Patient–Prosthesis Mismatch and Reduction in Left Ventricular Mass After Aortic Valve Replacement

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Background. The presence of patient–prosthesis mismatch (PPM) after aortic valve replacement may influence patient survival. We examined the relationship between PPM and changes in left ventricular mass index at 3 months follow-up and also overall survival.

Methods. From patients included in the Mosaic trial, we studied data from 266 patients who underwent aortic valve replacement with the Medtronic Mosaic porcine bioprosthesis and had an echocardiography performed 3 months postoperatively. Complete echocardiographic data, to calculate left ventricular mass index, was available in 78% of the patients. The primary outcome for this substudy was prevalence and severity of PPM. Secondary outcomes were reduction in left ventricular mass index at 3 months follow-up and medium-term survival. Patients without PPM were defined as having an indexed effective orifice area greater than 0.85 cm²/m², and those with moderate and severe PPM as having an indexed effective orifice area between 0.65 cm²/m² and 0.85 cm²/m² or below 0.65 cm²/m², respectively.

Results. PPM was found in 217 (82%) patients. No difference in overall survival was found between patients with PPM and those without PPM. The change in left ventricular mass index was significantly different between groups (no PPM \(-31.4 \pm 28.0\) g/m², moderate PPM \(1.1 \pm 34.4\) g/m², and severe PPM \(-5.9 \pm 29.7\) g/m², respectively \((p = 0.01)\).

Conclusions. The presence of PPM did not influence medium-term survival. However, patients without PPM showed a marked reduction in left ventricular mass index as soon as 3 months postoperatively.


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Patient–prosthesis mismatch (PPM) was first defined in 1978 as present when the implanted valve was smaller than the patient’s normal native valve [1]. More recently, an indexed effective orifice area (IEOA) equal to or less than 0.85 cm²/m² has been used as the definition of PPM [2].

The presence of PPM after aortic valve replacement has in some studies been shown to increase short-term and long-term mortality [3–5]. The prevalence of PPM, in general, is high and ranges from 20% to 88% in the current literature [2, 6]. PPM results in high transprosthetic gradients, in turn resulting in a higher afterload on the left ventricle. In theory this would reduce the improvement in the patient’s symptoms, lead to left ventricular mass (LVM) regression, and could lead to more cardiac events. Postoperative left ventricular hypertrophy has also been shown to increase mortality [7].

A few studies exists comparing LVM regression with regard to the presence of PPM. Some studies have shown no relationship between PPM and LVM regression [8–11], whereas others have found a significant regression of LVM in favor of patients without PPM [12, 13].

The object of this study was to evaluate the prevalence and severity of PPM after aortic valve replacement with the Medtronic Mosaic porcine bioprosthesis (MM) and furthermore to examine the relationship between PPM and LVM regression at 3 months follow-up and also the medium-term survival in this cohort of patients.

Patients and Methods

Between April 2005 and September 2011, 266 patients were included in the Mosaic trial (ClinicalTrials.gov Identifier: NCT01452568). The Mosaic trial is a single-center randomized open-label clinical trial in which patients were randomly allocated to either standard 3-month treatment with warfarin or 150 mg acetylsalicylic acid after aortic valve replacement with the MM. Primary outcome measures in the Mosaic trial are hemorrhagic or thromboembolic complications at 3 months follow-up. Enrollment in the Mosaic trial ended in 2012.

Patients were eligible for the Mosaic trial if they were aged above 60 years and had aortic valve disease suitable for operation with aortic valve replacement by a biological stented valve, with or without concomitant coronary artery bypass grafting.

Exclusion criteria were double valve procedures, active endocarditis, preoperative atrial fibrillation or flutter, preoperative anticoagulant therapy, and preoperative cerebrovascular events.

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The prosthesis size of choice was established intraoperatively with the Medtronic Mosaic sizer used for the Mosaic bioprosthesis. Calculation of the required effective orifice area based on the patient’s body surface area (BSA) was not done preoperatively.

Inasmuch as the Mosaic trial was not originally designed to evaluate PPM, this was a retrospective post-hoc analysis. For that reason, the results of this substudy are only hypothesis generating and are not in any way conclusive.

Outcomes
The primary outcome for our retrospective analysis was to investigate the prevalence and severity of PPM after heart surgical procedures involving aortic valve replacement with the MM. The postoperative effective orifice area (EOA) of the bioprosthesis was calculated after echocardiography at 3 months postoperatively, by use of the continuity equation.

