Prosthesis–patient mismatch in the mitral position: Old concept, new evidences

Philippe Pibarot, DVM, PhD, FACC, FAHA, and Jean G. Dumesnil, MD, FRCP(C), FACC

See related editorial on page 1464.

Previous studies have demonstrated that prosthesis–patient mismatch (PPM) is associated with inferior hemodynamics, less regression of left ventricular hypertrophy, more cardiac events, and higher mortality rates after aortic valve replacement.¹⁻¹² However, the hemodynamic and clinical impact of PPM after mitral valve replacement (MVR) are relatively unexplored.^{2,13-15} The elegant study presented by Lam and colleagues¹⁶ in this issue of the *Journal* is indeed one of the first reports to demonstrate that PPM is associated with worse outcome after MVR. The main findings of this study are that (1) the incidence of mitral PPM is much higher than previously believed; (2) it is associated with a 4-fold increase in the risk of congestive heart failure after MVR; and (3) it independently affects postoperative survival.

Mitral PPM is actually not a new concept. In the first report of mitral PPM published in 1981, Rahimtoola and Murphy¹³ described the case of a patient who remained symptomatic and had persistent pulmonary artery hypertension and progressive right-sided failure after MVR. In the early 1990s, Dumesnil and colleagues^{2,14} demonstrated the existence of a relationship between the indexed effective orifice area (EOA) and the transvalvular pressure gradient in normally functioning prostheses implanted in the mitral position. These findings are consistent with the concept that PPM occurs when the EOA of the prosthesis is too small in relation to the patient's body size, resulting in an abnormally high postoperative gradient.^{1,17,18} In patients with an aortic prosthesis, previous studies consistently found a strong correlation between the indexed EOA and the postoperative transprosthetic gradients measured at rest or during exercise.^{1,17,19,20} However, as first reported by Dumesnil and colleagues in 1990,¹⁴ and confirmed by Li and colleagues in 2005,¹⁵ the correlation between the indexed EOA and the mean transprosthetic pressure gradients is lower in patients with mitral prostheses ($r < 0.50$) than in patients with aortic prostheses ($r > 0.75$). In this context, it should be emphasized that the hemodynamics of the mitral valve are more sensitive to the chronotropic conditions than are those of the aortic valve and that these conditions may vary extensively from one patient to another. This difference may help explain the lower correlation between indexed EOA and pressure gradients that is observed in mitral prostheses. Subsequently, in a retrospective study of 56 patients who underwent MVR, we observed that the indexed mitral valve EOA correlated better with systolic pulmonary arterial pressure than with transprosthetic pressure gradients;¹⁵ this finding is consistent with the fact that pulmonary arterial pressure is probably less influenced by chronotropic conditions than are pressure gradients. In this study, we also found that mitral PPM is a frequent occurrence after MVR and that it is associated with persisting pulmonary hypertension.¹⁵ Given that pulmonary hypertension may cause right-sided failure and is an important risk factor for morbidity and mortality in patients with cardiovascular diseases, the next logical

From the Québec Heart Institute/Laval Hospital Research Center, Laval University, Quebec, Canada.

Dr Philippe Pibarot holds the Canada Research Chair in Valvular Heart Diseases, Canadian Institutes of Health Research, Ottawa, Ontario, Canada.

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Address for reprints: Philippe Pibarot, DVM, PhD, FACC, FAHA, Laval Hospital Research Center, 2725 Chemin Sainte-Foy, Sainte-Foy, Quebec, Canada, G1V-4G5 (E-mail: philippe.pibarot@med.ulaval.ca).

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step was to examine the association between mitral PPM and the occurrence of adverse events after MVR. In this regard, the results of the study by Lam and colleagues¹⁶ provide new compelling evidence that PPM is a powerful independent risk factor for morbidity and mortality after MVR. Furthermore, these results are consistent with those of another recent study from our laboratory showing that mitral PPM is independently associated with reduced survival after MVR.²¹

