.35 aortic or >0.45 mitral). Conversely, the combination of a high gradient and a low DVI suggests valvular obstruction. In such cases, an integrative evaluation must be performed and, in particular, the distinction must be made between obstruction due to PPM, which is by far the most frequent cause of high postoperative gradients and intrinsic prosthesis dysfunction. For this purpose, the following algorithm can be utilized (Fig. 15) [104]:

Step 1: As a first screening step, the possibility of PPM as a contributing factor can be assessed by calculating the projected indexed EOA of the prosthesis that was implanted. This is accomplished by dividing the EOA reference value for the model and size of the prosthesis (Table 2) by the patient's body surface area. If this projected indexed EOA is >0.85 cm^2/m^2 in the aortic position or >1.2 cm^2/m^2 in the mitral position (Table 2) then PPM is not a contributing factor. However, if the indexed EOA is below this value, PPM may be partially or totally responsible for the high gradient.

Step 2: The second step consists of comparing the EOA as measured by Doppler to the EOA reference value (Table 2). The measured EOA of a normally functioning prosthesis should be close to the reference value for the same model and size of prosthesis, whereas a substantially lower value is compatible with intrinsic prosthesis dysfunction.

Step 3: If the measured EOA is similar to its reference value ±1 SD, intrinsic dysfunction is unlikely and the presence/severity of PPM should be confirmed by calculating the indexed EOA. If no PPM is present, a technical pitfall or a high flow state is likely.

Step 4: If the EOA is below the reference value and if the prosthesis is not a bileaflet mechanical valve, prosthesis valve dysfunction should be envisioned and confirmation should be sought using other examinations such as transesophageal echocardiography, fluoroscopy, computed tomography, or cardiac catheterization. If, on the other hand, the prosthesis is a bileaflet mechanical valve and the patient is asymptomatic, localized high gradient is the likely cause. Unfortunately, this phenomenon is often difficult to confirm or infirm from the transthoracic echocardiography. In case of doubt, valve leaflet mobility can be evaluated using fluoroscopy (or transesophageal echocardiography) and by looking for indirect signs of prosthesis dysfunction.

CONCLUSION

PPM is a frequent and modifiable risk factor leading to more frequent adverse clinical outcomes in patients undergoing valve replacement. The risk of PPM should be systematically evaluated at the time of operation by calculating the projected indexed EOA of the prosthesis to be implanted and in the case of anticipated PPM, alternative options should be considered in light of the patient's overall clinical condition and risk-benefit ratio. Awareness of the concept of PPM is also essential to correctly interpret abnormally high gradients that may be recorded after valve replacement.

ACKNOWLEDGEMENTS

This study was supported in part by Canadian Institutes of Health Research grants (MOP-10929, MOP-57745, MOP-67123, MOP-86666). Dr Pibarot is the holder of the Canada Research Chair in Valvular Heart Disease, Canadian Institutes of Health Research, Ottawa, Canada.

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