Patient-prosthesis mismatch does not affect survival following aortic valve replacement

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Abstract

Objective: Patient-prosthesis mismatch (PPM) has been reported to increase perioperative mortality and reduce postoperative survival in patients undergoing aortic valve replacement (AVR). We analysed the effect of PPM at values predicting severe mismatch on survival following AVR in our unit. Methods: Prospectively collected data on 1481 consecutive patients who had undergone AVR with or without coronary artery revascularisation between 1997 and 2005 were analysed. Projected in vitro valve effective orifice area (EOA) and geometric prosthesis internal orifice area (GOA) were evaluated and values were indexed to body surface area (cm² m⁻²). PPM was defined as EOAi < 0.6 and/or GOAi < 1.1. Long-term survival data were obtained from the National Institute of Statistics. Results: One thousand four hundred and eighteen patients were identified. 67/1418 (4.7%) patients had GOAi < 1.1; 122/1418 (8.6%) had EOAi < 0.6 and 38 (2.6%) patients exhibited both forms of mismatch. One thousand two hundred and sixty-seven patients (89%) demonstrated no mismatch (reference group). There were 75 in-hospital deaths (overall mortality 5.3%) with no significant difference between the mismatch and the reference groups. Survival data were available for up to 8 years (median 36 months, IQR 6—60 months). There were 160 late deaths (13/143 PPM group vs 147/1198 reference group). The 5-year survival estimate was similar for both groups (83% PPM group; 81% reference group; p = 0.47). Cox-hazard analysis identified advanced age as the only predictor of reduced survival (age > 80, RR 2.13, 95% CI 1.38—4.586, p = 0.004). Conclusions: Severe patient-prosthesis mismatch was predicted in 4—10% of patients undergoing AVR but this did not affect in-hospital mortality or mid-term survival.

Keywords: Aortic valve disease; Aortic valve replacement

1. Introduction

The concept of patient-prosthesis mismatch (PPM) was introduced to describe the condition of when the effective orifice of aortic valve prosthesis is less than that of a normal human valve. Different methods have been proposed to calculate PPM using either the effective orifice area (EOA) of the prosthesis [1] or the geometric orifice area (GOA) derived from the internal diameter of the prosthesis [2]. These values are then indexed to the patient’s body surface area. Postoperative analysis by echocardiography has demonstrated an increased incidence of high transvalvular gradients in patients with EOAi < 0.6 cm² m⁻², which is associated with the internal valve diameter, but has failed to identify high gradients in patient groups classified with mismatch but with EOAi ≥ 0.6 cm² m⁻² [3]. It has been hypothesised that high residual transvalvular gradients due to PPM may affect left ventricular mass regression following aortic valve replacement and this can lead to an increased operative mortality, decreased long-term survival and reduced symptomatic benefit. There is, however, variable evidence to support this postulate. The purpose of this study was to analyse the effect of predicted PPM on in-hospital mortality and post-discharge survival in patients undergoing aortic valve replacement at our institution.

2. Methods

This study was conducted at a single Cardiothoracic Surgical Centre. We reviewed data from the computerised cardic surgical database, which holds clinical information on all the patients undergoing cardiac surgery at our unit since 1997. The data are acquired prospectively as part of the patients’ pathway and is based upon the Society of Cardiothoracic Surgeon of GB and Ireland minimal dataset with some customised additions. We analysed data on all
consecutive patients aged >18 years undergoing first time or redo AVR (±coronary artery revascularisation) between January 1997 and March 2005. Patients requiring other valve procedures, those with pre-existing valve prosthesis other than aortic valve and those with active endocarditis were excluded from the study.

2.1. Definition of patient-prosthesis mismatch

The predicted functional effective orifice area was obtained from the manufacturers’ in vitro data and indexed to the patient body surface area (EOAi) as previously described and validated [3]. The geometric orifice area (GOAi) was calculated from the manufacturers’ geometric internal valve orifice diameter, a constant physical dimension, using the simple equation: area = \( \pi r^2 \), and indexed to the patient body surface area [2].

