Comparison of the early haemodynamics of stented pericardial and porcine aortic valves

Vikas Sharmaa*, Salil V. Deob,f, Salah E. Altarabshehc, Yan Hyun Choa,d, Patricia J. Erwina and Soon J. Parkf

a Division of Cardiovascular Surgery, Mayo Clinic, Rochester, MN, USA
b Adventist Wockhardt Heart Institute, Athisalines, Surat, India
c Division of Cardiovascular Surgery, Queen Alia Heart Institute, Amman, Jordan
d Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
e Mayo Clinic Libraries, Mayo Clinic, Rochester, MN, USA
f Division of Cardiovascular Surgery, University Hospitals, Case Western Reserve University, Cleveland, OH, USA

* Corresponding author. Division of Cardiovascular Surgery, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA. Tel: +1-507-2551885; fax: +1-507-2557378; e-mail: ctvsteam@hotmail.com (V. Sharma).

Received 12 March 2014; received in revised form 16 April 2014; accepted 23 April 2014

Summary

Data comparing the haemodynamic performance of stented pericardial and porcine aortic valves are conflicting. Hence, we performed a systematic review and meta-analysis comparing the early haemodynamic parameters of stented pericardial and porcine valves in patients undergoing isolated aortic valve replacement. Medline, EMBASE and Web of Science were queried for English language original publications from 2000 to 2013. Studies comparing porcine (PoV) and pericardial (PeV) with regard to their haemodynamic parameters were included in this review. Continuous data were pooled using the mean difference (MD) or the standardized mean difference (SMD). A random-effect inverse weighted analysis was conducted; a P-value <0.05 is considered statistically significant. Results are presented with 95% confidence intervals. Thirteen studies (1265 PeV patients and 871 PoV patients) were included in this analysis. The pooled transvalvular mean gradient was lower for PeV [MD −4.6 (−6.45 to −2.77) mmHg; P < 0.01]. Limiting this analysis to small valves (19 and 21 mm; eight studies; 714 patients) revealed that the PeV gradients were significantly lower [MD −4.5 (−5.7 to −3.2); P = 0.001]. The corresponding effective orifice area of PeV was significantly larger than PoV [SMD 0.42 (0.15–0.69); P < 0.01]. A sensitivity analysis comprising only randomized controlled trials did not significantly alter results. When compared with porcine valves, stented pericardial aortic valves have lower mean transvalvular gradients early after implant. Even pericardial valves in smaller sizes (19 and 21 mm) have a better haemodynamic profile when compared with their counterparts.

Keywords: Aortic valve • Stented pericardial bioprosthesis • Stented porcine bioprosthesis • Transvalvular gradient • Patient-prosthesis mismatch

INTRODUCTION

Nearly 80 000 aortic valve replacements are performed annually in the USA [1]; predominantly for senile calcific aortic stenosis [2]. The clear advantage of tissue valves in the older population has spurred significant improvements in valve design. A poor haemodynamic profile may eventually predispose the patient to develop a patient-prosthesis mismatch (PPM). The adverse impact of a PPM after aortic valve replacement is well documented [3]. However, studies reporting a comparison of the haemodynamic performance of stented pericardial and porcine valves have presented conflicting data. There is no consensus regarding the superiority of one valve over the other. To answer this issue, we have pooled studies comparing aortic valve replacement after stented porcine and pericardial valve replacement.

PATIENTS AND METHODS

Inclusion criteria

We sought randomized controlled trials (RCTs) or observational studies that met the following criteria: (i) human subjects undergoing isolated aortic valve replacement with stented biological valve substitutes; (ii) studies presenting a comparison of bovine pericardial and porcine bioprosthesis; and (iii) the comparison included only haemodynamic performance parameters, i.e. mean transvalvular gradient, effective orifice area (EOA) and EOA indexed to body surface area, i.e. EOA index (EOAi).

