Impact of Valve Prosthesis-Patient Mismatch on Pulmonary Arterial Pressure After Mitral Valve Replacement

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**OBJECTIVES**
We sought to determine the impact of valve prosthesis-patient mismatch (PPM) on pulmonary arterial (PA) pressure after mitral valve replacement (MVR).

**BACKGROUND**
Pulmonary arterial hypertension is a serious complication of mitral valve disease, and it is a major risk factor for poor outcome after MVR. We hypothesized that valve PPM might be a determinant of PA hypertension after MVR.

**METHODS**
Systolic PA pressure was measured by Doppler echocardiography in 56 patients with normally functioning mitral prosthetic valves. Mitral valve effective orifice area (EOA) was determined by the continuity equation and indexed for body surface area.

**RESULTS**
Thirty patients (54%) had PA hypertension defined as systolic PA pressure >40 mm Hg, whereas 40 patients (71%) had PPM defined as an indexed EOA ≤1.2 cm²/m². There was a significant correlation (r = 0.64) between systolic PA pressure and indexed EOA. The average systolic PA pressure and prevalence of PA hypertension were 34 ± 8 mm Hg and 19% in patients with no PPM versus 46 ± 8 mm Hg and 68% in patients with PPM (p < 0.001). In multivariate analysis, the indexed EOA was by far the strongest predictor of systolic PA pressure.

**CONCLUSIONS**
Persistent PA hypertension is frequent after MVR and strongly associated with the presence of PPM. The clinical implications of these findings are important given that PPM can largely be avoided by using a simple prospective strategy at the time of operation. (J Am Coll Cardiol 2005;45:1034–40) © 2005 by the American College of Cardiology Foundation

Pulmonary arterial (PA) hypertension is a frequent and serious complication of mitral valve diseases, and it is a major risk factor for poor outcome after surgery for mitral stenosis (1) or mitral regurgitation (2–4). Not surprisingly, the impact of PA hypertension on morbidity and mortality is highly dependent on its degree of severity. Severe PA hypertension is associated with a high risk of perioperative mortality (10% to 15%) in patients undergoing mitral valve replacement (MVR) as well as with increased mortality in the long term (1–3). Nonetheless, mild PA hypertension is not necessarily benign because it is associated with significantly worse exercise capacity and higher morbidity and mortality. Therefore, the normalization of PA pressure is a crucial goal of MVR. Unfortunately, the regression of PA hypertension after operation varies extensively from one patient to the other and is often incomplete (5,6).

The effective orifice area (EOA) of prosthetic valves used for MVR is often too small in relation to body size, thus causing a mismatch between valve EOA and transvalvular flow (7–10). As a consequence, normally functioning mitral prostheses often have relatively high gradients that are similar to those found in patients with mild/moderate mitral stenosis (6,9–11). Residual pressure gradients across mitral prostheses may hinder or delay the regression of left atrial and PA hypertension (7–9). We, therefore, hypothesized that valve prosthesis-patient mismatch (PPM) might be an important determinant of the persistence of PA hypertension after MVR. The main objective of this study was, thus, to determine the impact of PPM on PA pressure after MVR.

**METHODS**

**Patient population.** We retrospectively analyzed the data of patients with a mitral prosthesis who were consecutively evaluated by Doppler echocardiography at the Quebec Heart Institute between January 2003 and August 2003. Exclusion criteria were as follows: 1) evidence of overt prosthetic valve dysfunction; 2) presence of >2+ aortic valve regurgitation and/or > mild aortic stenosis. Seventy-two patients met these eligibility criteria. Measurement of systolic PA pressure and/or mitral valve EOA could not be obtained in 14 of these patients. The study group was,
Doppler-echocardiography. The systolic PA pressure was calculated by adding the systolic right ventricular pressure derived from the tricuspid regurgitation to the estimated right atrial pressure (12–14). Right atrial pressure was estimated from the diameter and the degree of collapse of the inferior vena cava during inspiration (14–16). Pulmonary arterial hypertension was defined as a systolic PA pressure 40 mm Hg (17).

