Impact of Valve Prosthesis-Patient Mismatch on Short-Term Mortality After Aortic Valve Replacement

Claudia Blais, BSc; Jean G. Dumesnil, MD; Richard Baillot, MD; Serge Simard, MS; Daniel Doyle, MD; Philippe Pibarot, DVM, PhD

Background—The prosthesis used for aortic valve replacement (AVR) can be too small in relation to body size, thus causing valve prosthesis-patient mismatch (PPM) and abnormally high transvalvular pressure gradients. This study examined if there is a relation between PPM and short-term mortality after operation.

Methods and Results—The indexed valve effective orifice area (EOA) was estimated for each type and size of prosthesis being implanted in 1266 consecutive patients and used to define PPM as not clinically significant if >0.85 cm²/m², as moderate if 0.65 cm²/m² and ≤0.85 cm²/m², and as severe if ≤0.65 cm²/m²; it was correlated with 30-day mortality and compared with other relevant variables. Moderate or severe PPM was present in 38% of patients. Thirty-day mortality was 4.6% (58/1266 patients) and the strongest independent predictors in multivariate analysis were left ventricular ejection fraction <40% (P=0.007), infectious endocarditis (P=0.002), emergent/salvage operation (P=0.002), cardiopulmonary bypass time >120 minutes (P=0.001), and PPM (P=0.003). Relative risk of mortality was increased 2.1-fold (95% confidence interval, 1.2 to 3.7) in patients with moderate PPM and 11.4-fold (4.4 to 29.5) in those with severe PPM. Moreover, risk of mortality for every category of PPM was higher in patients with a left ventricular ejection fraction <40% as compared with ≥40% (nonsignificant PPM, 2.7 versus 1.0; moderate PPM, 7.1 versus 1.8; severe PPM, 77.1 versus 11.3).

Conclusion—PPM is a strong and independent predictor of short-term mortality among patients undergoing AVR, and its impact is related both to its degree of severity and the status of left ventricular function. In contrast to other risk factors, moderate-severe PPM can be largely avoided with the use of a prospective strategy at the time of operation.

Key Words: valves ▪ prosthesis ▪ mortality ▪ hemodynamics

Valve prosthesis-patient mismatch (PPM) was first defined by Rahimtoola as being present when the effective orifice area (EOA) of the prosthesis being implanted is less than that of the normal human valve. Based on this definition, most patients undergoing aortic valve replacement (AVR) thus have at least mild PPM. Moreover, previous studies have reported that more than mild PPM, defined as an indexed EOA <0.85 cm²/m², may be quite prevalent (19% to 70%), and that it is associated with less symptomatic improvement, worse hemodynamics at rest and during exercise, less regression of left ventricular hypertrophy, and more cardiac events after operation. However, the impact of PPM on survival remains controversial and largely unexplored. In particular, the relation between PPM and short-term mortality remains to be determined and it could theoretically be important given that the left ventricle is more vulnerable at that time and that it could thus be more sensitive to the increased hemodynamic burden imposed by PPM.

Methods

Patient Population
Baseline risk factors and subsequent short-term mortality were analyzed in 1266 consecutive patients undergoing AVR with a prosthetic heart valve at the Quebec Heart Institute between January 1992 and December 2001. Clinical, angiographic, echocardiographic, operative, and outcome data were prospectively collected in a computerized database. Left ventricular ejection fraction was determined within 3 months before operation by either echocardiography and/or angiography in 92.4% (1170/1266) of patients. The prosthetic valves implanted are presented in Table 1. Forty five percent (45.3%) of patients underwent concomitant coronary artery bypass graft surgery.

The indexed EOA for each prosthesis was derived from reference normal values of EOA (Table 1) divided by the patient’s body surface area, as previously described and validated. PPM was defined as not clinically significant (ie, mild or no PPM) if the indexed EOA was >0.85 cm²/m², as moderate if it was 0.65 cm²/m² and ≤0.85 cm²/m², and as severe if it was ≤0.65 cm²/m². Short-term mortality was defined as death from any cause within 30 days after operation if the patient was discharged from hospital or...
within any interval if the patient was not discharged. Baseline preoperative and operative variables used in this analysis and tested for association with mortality were defined according to the guidelines of the Society of Thoracic Surgeons.16

Statistical Analysis
Differences between groups for baseline variables were tested for statistical significance by t, Chi-squared, or Fischer Exact tests as appropriate. A stepwise logistic regression analysis was used to identify the independent predictors of mortality.