Exclusion criteria

(i) Studies measuring and analysing in vitro experimental valve parameters were excluded. (ii) Non-English language articles,

© The Author 2014. Published by Oxford University Press on behalf of the European Association for Cardio-Thoracic Surgery. All rights reserved.
review articles, single-patient case reports and editorials were also omitted from this analysis. (iii) Studies where additional procedures were performed in order to implant a larger prosthesis, viz., patch aortoplasty, were excluded.

Search strategy

The literature search was done using MEDLINE, EMBASE, Cochrane and Web of Science to identify relevant articles from January 2000 to May 2013. Search terms used the controlled vocabularies of MEDLINE and EMBASE alone or in combination including: ‘Aortic valve replacement’, ‘Bovine pericardial bioprosthesis/xenograft’, ‘porcine bio-prosthesis/xenograft’, ‘trans valvular gradient’ and ‘effective orifice area/index’. References from the selected studies were also manually searched to identify potential articles for inclusion.

Two reviewers (Vikas Sharma and Salil V. Deo) independently screened all studies for inclusion. Relevant abstracts were then retrieved in their full-text form and were independently evaluated. The search strategy adopted is in accordance with the PRISMA flow diagram [4] (Fig. 1). Disagreements were resolved by consensus. Agreement between reviewers regarding study inclusion was assessed using the Cohen κ statistic [5].

Data were abstracted from the articles using a pre-specified data abstraction form. Care was taken to ensure that duplication of data did not occur. Quality of included studies was assessed with the Newcastle–Ottawa scale for observational studies [6] and Jadad scale for RCTs [7].

Statistical analysis

Statistical analysis was performed with the ‘meta’ [8] in R version 3.0.1 [9]. When available data were presented separately in the article stratified by valve size, a pooled weighted mean and standard deviation was obtained [10]. Continuous data were pooled to obtain a mean difference (MD). An inverse variance weighted random-effect model (DerSimonian–Laird) was implemented [11]. A pooled estimate combining the EOA and EOAi was reported as the standardized mean difference (SMD) due to the difference in their scale of measurement. The SMD is chosen as the effect size when continuous data are presented with different units. The SMD is the difference in mean obtained in that study relative to the standard error. Hence, it can be used to pool continuous data presented in different units of scales of measurement.

A separate analysis of RCT was performed and compared with the overall pooled analysis. This sensitivity analysis was conducted for all end-points to confirm the results of the overall pooled result of 13 studies.

RESULTS

After analysing 20 full-text articles, 13 studies (PeV 1265 patients and PoV 871 patients) met the inclusion criteria [12–24]. We reached a 94% consensus (Cohen’s κ) in the systematic review process. The detailed flow chart of the selection process is outlined in Fig. 1. Among these, seven were RCTs [12–14, 19, 20, 23, 24], while the remaining were retrospective studies. Two RCTs were conducted by the same institution, but during differing time periods, and hence could be included [13, 14]. Dalmau et al. have presented results of their RCT at the end of 1 and 5 years [12, 25]. As other articles presented early haemodynamic data, only their 1-year data were selected for inclusion in the analysis. The Deutsches Herzzentrum Munchen presented data from their hospital registry as well as an RCT during the same study period (2000–04) [22, 24]. The registry data may have contained some patients from the RCT; however, as the registry data study only contained patients with small annulus (≤23 mm) implantation, overall patient duplication would be small. Tanigawa et al. [26] presented data comparing their results with aortic valve replacement using 19 mm tissue valves. However, this article was excluded from the analysis as they have performed a considerable number of concomitant procedures, which may confound results. The pre-operative demographic profile of patients is presented in Table 1. The seven RCTs naturally had a well-matched patient population in both cohorts. Even among retrospective studies, effort was taken to ensure a comparable cohort of patients. Two studies conducted a propensity-matched comparison of retrospective data [15, 21].