The EOA was indexed by BSA. An EOA between 0.65 cm²/m² and 0.85 cm²/m² and below 0.65 cm²/m² was used to define moderate and severe PPM, respectively [2, 14–17]. Patients were defined as not having PPM when the EOA exceeded 0.85 cm²/m².

Secondary outcome measures were changes in left ventricular mass index (LVMI) after 3 months and medium-term survival. The LVMI preoperatively and at follow-up was calculated by the formula of Devereux and Reichek [18], wherein LVMI = left ventricular internal diameter in diastole, PWTD = posterior wall thickness in diastole, and IVSTD = interventricular septum thickness in diastole: 0.8 (1.04 (LVIMDD + PWTD + IVSTD)² – [LVIMDD])² – 13.6 g. The LVMI was calculated by dividing LVMI by the patient’s BSA.

Echocardiography was performed preoperatively and 3 months postoperatively. All follow-up echocardiograms were performed at Rigshospitalet. Patients included in the trial had preoperative echocardiography performed at Rigshospitalet. However, in 5 patients, preoperative echocardiography was performed at a local hospital. In these 5 cases, the examination results were reinterpreted at Rigshospitalet. The interpretations of all echocardiograms were done by the same group of cardiologists at the core echocardiography lab at Rigshospitalet.

Statistical Analysis
Statistical analysis was performed with the statistical software package SPSS, version 18.0 (SPSS Inc; Chicago, IL).

Continuous variables were expressed as mean ± standard deviation and tested for significance between groups by one-way analysis of variance.

If the F value was significant and variance was homogenous, Tukey’s multiple comparison test was used to assess the differences between the groups. Otherwise, Tamhane’s T2 test was used. The Kruskal-Wallis one-way analysis of variance was used to compare the three groups in terms of dichotomous variables. An independent samples Kruskal-Wallis test was used to compare data that were not normally distributed. A Kaplan-Meier plot was used to illustrate survival between the groups and tested for significance using the log-rank (Mantel-Cox) test.

Investigation of the independent determinants of left ventricular mass regression was performed by multivariate linear regression analysis, which included all preoperative patient characteristics and preoperative echocardiographic data followed by a stepwise backward model selection. Variables were eliminated when the p value exceeded 0.1. Before performance of the stepwise backward model selection, all independent variables were checked for normality, homogeneity of variance, and linearity.

Differences were considered to be statistically significant when the p value was lower than 0.05.

Results
Of 274 patients enrolled in the Mosaic trial until December 2012, 8 patients died in the early follow-up period with no or incomplete echocardiographic data to calculate IEOA, leaving 266 eligible for analysis of survival. Changes in LVMI could be calculated in 208 of these patients (78%).

PPM
On the basis of IEOA, 49 (18%) patients were without PPM, 95 (36%) patients had moderate PPM, and 122 (46%) patients had severe PPM. The IEOA at follow-up was 1.03 ± 0.16 in the no-PPM group, 0.74 ± 0.06 in the moderate PPM group, and 0.54 ± 0.07 in the severe PPM group. No patients underwent enlargement of the aortic annulus. The patient characteristics are shown in Table 1. Body mass index (BMI) and BSA were significantly different between the groups. Perioperative data were comparable between groups (Table 2).

Left Ventricular Mass Index
There was a significant difference in LVMI regression and transvalvular pressure gradients between the groups (Table 3 and Fig 1). The mean time to follow-up was 3.3 ± 1.0 months.

No significant correlation was found between transaortic valve gradients and change in LVMI.

In the severe PPM group, LVMI regression was −0.9 ± 32.8 g/m² in the presence of arterial hypertension and −14.6 ± 21.1 g/m² in patients without arterial hypertension (p = 0.015). No significant differences were found when the influence of arterial hypertension on LVMI regression was compared between the no-PPM and moderate PPM groups.

Independent predictors of change in LVMI at follow-up, found by multivariate linear regression analysis, are shown in Table 4. The presence of PPM, male sex, and higher age were independent predictors of less regression in LVMI at follow-up. High preoperative LVMI was an independent predictor of more regression of LVMI.