Results
Preoperative and Operative Data
Based on the aforementioned definitions, 36% had moderate PPM and 2% severe PPM. Compared with patients with nonsignificant PPM, patients with moderate or severe PPM were older and had higher prevalence of female gender, coronary artery disease, hypertension, diabetes, small prosthesis (size ≤21 mm), concomitant coronary artery bypass graft, and emergent/salvage operation (Table 2). The overall short-term mortality in the cohort was 4.6% (58/1266 patients). Mortality rate was 3.0% in the group with nonsignificant PPM, 6.0% in the group with moderate PPM, and 25.9% in the group with severe PPM.

Predictors of Mortality
Nineteen patients died during or within 24 hours after operation, 33 patients died between 1 and 30 days, and 6 patients died between 31 and 132 days. The baseline variables associated with short-term mortality in univariate analysis are presented in Table 3. The independent risk factors for mortality in multivariate analysis were as follows: emergent/salvage operation (P=0.001), cardiopulmonary bypass time >120 minutes (P=0.001), active infectious endocarditis (P=0.002), moderate-severe PPM (P=0.003), preoperative left ventricular ejection fraction <40% (P=0.007), and chronic lung disease (P=0.03) (Table 3).

Impact of Mismatch Severity on Mortality
The risk of mortality was increased 2.1-fold (95% CI: 1.2 to 3.7) in patients with moderate PPM and 11.4-fold (95% CI: 4.4 to 29.5) in those with severe PPM as compared with patients with nonsignificant PPM (Figure 1). In multivariate analysis, these risk ratios were 2.0 (95% CI: 1.1 to 3.7) for moderate PPM and 12.6 (95% CI: 4.3 to 37.0) for severe PPM. In the subgroup of patients with moderate-severe PPM, the independent predictors of mortality in multivariate analysis were cardiopulmonary bypass time >120 minutes (P=0.002), preoperative left ventricular ejection fraction <40% (P=0.006), and severe PPM (P=0.0003) (Table 4). Moreover, for every category of PPM, the risk of mortality was greater in patients with a preoperative left ventricular ejection fraction <40% as opposed to ≥40% (Figure 2).

Table 5 shows the cause of death in relation to the severity of PPM. It should be noted that all patients with severe PPM died from cardiac cause (5 from low cardiac output syndrome and 2 from perioperative myocardial infarction).

Discussion
The major finding of this study is that PPM is an important and independent risk factor for short-term mortality in patients undergoing AVR. Indeed, the risk of mortality was increased 10-fold in patients with severe PPM as opposed to nonsignificant PPM. Moreover, PPM is particularly deleterious in patients with left ventricular dysfunction (Figure 2). The practical implications of these findings are important given that moderate-severe PPM is not a rare occurrence with a prevalence between 19 and 70% being reported in the literature. Furthermore, as opposed to other predictors of short-term mortality, moderate-severe

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### Table 1. Normal Reference Values of Effective Orifice Areas for the Prosthetic Valves

<table>
<thead>
<tr>
<th>Prosthetic Valve Size, mm</th>
<th>No. of Patients,*</th>
<th>19</th>
<th>21</th>
<th>23</th>
<th>25</th>
<th>27</th>
<th>29</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stented bioprosthetic valves</td>
<td>Medtronic Intact</td>
<td>129 (10.2)</td>
<td>0.85</td>
<td>1.02</td>
<td>1.27</td>
<td>1.40</td>
<td>1.66</td>
<td>2.04</td>
</tr>
<tr>
<td>Medtronic Mosaic</td>
<td>390 (30.8)</td>
<td>1.20</td>
<td>1.22</td>
<td>1.38</td>
<td>1.65</td>
<td>1.80</td>
<td>2.00</td>
<td>23</td>
</tr>
<tr>
<td>Hancock II</td>
<td>53 (4.2)</td>
<td>...</td>
<td>1.18</td>
<td>1.33</td>
<td>1.46</td>
<td>1.55</td>
<td>1.60</td>
<td>4</td>
</tr>
<tr>
<td>Carpentier-Edwards Perimount</td>
<td>59 (4.7)</td>
<td>1.10</td>
<td>1.30</td>
<td>1.50</td>
<td>1.80</td>
<td>1.80</td>
<td>...</td>
<td>4</td>
</tr>
<tr>
<td>St. Jude Medical X-cell</td>
<td>21 (1.7)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Stentless bioprosthetic valves</td>
<td>Medtronic freestyle</td>
<td>368 (29.1)</td>
<td>1.15</td>
<td>1.35</td>
<td>1.48</td>
<td>2.00</td>
<td>2.32</td>
<td>...</td>
</tr>
<tr>
<td>St Jude Medical Toronto SPV</td>
<td>60 (4.7)</td>
<td>...</td>
<td>1.30</td>
<td>1.50</td>
<td>1.70</td>
<td>2.00</td>
<td>2.50</td>
<td>4</td>
</tr>
<tr>
<td>Mechanical valves</td>
<td>St Jude Medical Standard</td>
<td>151 (11.9)</td>
<td>1.04</td>
<td>1.38</td>
<td>1.52</td>
<td>2.08</td>
<td>2.65</td>
<td>3.23</td>
</tr>
<tr>
<td>St. Jude Medical Regent</td>
<td>13 (1.0)</td>
<td>1.50</td>
<td>2.00</td>
<td>2.40</td>
<td>2.50</td>
<td>3.60</td>
<td>4.80</td>
<td>24</td>
</tr>
<tr>
<td>MCR On-X</td>
<td>18 (1.4)</td>
<td>1.50</td>
<td>1.70</td>
<td>2.00</td>
<td>2.40</td>
<td>3.20</td>
<td>3.20</td>
<td>25</td>
</tr>
<tr>
<td>Carbomedics</td>
<td>3 (0.2)</td>
<td>1.00</td>
<td>1.54</td>
<td>1.63</td>
<td>1.98</td>
<td>2.41</td>
<td>2.63</td>
<td>4</td>
</tr>
<tr>
<td>Björk Shiley CC</td>
<td>1 (0.1)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Effective orifice area is expressed as mean values available in the literature.