Mitral valve EOA was determined by the continuity equation using the stroke volume measured in the left ventricular outflow tract divided by the integral of the mitral valve transprosthetic velocity during diastole; PPM was defined as an indexed EOA 40 mm Hg was present in 67% of patients. A mechanical prosthesis was inserted in 84% of patients, whereas 16% received a bioprosthesis. The model of prosthetic valve was Standard St. Jude Medical (St. Jude Medical, Minneapolis, Minnesota) in 34 (61%) patients; On-X (MCRI, Austin, Texas) in 5 (9%); Advantage (Medtronic) in 4 (7%); Medtronic-Hall (Medtronic) in 4 (7%); Mosaic (Medtronic) in 4 (7%); Hancock (Medtronic) in 2 (3.5%); Intact (Medtronic) in 2 (3.5%); and homograft (Cryolife, Kennesaw, Georgia) in 1 (2%). The mitral valve leaflets and chordae were totally or partially (posterior) preserved in 41% of patients. Concomitant procedures included left atrial appendage obliteration in 23%, Maze procedure in 9%, and coronary artery bypass graft surgery in 16%. The proportion of small (27 mm) valves was 52%, which is comparable with that reported in previous recent series (20–24). There was no significant difference between patients having total, partial, or no preservation of the valve leaflets and chordae with regard to prosthesis size.

Based on an indexed EOA 1.2 cm²/m², 40 of the 56 patients (71%) were classified as having PPM. In comparison to patients with no PPM, patients with PPM had a significantly larger body surface area, a higher prevalence of systemic hypertension, and a higher proportion of smaller prostheses; indeed, prosthesis size was 27 mm in 66% of patients with PPM as compared to only 19% of patients without PPM. The other preoperative and operative data were similar in both groups.

The postoperative Doppler-echocardiographic data are presented in Table 2. The mean systolic PA pressure for the whole group after operation was 42 ± 10 mm Hg (range 22 to 61 mm Hg), whereas evidence of PA hypertension defined as a systolic PA pressure >40 mm Hg was found in 30 of the 56 patients (54%).
Impact of PPM on PA pressure. As expected, mitral valve EOA and indexed mitral valve EOA were significantly lower in patients with PPM as compared to patients with no PPM. The former patients also had significantly higher peak and mean transvalvular pressure gradients, PA pressure, and prevalence of PA hypertension, whereas their net atrioventricular compliance was significantly lower (Table 2). The indexed EOA (i.e., the degree of PPM) correlated well with postoperative PA pressures ($r = 0.64$; Fig. 1) and to a lesser extent with peak ($r = 0.50$) and mean ($r = 0.46$) gradients, and atrioventricular compliance ($r = 0.37$). Hence, the average systolic PA pressure was significantly higher ($p < 0.001$) in patients with PPM (46 ± 8 mm Hg) compared to patients with no PPM (34 ± 8 mm Hg) (Table 2).
Likewise, the prevalence of persistent PA hypertension after MVR was 68% in patients with PPM versus 19% in patients with no PPM (Fig. 2). An indexed mitral valve EOA ≥1.2 cm²/m² had a sensitivity of 68% and a specificity of 81% to predict PA hypertension.

Impact of atrioventricular compliance on PA pressure. Systolic PA pressure also correlated (r = 0.53) with net atrioventricular compliance (Fig. 3). On average, patients with an atrioventricular compliance ≥4 ml/mm Hg had a significantly higher (p < 0.001) postoperative systolic PA pressure (46 ± 8 mm Hg) compared to those with compliance >4.0 ml/mm Hg (36 ± 8 mm Hg).

Independent determinants of PA pressure. In multivariate analysis, the independent determinants of systolic PA pressure were: indexed mitral valve EOA (p < 0.001), net atrioventricular compliance (p < 0.001), and mean transvalvular flow rate (p = 0.04) (Table 3). Indexed EOA had the most important contribution in the multivariate model followed by atrioventricular compliance. Mean transvalvular flow rate had a minimal contribution with borderline significance. There was a weak (r = 0.35, p = 0.007) correlation between time to follow-up and postoperative PA pressure in univariate analysis, but this variable was not a significant independent predictor of PA pressure in multivariate analysis.

In the subgroup of 48 patients in whom the preoperative PA pressure was available, this variable did not come out as a significant predictor of postoperative PA pressure in multivariate analysis, and the only significant predictors were the indexed MVA (ΔR² = 0.39, p = 0.003) and the net atrioventricular compliance (ΔR² = 0.08, p = 0.01).

In Figure 4, the patients were separated into four subgroups depending on the presence of PPM and of low atrioventricular compliance defined as being ≤4.0 ml/mm Hg. The systolic PA pressure and prevalence of PA hypertension were 33 ± 9 mm Hg and 23% in patients (n = 13) with no PPM and normal compliance, 34 ± 2 mm Hg and 0% in patients (n = 3) with no PPM and low compliance, 40 ± 5 mm Hg and 36% in patients (n = 11) with PPM and normal compliance, and 48 ± 7 mm Hg and 79% in patients (n = 29) with PPM and low compliance.