Survival
Figure 2 shows a Kaplan-Meier plot comparing survival between groups with a mean follow-up time of
Table 1. Preoperative Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>No PPM</th>
<th>Moderate PPM</th>
<th>Severe PPM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>49 (18)</td>
<td>95 (36)</td>
<td>122 (46)</td>
<td>-</td>
</tr>
<tr>
<td>Male sex</td>
<td>31 (63)</td>
<td>63 (66)</td>
<td>90 (74)</td>
<td>0.307</td>
</tr>
<tr>
<td>Age (years)</td>
<td>72.3 ± 7.0</td>
<td>72.9 ± 6.9</td>
<td>72.1 ± 7.3</td>
<td>0.755</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>25.7 ± 4.0&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>26.0 ± 3.7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>27.9 ± 4.3</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI &gt;25 (kg/m²)</td>
<td>25 (51)</td>
<td>57 (60)</td>
<td>86 (70)</td>
<td>0.042</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.84 ± 0.24&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>1.86 ± 0.21&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1.96 ± 0.26</td>
<td>0.001</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>5.7 ± 2.5</td>
<td>5.3 ± 2.0</td>
<td>5.5 ± 2.4</td>
<td>0.571</td>
</tr>
<tr>
<td>NYHA III/IV</td>
<td>31%</td>
<td>41%</td>
<td>36%</td>
<td>0.458</td>
</tr>
<tr>
<td>EF &lt;50%</td>
<td>20%</td>
<td>24%</td>
<td>27%</td>
<td>0.655</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57%</td>
<td>60%</td>
<td>59%</td>
<td>0.905</td>
</tr>
<tr>
<td>NIDDM</td>
<td>20%</td>
<td>12%</td>
<td>17%</td>
<td>0.295</td>
</tr>
<tr>
<td>IDDM</td>
<td>2%</td>
<td>2%</td>
<td>3%</td>
<td>0.808</td>
</tr>
<tr>
<td>PVD</td>
<td>8%</td>
<td>7%</td>
<td>10%</td>
<td>0.792</td>
</tr>
<tr>
<td>COPD/asthma</td>
<td>16%</td>
<td>16%</td>
<td>16%</td>
<td>0.979</td>
</tr>
</tbody>
</table>

<sup>a</sup> No PPM versus moderate PPM: p = 0.925.  <sup>b</sup> No PPM versus severe PPM: p = 0.005.  <sup>c</sup> Moderate PPM versus severe PPM: p = 0.002.  <sup>d</sup> No PPM versus moderate PPM: p = 0.973.  <sup>e</sup> No PPM versus severe PPM: p = 0.007.  <sup>f</sup> Moderate PPM versus severe PPM: p = 0.084.

Continuous data are given as mean ± standard deviation. Dichotomous variables are given as number (percentage).

BMI = body mass index; BSA = body surface area; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; IDDM = insulin-dependent diabetes mellitus; NIDDM = non-insulin-dependent diabetes mellitus; NYHA = New York Heart Association stage; PPM = patient-prosthesis mismatch; PVD = peripheral vessel disease.

1417 ± 576 days. No significant differences were found (p = 0.534). Subgroup analysis comparing BSA and BMI divided into groups above or under 1.90 m² and 27 kg/m², respectively, did not show any significant differences regarding survival (log rank p = 0.495 and p = 0.912).

Comment

This study exclusively included patients who received the MM, and this is the first study comparing LVMI regression as early as 3 months after operation.

First of all, we found a high prevalence of PPM, which was observed in 82% of patients. This number is among the higher of previously published results, wherein PPM ranges from 20% to 88%, all types of bioprostheses having been studied [2, 6]. Our study found similar results to those of our study, with a total of 88% of patients with PPM, divided into groups above or under 1.90 m² and 27 kg/m², respectively. We found mean BSA values to be 1.9 ± 0.2 m². This also leads to the speculation that there is a great deal of publication bias in regard to the prevalence of PPM.

Most studies find an increasing BSA and BMI according to the degree of PPM [4, 6, 11, 13]. One study found mean BSA values of 1.74 ± 0.2, 1.79 ± 0.17, and 1.84 ± 0.2 in a comparison of patients without PPM with moderate and severe PPM, respectively. We found mean BSA values to

Table 2. Perioperative Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>No PPM</th>
<th>Moderate PPM</th>
<th>Severe PPM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time (minutes)</td>
<td>207 ± 55</td>
<td>204 ± 61</td>
<td>207 ± 56</td>
<td>209 ± 52</td>
<td>0.820</td>
</tr>
<tr>
<td>ECC time (minutes)</td>
<td>104 ± 29</td>
<td>97 ± 26</td>
<td>107 ± 30</td>
<td>105 ± 29</td>
<td>0.137</td>
</tr>
<tr>
<td>Clamp time (minutes)</td>
<td>78 ± 22</td>
<td>75 ± 22</td>
<td>79 ± 21</td>
<td>79 ± 23</td>
<td>0.475</td>
</tr>
<tr>
<td>ICU stay&lt;sup&gt;g&lt;/sup&gt; (hours)</td>
<td>21 (221)</td>
<td>21 (216)</td>
<td>21 (159)</td>
<td>21 (201)</td>
<td>0.537</td>
</tr>
<tr>
<td>In-hospital stay (days)</td>
<td>9 ± 5</td>
<td>9 ± 4</td>
<td>9 ± 4</td>
<td>9 ± 5</td>
<td>0.844</td>
</tr>
<tr>
<td>Stand-alone AVR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>162</td>
<td>34 (69%)</td>
<td>55 (58%)</td>
<td>73 (60%)</td>
<td>0.844</td>
</tr>
<tr>
<td>AVR + CABGb</td>
<td>98</td>
<td>11 (23%)</td>
<td>40 (42%)</td>
<td>47 (38%)</td>
<td>0.475</td>
</tr>
<tr>
<td>AVR + other&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6</td>
<td>4 (8%)</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Median (range).  <sup>b</sup> Values given as number (percentage of total in subgroup).