*No. of patients with the prosthesis in the present study.
PPM can be largely avoided with the use of a proper preventive strategy at the time of operation.4,12,17

Independent Predictors of Short-Term Mortality

Previous studies have identified several independent predictors of short-term mortality related to AVR,15,18–22 and most of them were also found to be present in this study (Table 3): emergent/salvage operation, cardiopulmonary bypass time, infectious endocarditis, poor left ventricular ejection fraction, and chronic lung disease. Other factors, also previously reported as independent predictors of mortality but not found to be predictors in the present study were age, female gender, advanced New York Heart Association functional class, diabetes, hypertension, renal failure, coronary artery disease, recent myocardial infarction, left ventricular hypertrophy, and smaller prosthetic valve. However, the influence of PPM was not analyzed in these studies and it would appear evident that most previously identified risk factors were hardly preventable or modifiable. Hence, although this information could be used to evaluate operative risk, it could not contribute to the development of a prospective strategy that would reduce mortality risk related to AVR.

Mismatch as a Predictor of Short-Term Mortality

To our knowledge, there has been only one other study that has attempted to quantify the influence of PPM on short-term mortality. In a cohort of 2154 patients who underwent AVR, Rao et al10 found that 30-day mortality was significantly higher (7.9% versus 4.6%; P=0.03) in patients with evidence of moderate-severe PPM. In multivariate analysis, PPM was an independent predictor only of long-term valve-related mortality but not short-term mortality. However, in the latter study, no distinction was made between patients with and without left ventricular dysfunction and in vitro rather than in vivo values were used to calculate the indexed EOA, resulting in potentially higher values for indexed EOA.2,4

The indexed valve EOA was also used by Milano et al6 to analyze the influence of PPM in patients undergoing AVR. As in a previous study from our laboratory,7 these authors identified severe PPM as an independent predictor of late cardiac events but not of late mortality. However, short-term mortality was not analyzed nor was left ventricular function taken into account. Nonetheless, when considered collectively, these previous studies6,7,10,11 might indirectly suggest that the greatest impact of PPM with regards to survival is in the early postoperative period when the left ventricle is most vulnerable. Our results also suggest that there could be a natural selection process at that time of operation during which many patients at risk do not survive beyond the early postoperative period, which in turn could explain the relatively better prognosis of moderate-severe PPM beyond that critical period.

Other studies have also purported to analyze the influence of moderate-severe PPM on mortality after AVR8,9 and they could not identify any major influence. It should however be emphasized that in these studies, PPM was defined on the basis of the indexed internal geometric area calculated from
the anatomically measured internal diameter of the prosthesis divided by the patient’s body surface area. However, physiological studies have repeatedly shown that the latter parameter cannot be related to transvalvular pressure gradients and/or left ventricular workload and that it overestimates EOA in varying proportions depending on prosthesis type and geometry. Hence, it would appear that the conclusion that PPM is not related to mortality based on measurements of the internal geometric area or labeled valve size is not valid and/or left ventricular workload and that it overestimates EOA in varying proportions depending on prosthesis type and geometry. Hence, it would appear that the conclusion that PPM is not related to mortality based on measurements of the internal geometric area or labeled valve size is not valid because it has been shown that neither parameter can be used to identify patients who have a high postoperative gradient on the basis of PPM. In this context, the present study is the first to examine the impact of PPM on short-term mortality based on the only parameter yet demonstrated as being valid to identify PPM, ie, the indexed EOA.