Prostheses used in the individual studies

Among pericardial valves, the Carpentier Edwards Perimount® and Carpentier Edwards Perimount Magna® (Edwards Lifesciences, Irvine, CA, USA) were most commonly used.
### Preoperative demographics for all studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Study quality</th>
<th>Number</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>BSA (m²)</th>
<th>NYHA class 3/4 (%)</th>
<th>Specifics of valves implanted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okamura et al. [17]</td>
<td>OBS</td>
<td>6/10</td>
<td>67</td>
<td>10</td>
<td>76 ± 5</td>
<td>46</td>
<td>1.5 ± 0.15</td>
<td>CE-PM MM</td>
</tr>
<tr>
<td>Suri et al. [13]</td>
<td>RCT</td>
<td>3/5</td>
<td>201</td>
<td>99</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>CE-PM St. Jude Epic®</td>
</tr>
<tr>
<td>Wendt et al. [21]</td>
<td>OBS</td>
<td>8/10</td>
<td>125</td>
<td>102</td>
<td>75 ± 7</td>
<td>34</td>
<td>2.6 ± 7</td>
<td>CE-PM MM</td>
</tr>
<tr>
<td>Suri et al. [14]</td>
<td>RCT</td>
<td>3/5</td>
<td>76</td>
<td>76</td>
<td>75 ± 7</td>
<td>62</td>
<td>1.9 ± 0.2</td>
<td>CE-P MM</td>
</tr>
<tr>
<td>Ruzicka et al. [18]</td>
<td>OBS</td>
<td>7/10</td>
<td>169</td>
<td>46</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>SS, CE-P MM, MM Ultra</td>
</tr>
<tr>
<td>et al. [19]</td>
<td>RCT</td>
<td>3/5</td>
<td>48</td>
<td>51</td>
<td>75</td>
<td>45</td>
<td>1.8 ± 0.2</td>
<td>CE-P MM</td>
</tr>
<tr>
<td>Dalmau et al. [12]</td>
<td>RCT</td>
<td>3/5</td>
<td>43</td>
<td>43</td>
<td>76 ± 4</td>
<td>63</td>
<td>1.75 ± 0.17</td>
<td>CE-P MM</td>
</tr>
<tr>
<td>Borger et al. [15]</td>
<td>OBS</td>
<td>8/10</td>
<td>57</td>
<td>57</td>
<td>72 ± 9</td>
<td>75</td>
<td>1.9 ± 0.3</td>
<td>CE-P HC</td>
</tr>
<tr>
<td>et al. [22]</td>
<td>OBS</td>
<td>7/10</td>
<td>50</td>
<td>44</td>
<td>75 ± 6</td>
<td>26</td>
<td>1.75 ± 0.2</td>
<td>CE-P, SS, CE-PM MM</td>
</tr>
<tr>
<td>V. Sharma et al. [24]</td>
<td>RCT</td>
<td>3/5</td>
<td>70</td>
<td>66</td>
<td>75 ± 6</td>
<td>40</td>
<td>1.81 ± 0.2</td>
<td>CE-P MM</td>
</tr>
</tbody>
</table>

**CE-P: Carpentier Edward Perimount® valve; CE-PO: Carpentier Edward Porcine® valve; CE-PM: Carpentier Edward Perimount Magna® valve; HK: Hancock II® porcine valve; MM: Medtronic Mosaic® porcine valve; NYHA: New York Heart Association; OBS: observational study; PeV: pericardial valve cohort; PoV: porcine valve cohort; RCT: randomized controlled trials.**

**a) Body mass index (kg/m²).**

**b) Mean NYHA class.**

**c,d) Walther et al. and Jamieson et al. have not presented data separately for both cohorts.**

### Mean transvalvular gradient

The mean transvalvular gradient (at rest) was estimated and compared in 11 studies (seven RCTs and four retrospective). In three studies [13, 15, 20], echocardiographic measurement was conducted prior to dismissal, while the remaining eight studies evaluated this parameter after a follow-up period of 6 months to 1 year. The pooled analysis demonstrates that pericardial valves had a significantly lower mean gradient when compared with porcine valves [MD −6.41 (−6.45 to −2.77) mmHg; P < 0.0001]. A separate analysis of only the seven RCTs confirmed the pooled results [MD −4.23 (−6.13 to −2.33)] (Fig. 2).