AVR = aortic valve replacement;  CABG = coronary artery bypass grafting;  ICC = intensive care unit;  ECC = extracorporeal circulation;  PPM = patient-prosthesis mismatch.
Table 3. Echocardiographic Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>No PPM</th>
<th>Moderate PPM</th>
<th>Severe PPM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>37</td>
<td>76</td>
<td>95</td>
<td>-</td>
</tr>
<tr>
<td>Time to follow-up (months)</td>
<td>3.3 ± 1.1</td>
<td>3.4 ± 1.1</td>
<td>3.4 ± 0.9</td>
<td>0.876</td>
</tr>
<tr>
<td>Preoperative mean gradient (mm Hg)</td>
<td>39 ± 21</td>
<td>47 ± 18</td>
<td>42 ± 16</td>
<td>0.120</td>
</tr>
<tr>
<td>Mean gradient at follow-up (mm Hg)</td>
<td>13 ± 5ab</td>
<td>17 ± 6c</td>
<td>19 ± 6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Preoperative peak gradient (mm Hg)</td>
<td>65 ± 31d</td>
<td>76 ± 28d</td>
<td>67 ± 26</td>
<td>0.048</td>
</tr>
<tr>
<td>Peak gradient at follow-up (mm Hg)</td>
<td>27 ± 10ab</td>
<td>33 ± 11e</td>
<td>35 ± 12</td>
<td>0.002</td>
</tr>
<tr>
<td>Preop. LVMI (g/m²)</td>
<td>126 ± 38</td>
<td>125 ± 36</td>
<td>123 ± 39</td>
<td>0.913</td>
</tr>
<tr>
<td>ð LVMI (g/m²)</td>
<td>-31 ± 28ab</td>
<td>1 ± 34f</td>
<td>-6 ± 30</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Preop. EOA (cm²)</td>
<td>0.76 ± 0.22</td>
<td>0.78 ± 0.24</td>
<td>0.77 ± 0.20</td>
<td>0.950</td>
</tr>
<tr>
<td>EOA at follow-up (cm²)</td>
<td>1.90 ± 0.30ab</td>
<td>1.36 ± 0.17g</td>
<td>1.10 ± 0.16</td>
<td>&lt;0.000001</td>
</tr>
</tbody>
</table>

*No PPM versus moderate PPM: p < 0.05.  **No PPM versus severe PPM: p < 0.05.  ***Moderate PPM versus severe PPM: p = 0.205.  ^No significance was found in a comparison of means within groups.  ****Moderate PPM versus severe PPM: p = 0.505.  $$$Moderate PPM versus severe PPM: p = 0.412.  £Moderate PPM versus severe PPM: p < 0.05.

EOA = effective orifice area; LVM = left ventricular mass index; PPM = patient–prosthesis mismatch.

be 1.84 ± 0.24, 1.86 ± 0.21, and 1.96 ± 0.26 in the same groups. The values are lower compared with our findings; however, the differences between the groups are similar. This shows a weakness of the PPM definition, wherein overweight patients are wrongly defined as having PPM because the definition includes overweight patients with small aortic annuli in the PPM groups (ie, they can switch groups if they lose weight). It could also mean that more care should be taken to avoid PPM in patients with high BMI and BSA. In our study, more than 50% of the patients were overweight according to BMI (>25 kg/m²), which could explain the high number of patients with PPM.

The wide range of the reported prevalence of PPM in the literature is striking. Clearly, one contributing factor is that many studies compare different brands and types of valves in the same study. Considering the broad range of prostheses available on the market, this could clearly contribute to this inconsistency. The question should be raised, however, whether the definition of PPM or the way we measure it should be revised.