Our results suggest that not only severe PPM but also moderate PPM are independent predictors of short-term mortality. Although the mortality risk ratio of moderate PPM (2.0) is lower than that of severe PPM (12.6), infectious endocarditis (9.2), emergent/salvage operation (5.8), and LV ejection fraction <40% (2.8), it should also be emphasized that its prevalence (36.0%) is much higher than that of these factors (2.2%, 0.9%, 1.7%, and 10.7%, respectively). Hence, according to these results, the total number of deaths related to moderate PPM would be higher than that related to other factors having high risk ratio but low prevalence.

**Impact of Mismatch in Patients With Poor Left Ventricular Function**

It is striking to note the dramatic increase in mortality risk due to the combination of poor left ventricular function and moderate-severe PPM (Figure 2). This result is indirectly consistent with the study of Connolly et al that reported a markedly higher mortality (47 versus 15%; \( P=0.03 \)) in patients with aortic stenosis and poor left ventricular ejection fraction (≤35%) receiving a small (≤21 mm) prosthesis as compared with a larger prosthesis. Although this study was not a direct analysis of PPM based on the indexed EOA, it nonetheless underlines the concept that a diseased ventricle is much more sensitive to an increase in afterload than a normal ventricle. The present study further characterizes this phenomenon by establishing a more quantitative relation between the extent of PPM as defined by the indexed EOA and survival rates. From this relation, we would like to propose a refinement of preventive strategies that would go beyond the simplistic paradigm that states that a prosthesis as large as possible should be used.

**Clinical Implications: A Preventive Strategy**

Contrary to other risk factors for short-term mortality, moderate-severe PPM can be largely prevented by implementing a simple

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**Table 3. Predictors of Short-Term Mortality in Univariate and Multivariate Analysis for the Whole Cohort (n=1266)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients With Variable (%)</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Risk Ratio (95% CI)</td>
<td>Risk Ratio (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>1266 (100)</td>
<td>0.01</td>
<td>1.04 (1.01–1.07)</td>
</tr>
<tr>
<td>NYHA functional class IV</td>
<td>140 (11.1)</td>
<td>&lt;0.0001</td>
<td>3.7 (2.0–6.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>293 (23.1)</td>
<td>0.04</td>
<td>1.8 (1.03–3.2)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>305 (24.1)</td>
<td>0.01</td>
<td>2.0 (1.2–3.5)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>43 (3.4)</td>
<td>0.03</td>
<td>2.9 (1.1–7.7)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>198 (15.6)</td>
<td>0.001</td>
<td>2.6 (1.4–4.6)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>306 (24.2)</td>
<td>0.01</td>
<td>2.0 (1.2–3.4)</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>154 (12.2)</td>
<td>0.04</td>
<td>2.0 (1.01–3.8)</td>
</tr>
<tr>
<td>Infectious endocarditis</td>
<td>12 (0.9)</td>
<td>0.0007</td>
<td>7.3 (1.9–27.6)</td>
</tr>
<tr>
<td>LV ejection fraction &lt;40%</td>
<td>125 (10.7)</td>
<td>&lt;0.0001</td>
<td>3.3 (1.7–6.2)</td>
</tr>
<tr>
<td>Operative variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergent/salvage operation</td>
<td>21 (1.7)</td>
<td>&lt;0.0001</td>
<td>9.2 (3.4–24.6)</td>
</tr>
<tr>
<td>Cardiopul. bypass time &gt;120 minutes</td>
<td>479 (37.8)</td>
<td>&lt;0.0001</td>
<td>2.8 (1.6–4.9)</td>
</tr>
<tr>
<td>Prosthetic valve size ≤21 mm</td>
<td>241 (19.0)</td>
<td>0.04</td>
<td>1.8 (1.01–3.3)</td>
</tr>
<tr>
<td>Moderate-severe PPM</td>
<td>474 (38.1)</td>
<td>&lt;0.0001</td>
<td>2.5 (1.5–4.3)</td>
</tr>
<tr>
<td>Concomitant surgery of the aorta</td>
<td>37 (2.9)</td>
<td>0.02</td>
<td>3.5 (1.3–9.3)</td>
</tr>
</tbody>
</table>

Only the variables that are significantly associated with mortality in univariate analysis are shown in this table.