Definition of Prosthesis–Patient Mismatch in the Mitral Position

There have been controversies in regard to the clinical impact of PPM in the aortic position, in large part because the investigators used different parameters and criteria to define PPM. The parameter first proposed to identify PPM was the indexed EOA.^{1,2} The EOA of the prosthesis can be measured directly by Doppler echocardiography or “projected” from the normal reference values of EOA provided in the literature for the different types and sizes of prostheses. Some authors also attempted to characterize PPM in terms of the indexed internal geometric orifice area (GOA) rather than the indexed EOA.^{22–24} The GOA is a parameter calculated from the static measurement of the internal diameter of the prosthesis stent. However, as opposed to the measured or projected indexed EOA, the indexed GOA has consistently been shown to be unrelated to either postoperative hemodynamics^{20,24,25} or outcomes^{8,11,22–24} after aortic valve replacement. Similarly, we also recently reported that, in patients with MVR, the indexed GOA grossly overestimates the indexed EOA and in varying proportion depending on the type and size of prostheses.²¹ Furthermore, this parameter was not significantly associated with postoperative outcomes. Thus, it would seem that, as for the aortic valve, the indexed EOA is the only valid parameter to identify PPM in the mitral position. In the majority of patients included in the present study, the authors used the projected indexed EOA derived from reference EOA values published in the literature to identify mitral PPM, and by using this parameter they found that PPM is independently associated with worse outcome after MVR.¹⁶ However, in a proportion of the patients included in this series, they used the GOA of the prosthesis when the reference value of EOA was not available. As acknowledged by the authors, this may have contributed to underestimating the prevalence of PPM in this series.

When the projected indexed EOA is used, it is important to use reference values that are as reliable as possible. To this effect, the values should be derived from large, preferably multicenter series with a sufficient number of patients for each type and size of prostheses. This is, however, more difficult to achieve for mitral prostheses than for aortic prostheses because there are less data available in the literature on the normal EOAs of mitral prostheses. Moreover,

the reference values should be derived from studies that used an appropriate method to measure the EOA. In this regard, it has been shown that the pressure half-time method is not valid to measure the EOA of mitral prostheses and that only the continuity equation method can be used for this purpose.^{14,26,27} The pressure half-time method indeed overestimates the EOA of mitral prostheses and in varying proportion depending on the chronotropic conditions and the atrioventricular compliance. In the present article, the authors made no distinction between the EOAs derived from the pressure half time versus those derived from the continuity equation,¹⁶ and this may have further contributed to underestimate the prevalence of PPM in this series. Thus, the reference values of EOA presented in the present article should not be taken at face value and will need to be further validated and updated.

In the aortic position, PPM is generally considered mild or not clinically significant when the indexed EOA is greater than $0.85 \text{ cm}^2/\text{m}^2$, moderate when it is equal to or less than 0.85 and greater than $0.65 \text{ cm}^2/\text{m}^2$, and severe when it is $0.65 \text{ cm}^2/\text{m}^2$ or less. Moderate PPM may be prevalent (20%–70%) in patients undergoing AVR, whereas the prevalence of severe PPM ranges from 2% and 11% depending on the series.^{17,18} Because of the lower pressure regimen, the threshold values for mitral PPM are higher than for aortic PPM. Mitral PPM is considered moderate when the indexed EOA is 1.2 to $1.3 \text{ cm}^2/\text{m}^2$ or less and severe when it is 0.9 to $1.0 \text{ cm}^2/\text{m}^2$ or less.^{2,14–16,21} In the present study, the prevalence of PPM defined as an indexed EOA of $1.25 \text{ cm}^2/\text{m}^2$ or less was 32%. In our series, the prevalence of moderate PPM (indexed EOA $\leq 1.2 \text{ cm}^2/\text{m}^2$) was 60% to 70% and of severe PPM (indexed EOA $\leq 0.9 \text{ cm}^2/\text{m}^2$) was 5% to 10%.^{15,21} Thus, in light of these findings, it seems that PPM is a frequent occurrence not only in the aortic position but also in the mitral position. The lower prevalence of PPM in the present series¹⁶ compared with our previous series^{15,21} may be related to the lower proportion of smaller prostheses ($\leq 27 \text{ mm}$) than in our series. As outlined, the fact that Lam and colleagues¹⁶ used the GOA or the EOA derived from the pressure half time to project the postoperative indexed prosthetic valve area in a substantial proportion of patients may also have contributed to underestimate the prevalence of PPM in their series.

Does Mitral Prosthesis–Patient Mismatch Matter?