For the purpose of this study, an EOAi < 0.6 cm² m⁻² and/or GOAi < 1.1 cm² m⁻² were used as markers of severe PPM [2,4]. Patients without PPM are referred to as the reference group. For the purpose of the survival analysis, the group with PPM by any method was compared with those with no PPM.

2.2. Study end points

The study end points were all-cause in-hospital mortality and late survival. Post-discharge survival data was obtained from the National Office of Statistics, UK.

2.3. Data analysis

The data were analysed using SPSS® Version 12.0.1 for Windows. The difference between groups, for preoperative and operative variables was tested by Fischer Exact test. Continuous data were compared by Student’s t-test and are expressed as mean ± standard deviation. Backward conditional stepwise logistic regression analysis with a selection cut-off set at 0.05 using variables found to be significant in univariate analysis was performed to identify independent predictors of in-hospital mortality. Survival data was analysed by Kaplan–Meier life actuarial methods. Difference in survival between groups was tested by the log rank statistic. Cox proportional regression analysis was performed to identify independent predictors of late mortality.

3. Results

The study population consists of 1418 patients and their baseline and operative characteristics are summarised in Table 1.

3.1. In-hospital outcomes

The overall in-hospital mortality was 5.3% (75/1418 patients). Mortality for patients undergoing first time or redo isolated AVR was 3.8% (36/944) and for patients undergoing AVR + CABG was 8.2% (39/474) \( (p < 0.001) \). The EOAi method identified 122 patients with PPM (Fig. 1A), the GOAi method identified 67 patients with PPM (Fig. 1B), 38 patients reached both EOAi and GOAi criteria for PPM and 151 patients had PPM by either method (Table 2). Mismatch and reference patient groups were comparable for most risk factors, except for patients with EOAi < 0.6 cm² m⁻². This group was older and had a higher prevalence of female gender (Table 1). There was no significant difference for in-hospital mortality between patients with any form of PPM and the reference group (Table 2). At multivariate analysis, independent predictors of in-hospital mortality were advanced age (>80 years), female gender, diabetes, impaired left ventricular function, need for CABG and emergency surgery (Table 3).
There were 71 patients with poor LV (ejection fraction < 30%), of whom 6 (7%) reached the criteria for PPM. There was no significant difference in mortality between these two groups as there was one death in the PPM group (16.7%) and 11 deaths in the reference group (16.9%), \( p = 0.99 \).

### 3.2. Survival analysis

Survival data were available on all 1343 patients discharged from hospital. The median follow-up time was 3 years (IQR 18—44 months) (4029 patient-years follow-up). The 5-year survival estimate was similar for both groups (94% PPM group; 83.8% reference group; \( p = 0.37 \)) (Fig. 2).
Patient-prosthesis mismatch has been vaguely defined, often on the basis of small aortic prosthesis size, EOA, GOA and indexed values of EOA and GOA. In our study we defined PPM using values of EOAi and GOAi uniformly recognised to represent severe mismatch. In this study severe PPM occurred in 4–10% of patients undergoing AVR. This, however, did not translate into increased early in-hospital mortality or a decreased survival after discharge from hospital. Some reports have indicated that PPM can be associated with an increase in short-term mortality following AVR [1,5,6] and this phenomenon has been attributed to reduced cardiac performance following surgery. Most of these reports, however, have not been risk adjusted. Patients with a small aortic annulus are usually older, and they have more severe left ventricular hypertrophy with advanced diastolic dysfunction and coronary artery disease [7]. A recent study has identified a small increase (1%) in early postoperative mortality when using small aortic prostheses, but this finding was only evident after analysing a very large patient population [2]. Furthermore, the surgical alternative in these patients would have involved some form of aortic root enlargement, a procedure known to be associated with a significant increase in mortality [8].