**Figure 1.** Relative risk ratio for short-term mortality according to the presence and severity of valve prosthesis-patient mismatch. Numbers above the bars indicate the relative risk ratio for mortality compared with the group with nonsignificant mismatch.
three-step previously validated prospective strategy as follows: (1) Calculate patient’s body surface area from patient’s weight and height; (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 moderate-severe PPM; for instance, if patient’s body surface area is 1.60 m$^2$, then 1.60$\times$0.85=1.36 cm$^2$=minimal EOA to avoid moderate-severe PPM; and (3) Verify if the reference EOA (see Table 1) for the patient’s body surface area is 1.60 m$^2$, then 1.60$\times$0.85=1.36 cm$^2$=minimal EOA to avoid moderate-severe PPM; and (3) Verify if the reference EOA (see Table 1) for the model and size of prosthesis selected by the surgeon is equal or greater than the result of step 2 (ie, >1.36 cm$^2$ in the example chosen); if not, there is a risk of moderate-severe PPM and the surgeon should either attempt to implant another type of prosthesis with a larger EOA (eg, stentless prosthesis, homograft, mechanical prosthesis) or alternatively, perform an aortic root enlargement to accommodate a larger valve of the same type.

Such a strategy was recently utilized by Castro et al$^{17}$ who systematically performed an aortic root enlargement in 114 of 657 consecutive patients undergoing AVR and in whom the prosthesis initially selected did not meet the minimum requirement of 0.85 cm$^2$/m$^2$ given by step 2. As a result, incidence of moderate-severe PPM in their population was only 2.5% instead of the 17% that would have occurred had this prospective strategy not been used. Moreover, operative mortality was not increased as a result of the aortic root enlargement (overall mortality=3.6%). Nonetheless, in considering the different options, it is important to evaluate the potential benefits of avoiding moderate-severe PPM vis-à-vis the drawbacks of using alternative techniques. In particular, as the results of the present study suggest, a prolongation of the cardiopulmonary bypass time beyond 120 minutes could have a negative impact. In this context, moderate PPM in a relatively inactive and old patient with normal left ventricular function might be acceptable.

**Limitation of the Study**

Many patients in this study were directly referred to surgery without having had a preoperative echocardiogram in our institution, and as a consequence, reliable measurement of LV mass by echocardiography was available in a limited number of patients. In a subset of 473 patients who had echocardiographic measurements of LV dimensions before operation, Mehta et al$^{22}$ found that LV hypertrophy was a strong independent risk factor for in-hospital mortality after AVR. These authors did not however include the influence of PPM or prosthesis size in their analysis. Further studies will thus be necessary to determine if PPM is not only important in patients with left ventricular dysfunction but also in those with significant LV hypertrophy, given that PPM has been shown to seriously hamper LV mass regression after AVR.$^5$

The valve EOA indexed for body surface area may potentially overestimate the degree of PPM in obese patients. An alternative method would be to use valve EOA indexed for a power of patient’s height to define PPM. In our population, the EOA indexed for height squared was not found to be superior compared with the EOA indexed for body surface area for the prediction of short-term mortality. However, one cannot exclude that in a population with a higher proportion of obese patients, this index based on height would have been superior.

**Comorbid factors such as older age, female gender, coronary artery disease, hypertension, diabetes, and emergent/salvage operation were more prevalent in patients with moderate-severe PPM and it cannot be completely excluded that they might have contributed to the higher mortality in these patients. However, it should be considered that all these comorbidities, except emergent/salvage operation, were not significantly associated with increased short-term mortality. Also, moderate-severe PPM remained an independent predictor of short-term mortality when these potentially confounding factors were entered in multivar-
imate analysis (Table 3). Finally, the multivariate analysis performed separately in the patients with moderate-severe PPM confirmed that severe PPM is a strong and independent predictor of mortality (Table 4). The coherence of these results suggests that the contribution of other comorbid factors to the PPM-related mortality was minimal. Moreover, it should be emphasized that among these factors, PPM is the only one that can be prospectively prevented.

Conclusion

This study demonstrates that PPM is a strong and independent predictor of short-term mortality and that its impact is dependent both on its degree of severity and the status of left ventricular function. Moreover, moderate-severe PPM can be largely avoided by adopting a simple prospective strategy in every patient undergoing AVR.

Acknowledgments

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References

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