Table 3. Independent Determinants of Postoperative Systolic Pulmonary Arterial Pressure

<table>
<thead>
<tr>
<th>Variables</th>
<th>Standardized Coefficient</th>
<th>ΔR²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.14</td>
<td>—</td>
<td>0.11</td>
</tr>
<tr>
<td>Gender</td>
<td>0.85</td>
<td>—</td>
<td>0.68</td>
</tr>
<tr>
<td>Indexed mitral valve EOA</td>
<td>−0.52</td>
<td>0.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Net atrioventricular compliance</td>
<td>−0.39</td>
<td>0.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean transvalvular flow rate</td>
<td>0.23</td>
<td>0.04</td>
<td>0.049</td>
</tr>
</tbody>
</table>

The ΔR² value represents the respective contribution of the variable to the variance of the systolic pulmonary arterial pressure in the multivariate model. EOA = effective orifice area.
An increase in PA pressure can result from elevation of pulmonary blood flow, pulmonary venous pressure, and/or vascular resistance (25–27). The major consequence of PA hypertension is right ventricular failure, which generally results from chronic pressure overload and associated volume overload with the development of tricuspid regurgitation (26); PA hypertension is an important risk factor for morbidity and mortality in patients with cardiovascular diseases (28–33). The clinical course of patients with PA hypertension can be highly variable depending on the underlying disease. However, with the onset of right ventricular failure, patient survival is generally limited to approximately six months (26); PA hypertension is frequently (30% to 70%) observed in patients with mitral valve disease (2–6,34). The passive elevation of PA pressure due to elevated left atrial pressure is the main mechanism leading to PA hypertension in these patients. In addition to this passive elevation of PA pressure, there is often a reactive vasoconstriction of the pulmonary arterioles that causes an increase in pulmonary vascular resistance and, thus, contributes to the elevation of PA pressure. Moreover, in patients with longstanding disease, potentially irreversible structural changes may occur in the pulmonary vasculature.

Given that PA hypertension is quite prevalent in patients with severe mitral valve disease and that it is associated with poor functional capacity and dismal prognosis (1–3,35), normalization of PA pressure, therefore, constitutes a crucial goal of MVR. Successful surgical relief of the mechanical cause of pulmonary venous hypertension generally reduces PA pressure and promotes regression of the reversible components of pulmonary vascular changes (25,26). Unfortunately, the relief of the passive elevation of left atrial pressure and, thus, of PA pressure is often incomplete, (5,6) likely due to the interaction of prosthesis- and/or patient-related factors. Zielinski et al. (5) reported PA pressure data obtained by catheterization before and one year after MVR. In 14 patients with PA hypertension (defined as systolic PA pressure >40 mm Hg) before operation, PA hypertension was still present in seven patients (50%) one year after operation. Furthermore, among the eight patients who had normal PA pressure before MVR, three (38%) developed PA hypertension after MVR. In addition, all patients except two had PA pressure >50 mm Hg when they were submitted to mild exercise (25 W workload). Of the 56 patients included in the present study, 30 (54%) still had PA hypertension after MVR.

Impact of PPM on PA pressure. Previous studies have demonstrated that PPM is associated with inferior hemodynamics, less regression of left ventricular hypertrophy, more cardiac events, and higher mortality rates after aortic valve replacement (7,10,36–44). However, the hemodynamic and clinical impact of PPM after MVR is relatively unexplored (8–10). In the first published report of mitral PPM, Rahimtoola and Murphy (8) described the case of a patient who remained symptomatic and had persistent PA hypertension and progressive right-sided failure after MVR. Accordingly, the major finding of the present study is that PPM is a strong risk factor for the persistence of PA hypertension after MVR. Hence, the prevalence of PA hypertension decreased from 69% to 19% after operation in patients with no PPM, whereas it remained unchanged in patients with PPM (66% before operation vs. 68% after operation) (Fig. 2).

In patients with an aortic prosthesis, previous studies also consistently found a strong correlation between the indexed EOA and the postoperative transprosthetic gradients measured at rest or during exercise (36,40,45). However, as reported in the present study as well as in the previous study by Dumesnil et al. (9), 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 much more sensitive to the chronotropic conditions than that of the aortic valve. Indeed, for similar indexed EOA, the pressure gradients across the mitral valve are highly influenced by the transvalvular flow rate, which is essentially determined by two factors: the diastolic filling volume and the diastolic filling time. In turn, diastolic time is highly dependent on heart rate. A change in heart rate has a much greater impact on the diastolic duration than on the systolic duration. This difference may contribute to the explanation of the lower correlation between indexed EOA and pressure gradients that is observed in mitral prostheses. In this context, it is also interesting to note that the indexed mitral EOA correlated better with systolic PA pressure than with transprosthetic pressure gradients; this finding is consistent with the fact that PA pressure is probably less influenced by chronotropic conditions than are pressure gradients.