It has been suggested that PPM is particularly harmful in patients with poor LV function preoperatively. Our study includes a small number of patients with poor LV function and is therefore not powerful enough to identify differences in outcome in this cohort.

Rao et al. [5] reported that severe PPM following AVR was associated with decreased long-term survival and hypothesised that this was due to the persistence of left ventricular hypertrophy in patients with small aortic prostheses. In that study, however, patients with PPM had an increase in valve-related mortality, whilst the overall survival was similar. This valve-related mortality may have included mechanisms of death probably unrelated to PPM such as embolic stroke, endocarditis, valve failure, and re-operation. In contrast a study by Hanayama et al. [4] has shown that patients with postoperative echocardiographic evidence of severe PPM (EOAi < 0.6 cm² m⁻²) had long-term survival similar to patients without mismatch. Furthermore, left ventricular mass index was not different between the two groups in that study. A recent multicentre report including more than 13,000 patients [2] has confirmed that PPM does not affect intermediate and long-term survival. Left ventricular mass regression following AVR depends not only upon post-operative transvalvular gradients but also on the control of blood pressure, the use of angiotensin-converting enzyme inhibitors and the degree of preoperative hypertrophy and myocardial fibrosis. Studies that address LV hypertrophy regression do not usually include details of these confounding variables. More recent studies comparing stented to stentless aortic prostheses, which are hypothesised to be associated with lower postoperative transvalvular gradients, have failed to detect significant differences in hypertrophy regression and survival when using these prostheses [9].

In our study, advanced age at the time of surgery was the only adverse predictor of adverse long-term survival post AVR, as previously shown [5].

### 4. Discussion

Patient-prosthesis mismatch has been vaguely defined, often on the basis of small aortic prosthesis size, EOA, GOA and indexed values of EOA and GOA. In our study we defined PPM using values of EOAi and GOAi uniformly recognised to represent severe mismatch. In this study severe PPM occurred in 4–10% of patients undergoing AVR. This, however, did not translate into increased early in-hospital mortality or a decreased survival after discharge from hospital. Some reports have indicated that PPM can be associated with an increase in short-term mortality following AVR [1,5,6] and this phenomenon has been attributed to reduced cardiac performance following surgery. Most of these reports, however, have not been risk adjusted. Patients with a small aortic annulus are usually older, and they have

### 4.1. Study limitations

We have used in vitro manufactures’ EOA which may overestimate in vivo echocardiographic EOA [10] and we have no data on postoperative transvalvular gradients. However, controversy exists on the appropriate timing for the acquisition of in vivo echocardiographic data, as haemodynamic changes can occur up to 1 year post-AVR [11–13]. There is a poor correlation between PPM and postoperative gradients [4]. Furthermore, Doppler studies may underestimate EOA in bi-leaflet prostheses due to localised high velocity jets [14,15].

We could not address the impact of PPM on exercise capacity and quality of life following AVR in our study. The impact of PPM on the functional outcome following AVR is

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**Table 2**

<table>
<thead>
<tr>
<th>In-hospital mortality by mismatch group</th>
<th>Number of patients</th>
<th>Deaths</th>
<th>Mortality</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPM by either method</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mismatch group</td>
<td>151</td>
<td>8</td>
<td>5.29</td>
<td></td>
</tr>
<tr>
<td>Reference group</td>
<td>1267</td>
<td>67</td>
<td>5.28</td>
<td>0.99</td>
</tr>
<tr>
<td>EOAi method</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mismatch group</td>
<td>122</td>
<td>7</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>Reference group</td>
<td>1296</td>
<td>68</td>
<td>5.2</td>
<td>0.83</td>
</tr>
<tr>
<td>GOAi method</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mismatch group</td>
<td>67</td>
<td>3</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Reference group</td>
<td>1351</td>
<td>72</td>
<td>5.2</td>
<td>0.79</td>
</tr>
<tr>
<td>PPM by both methods</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mismatch group</td>
<td>38</td>
<td>2</td>
<td>5.26</td>
<td></td>
</tr>
<tr>
<td>Reference group</td>
<td>1380</td>
<td>73</td>
<td>5.29</td>
<td>0.99</td>
</tr>
</tbody>
</table>

PPM: patient-prosthesis mismatch; EOAi: effective orifice area index; GOAi: geometric orifice area index.