PPM in the aortic position is associated with less improvement in symptoms and functional class,⁶ less regression of left ventricular hypertrophy,⁷ and more adverse cardiac events.^{4,8,10} Aortic PPM has a major impact on short-term mortality,^{5,12} particularly if left ventricular dysfunction is present, and it has a moderate impact on long-term mortality.^{8–12}

For a long time, mitral PPM remained unexplored and might have been thought to be a relatively rare phenomenon with minimal impact on postoperative outcomes. The compelling data presented by Lam and colleagues¹⁶ in this issue of the *Journal*, however, demonstrate that this is not the case and that mitral PPM is not uncommon and is independently associated with worse outcomes after MVR. In this study, mitral PPM was indeed associated with a 4-fold increase in the risk of recurrence of congestive heart failure and a 2.4-fold increase in the risk of mortality.¹⁶ This is consistent with the results of a recent study from our laboratory that included 929 consecutive patients undergoing MVR in whom PPM was associated with a 3-fold increase in postoperative mortality after adjustment for other risk factors.²¹ Furthermore, this association was maintained in the subset of patients who underwent isolated MVR without concomitant coronary artery bypass grafting. The fact that 2 large studies from 2 independent laboratories both demonstrate that PPM is a strong independent risk factor for mortality after MVR further supports the notion that mitral PPM does matter.

Why Does Mitral Prosthesis–Patient Mismatch Matter?

PPM in the mitral position can be equated to residual mitral stenosis with similar consequences, that is, the persistence of abnormally high mitral gradients and increased left atrial and pulmonary arterial pressures. In turn, pulmonary arterial hypertension may cause right-sided failure, and the persistence of high left atrial pressures may predispose one to atrial fibrillation. This arrhythmia may compromise cardiac output and increase the incidence of thromboembolic complications. The passive elevation in pulmonary capillary pressure caused by the elevated left atrial pressure may also lead to the development of pulmonary edema.

In the present study, PPM was not significantly associated with postoperative pulmonary hypertension, but smaller valve size and elevated transprosthetic gradients were. The lack of association between indexed EOA and pulmonary arterial pressure is intriguing and in contrast with the results of other studies.^{15,21} The incomplete echocardiographic follow-up of pulmonary arterial pressure and the use of GOA or EOA derived from the pressure half time to estimate the indexed EOA in a certain number of cases may explain this result. Masuda and colleagues²⁸ reported that the pulmonary arterial pressure correlated with the transprosthetic gradient but not with the indexed prosthetic valve area. However, it should be emphasized that these authors used the indexed GOA in lieu of the indexed EOA to characterize prosthesis hemodynamic performance. As outlined, the indexed GOA is not a valid parameter to predict gradients or outcomes whether in the mitral or the aortic position. Another possible explanation for these apparent discrepancies is that a certain proportion of the patients with PPM were in a low output state and had a pseudo-

normalization of gradients and pulmonary pressures, which in turn could explain why PPM was more predictive of outcomes than the latter variables.

Prevention of Mitral Prosthesis–Patient Mismatch: An Important Challenge

Previous studies demonstrated that the risk of PPM can be predicted at the time of aortic valve replacement with the use of the projected indexed EOA derived from normal reference values. Some studies have also provided robust evidence that the prevention of aortic PPM is feasible.^{25,29} Thus, in light of these findings, it seems that there is a significant advantage to systematically calculate the projected indexed EOA of the prosthesis to be inserted at the time of operation and in the case of anticipated PPM to consider alternate procedures, such as aortic root enlargement or insertion of a better-performing valve substitute such as supra-annular stented bioprostheses, stentless bioprostheses, newer-generation mechanical valves, homografts, or the Ross operation. Moreover, most manufacturers now provide user-friendly charts allowing easy calculation of the projected indexed EOA within the operating room.

The prevention of PPM in the mitral position represents a much greater challenge than in the aortic position. Indeed, mitral valve surgery does not allow annular enlargement, and the implantation of a homograft or a stentless prosthesis is technically more demanding and associated with poor long-term durability. Thus, the only alternative at present is the implantation of a prosthesis with a larger EOA for a given annulus size, which unfortunately may not be sufficient to completely avoid PPM in some cases. In this sense, the findings of the present study¹⁶ provide further impetus for the development of better-performing mitral prostheses and alternative techniques allowing more frequent repair or implantation of better-performing prostheses. As opposed to aortic prostheses, efforts to improve the hemodynamic performance of mitral prostheses have been more limited, but a comparison of existing prostheses nonetheless shows that size for size the type of prosthesis chosen may make a difference. Thus, these new compelling results^{16,21} should further encourage manufacturers to pursue their efforts in this direction more intensively and to provide reliable EOA reference values and user-friendly charts allowing easy calculation of the projected indexed EOA within the operating room.

Finally, it should be emphasized that the best way to avoid PPM in the mitral position is to repair rather than to replace the valve, but this is unfortunately not possible in all cases. Moreover, relatively unexplored but not excluded is the fact that mitral valve annuloplasty, particularly if restrictive, might cause some degree of stenosis with consequences similar to those observed with mitral PPM.

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