Atrioventricular compliance, a physiological modulator of PA pressure. Patients with chronic mitral valve disease often have an abnormally low atrial compliance due to left atrial remodeling and hypertrophy. In turn, a reduction in atrial compliance will necessarily result in a decrease in net
atrioventricular compliance because, according to equation 2, the latter is always lower than either of its two components (i.e., left ventricular and left atrial compliances). In patients with native mitral valve stenosis, Schwammenthal et al. (19) demonstrated that atrioventricular compliance is an important physiological modulator of left atrial and PA pressures. In the context of MVR, it, however, becomes evident that compliance is also influenced by PPM. This observation appears to be confirmed by the results of univariate and multivariate analysis (Table 3), whereby, in univariate analysis, PPM (i.e., indexed EOA) accounts for 41% of the variance of PA pressure compared to 28% for compliance, whereas, in multivariate analysis, the independent contribution of PPM remains at 41%, but that of compliance decreases to 10%, suggesting that compliance is indeed influenced by PPM. Also consistent with this observation is the fact that reduced atrioventricular compliance had a minimal effect on PA pressure in the absence of PPM, whereas the combination of PPM and low atrioventricular compliance was associated with a dramatic increase in the prevalence of PA hypertension (Fig. 4). Hence, it would appear that a decrease in atrial compliance may be relatively well tolerated in patients with a prosthetic valve with a large EOA and no PPM but that the same condition may be much less well tolerated in patients with a relative obstruction to flow due to the prosthesis.

Clinical implication. The clinical implications of these results are important given that PPM is frequent in patients undergoing MVR. Moreover, as opposed to most other risk factors for PA hypertension, PPM may eventually be avoided by using a prospective strategy at the time of operation. Such a strategy has been well described and validated for the prevention of PPM in the aortic position (40,43,46,47). Suggested options to avoid PPM in the aortic position are either to perform an aortic root enlargement to accommodate a larger prosthesis or to use another type of prosthesis with a better hemodynamic profile (i.e., with a larger EOA; e.g., a stentless bioprosthesis or a mechanical valve).

In the mitral position, there is no alternative technique allowing implantation of a larger prosthesis size. The preventive strategy should, therefore, be focused on the implantation of the prosthesis having the largest EOA for a given size. The objective would be to obtain a postoperative indexed EOA >1.2 to 1.3 cm²/m². To this effect, the bileaflet mechanical valves of new generation may be an important physiological modulator of left atrial and PA pressures. In the context of MVR, it, however, becomes evident that compliance is also influenced by PPM. This observation appears to be confirmed by the results of univariate and multivariate analysis (Table 3), whereby, in univariate analysis, PPM (i.e., indexed EOA) accounts for 41% of the variance of PA pressure compared to 28% for compliance, whereas, in multivariate analysis, the independent contribution of PPM remains at 41%, but that of compliance decreases to 10%, suggesting that compliance is indeed influenced by PPM. Also consistent with this observation is the fact that reduced atrioventricular compliance had a minimal effect on PA pressure in the absence of PPM, whereas the combination of PPM and low atrioventricular compliance was associated with a dramatic increase in the prevalence of PA hypertension (Fig. 4). Hence, it would appear that a decrease in atrial compliance may be relatively well tolerated in patients with a prosthetic valve with a large EOA and no PPM but that the same condition may be much less well tolerated in patients with a relative obstruction to flow due to the prosthesis.

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Study limitations. The main limitation of this study is its retrospective design. This may have introduced some selection bias. Also, the preoperative values of systolic PA pressure could not be obtained in several patients. Further prospective studies are, thus, necessary to determine the impact of PPM on the regression or progression of PA hypertension.

Beyond PPM and atrioventricular compliance, other factors, such as pulmonary vascular resistance or PA compliance, may also influence the normalization of PA pressure after MVR. However, these factors are difficult to estimate by Doppler-echocardiography, and they were indeed not measured in this study. Nonetheless, it should also be considered that, as opposed to PPM, these factors are hardly preventable or modifiable. Hence, although this information could be used to evaluate postoperative outcome, it could not contribute to the development of a prospective strategy that would optimize the regression of PA hypertension after MVR.

Conclusions. Persistent PA hypertension is frequent after MVR and strongly associated with the presence of valve PPM. The clinical implications of these findings are important given that PPM may be avoided by using a simple prospective strategy at the time of operation.

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