Our results indicate that patients without PPM, in contrast to patients with PPM, have LVM regression as soon as 3 months postoperatively.

Patient–prosthesis mismatch, age, sex, and preoperative LVMI were found to be independent predictors of change in LVMI. The latter showed a negative relationship with ð LVMI, meaning that smaller ventricles regress less in grams, compared with larger ventricles.

Some studies describe LVM regression in all groups but more pronounced regression in the no-PPM group [10, 13]. One study found a LVM regression of 47 g/m² in the no-PPM group and 28 g/m² in the PPM group at 18 months follow-up [13]. However, the groups were not divided into severity of PPM, and PPM was defined as an IEOA below 0.90 cm²/m². These findings indicate that LVM regression occurs earlier, and is more pronounced, in patients without PPM. Furthermore, we found that patients without preoperative arterial hypertension in the severe PPM group experienced a significant reduction in LVM compared with patients with arterial hypertension. This could indicate that as a result of arterial hypertension, hypertrophic ventricles still have to work against a higher pressure after the operation (ie, the reduced systemic arterial compliance) although the stenotic valve has been replaced. This might be the reason why we see none, or perhaps slower, regression of LVM in patients with arterial hypertension and severe PPM, as an indication that the left ventricle is only partially relieved by the operation. Reduced systemic arterial compliance has been shown to independently contribute to increased afterload and decreased left ventricular function in elderly patients with aortic stenosis [20].

We were not able to show any relationship between mortality and PPM. A recently published meta-analysis of 34 observational studies showed a significant increase in long-term all-cause-related and cardiac-related mortality in patient populations with moderate PPM (hazard...
**Table 4. Independent Predictors of Change in LVMI**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficient</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher age (years)</td>
<td>0.78</td>
<td>0.12 to 1.43</td>
<td>0.020</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>10.27</td>
<td>0.20 to 20.34</td>
<td>0.046</td>
</tr>
<tr>
<td>Higher preoperative LVMI (g/m²)</td>
<td>-0.33</td>
<td>-0.45 to -0.20</td>
<td>0.000001</td>
</tr>
<tr>
<td>PPM (present)</td>
<td>25.66</td>
<td>13.31 to 38.00</td>
<td>0.000065</td>
</tr>
</tbody>
</table>

Model statistics: Stepwise backwards linear regression analysis - Adjusted \( r^2 = 0.22 \) – Analysis of variance \( F = 12.549; p = 0.0000001 \) – Probability of \( F \) to remove: \( p > 0.1 \).

LVMI = left ventricular mass index; PPM = patient-prosthesis mismatch.

ratio = 1.19, 95% confidence interval 1.07 to 1.33) and severe PPM (hazard ratio = 1.84, 95% confidence interval 1.38 to 2.45) compared with patients without PPM [5]. In our study, patients with PPM are highly overrepresented and the sample size of patients without PPM is small. Thus, a population more evenly distributed among PPM categories, or a larger population, might yield different results.

Several studies exist on the subject of PPM and mortality; however, studies investigating the effect of PPM on postoperative functional recovery are sparse. One study found no relationship between the degree of PPM and functional recovery, by use of the Duke Activity Status Index survey on a cohort of 1108 patients [21]. These patients were operated on during the years 1995 to 1998. Large studies are needed to confirm these findings in the patients of today.

Finally, we found a significant difference between groups by comparing aortic valve mean and peak gradients postoperatively. The mean aortic valve gradients were 13 ± 5 mm Hg in the no-PPM group, 17 ± 6 mm Hg in the moderate PPM group, and 19 ± 6 mm Hg in the severe PPM group (significant difference between all groups). This comes as no surprise, given that the definition of PPM is derived from the exponentially increasing gradients when IEOA is less than or equal to 0.85. However, it validates the data.

**Limitations**

This study is retrospective with all its limitations. We analyzed PPM in patients included in the Mosaic trial, which was not designed to answer this question, and therefore these results can only be hypothesis generating but not conclusive.

In 22% of the patients, the echocardiographic data were too sparse to be included in the comparison of LVM regression between the groups. Inclusion criteria were patients above 60 years of age.

The study used echocardiographic data, which is subject to variability between physicians, regarding both the examination itself and the interpretation of the results.

The short time period until follow-up could also have influenced on the results.

**Conclusions**

Our results indicate that avoiding PPM could be beneficial regarding the regression of LVM. No significant differences in survival were found in a comparison of different degrees of PPM. More studies are needed to compare conventional valves with stentless valves, homografts, and surgical methods of aortic root enlargement with regard to PPM and survival.

**References**