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**Table 3**

<table>
<thead>
<tr>
<th>Multivariate analysis of predictors for in-hospital mortality following AVR</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency surgery</td>
<td>&lt;0.001</td>
<td>8.8</td>
<td>3.13–24.82</td>
</tr>
<tr>
<td>LVEF &lt; 30%</td>
<td>&lt;0.001</td>
<td>5.8</td>
<td>2.56–13.03</td>
</tr>
<tr>
<td>Female gender</td>
<td>&lt;0.001</td>
<td>3.1</td>
<td>1.85–5.88</td>
</tr>
<tr>
<td>Concomitant CABG</td>
<td>0.003</td>
<td>2.2</td>
<td>1.30–3.66</td>
</tr>
<tr>
<td>Age &gt; 80 years</td>
<td>0.03</td>
<td>2.2</td>
<td>1.08–4.50</td>
</tr>
<tr>
<td>XC time (min)</td>
<td>&lt;0.001</td>
<td>1.016</td>
<td>1.01–1.02</td>
</tr>
</tbody>
</table>

OR: odds ratio; CI: confidence interval; LVEF: left ventricular ejection fraction; CABG: coronary artery bypass grafting; XC time: aortic clamp time in minutes.
difficult to evaluate because of the confounding effects of concomitant cardiovascular and non-cardiovascular disease. Conflicting results are reported when exercise capacity is measured directly after AVR [16–19]. A recent study has shown that the majority of patients after AVR report improvements in functional quality of life and these are not affected by PPM [20]. Finally, the follow-up data obtained from the Office of National Statistics only provides knowledge of the survival status with no cause of death, this does not allow differentiation between cardiovascular and other cause mortality and we have neither follow-up data on patient functional status nor follow-up echocardiographic data on EOA or left ventricular mass regression.

In conclusion, our study indicates that severe PPM may occur in a small number of patients undergoing AVR, but its clinical significance may be less then previously hypothesised.

Acknowledgment

In this study, statistical advice was provided by the University of Birmingham.

References


Appendix A. Conference discussion

Dr M. Thubrikar (Irvine, California): I have a basic question which I have pondered for several years and don’t seem to quite find an answer to. When we are looking at the size of the annulus and the size of the valve to try to match, the way we measure the annulus is the standard way, but my question relates to how do we know at what point in the cardiac cycle has the heart been arrested so the annulus of the valve now is either in a diastolic profile or in a systolic profile. That could easily make a difference of 2–3 mm.

Mr Howell: By necessity we size the aortic annulus in the arrested heart and therefore in conditions resembling diastole.

Dr Thubrikar: Is there any attempt to see if you have a valve size on the basis of angiogram or echo beforehand and then try to match the valve to that?

Mr Howell: It is not routinely done in our department. We adopt transoesophageal echocardiography to size the aortic annulus in patients in whom we plan to use an aortic homograft in order to defrost the right prosthesis.

Dr A. Wahba (Trondheim, Norway): There is one question that I would like you to answer, and that is the small group of patients with bad left ventricular function, was there a difference between those that had a patient-prosthesis mismatch and the other ones that didn’t? And was your study big enough, were there enough patients in the groups to see a difference, if there was one?

Mr Howell: This is a well-debated issue. In our study there were only 72 patients with poor LV function and therefore our data are not powered to answer this specific question.

Dr J. Tsai (Pirang, Taiwan): I have a question. It puzzled me for years. The mismatch was found very serious in females from your study, I agree with you, and the disaster also in the females. Would you tell us the reason why?

Mr Howell: It often reported in the literature that smaller EOAs occur more commonly in female and in elderly patients, and this was the case in our study.