### Mean transvalvular gradient in small valves

Eight articles [12, 16–20, 22, 24] (787 patients) presented separate data regarding the mean transvalvular gradient (at rest) in small valves (19 and 21 mm). The mean transvalvular gradient was again significantly lower in the PeV cohort [MD −4.49 (−3.21 to −5.77) mmHg; P < 0.001]. Analysis of only RCT did not change the overall direction of the pooled result (Fig. 3).

### Effective orifice area/effective orifice area index

Nine studies [12, 13, 15, 16, 19, 20, 23, 24] (1431 patients) presented data regarding either the EOA or the EOAi at the time of follow-up. A PeV cohort has a significantly higher pooled EOA/EOAi when compared with the PoV cohort [SMD 0.42 (0.15–0.69); P < 0.001]. These data were provided by six of the seven RCTs selected for review. A combined analysis of these six RCTs [12, 13, 19, 20, 23, 24] confirmed the overall analysis favouring pericardial valves (Fig. 4).

### Patient–prosthesis mismatch

Data regarding PPM were presented in six studies [12, 13, 15, 18, 22, 24]. A brief review of presented data from these studies is outlined in Table 2. Variability of the presentation of data precluded statistical analysis of these results. Four studies [12, 15, 18, 22] clearly demonstrated a lower incidence of PPM with pericardial valves, while comparable results were found in the remaining two studies.

### Left ventricular mass index

The regression in the left ventricular mass index (LVMI) was discussed in four studies [14, 17, 19, 23]. Again, variation in the presentation of results precluded us from pooling the data. However, only one RCT [23] demonstrated a benefit for pericardial valves over porcine ones. All other studies demonstrated a comparable reduction in the LVMI at the end of follow-up.
Figure 2: The forest plot of the pooled mean transvalvular gradient from 11 studies demonstrates that pericardial valves have significantly lower gradients than porcine valves. Results are stratified according to the type of study. RCT: randomized controlled trial; OBSs: observational studies.

Figure 3: The forest plot demonstrates that the pooled mean transvalvular gradient is lower in pericardial valves when compared with porcine valves. The separate pooled analysis of observational studies (OBSs) and randomized controlled trials (RCTs) support this final result.
Aortic valve replacement is one of the most common procedures performed by cardiac surgeons. A gradual improvement in tissue valve design has resulted in better results [2]. However, valve-related problems still arise from time to time in our clinical practice and there is an ongoing endeavour to produce the ideal bioprosthesis, which would have a low profile, a large EOA and be relatively resistant to structural degeneration.

We have pooled together data from 13 studies published since 2000. They have all implanted either second or third generation commercially available tissue valves. Thus, we present data regarding bioprostheses relevant to our daily surgical practice. Our meta-analysis of 2136 patients (48% from RCTs) demonstrates that pericardial valves have a significantly larger EOA/EOAi when compared with porcine valves.

Figure 4: The forest plot presenting the standardized mean difference (SMD) of combined effective orifice area (EOA)/effective orifice area index (EOAi) obtained from pooling nine studies. While three observational studies (OBSs) demonstrate comparable results, the remaining six RCTs when combined demonstrate that pericardial valves had a significantly larger EOA/EOAi when compared with porcine valves.

Table 2: Data regarding the patient-prosthesis mismatch (PPM) obtained from the studies included in this systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of valve</th>
<th>Number</th>
<th>Moderate/severe PPM (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eichinger et al. [24]</td>
<td>Pericardial</td>
<td>70</td>
<td>52</td>
<td>NA</td>
</tr>
<tr>
<td>Dalmau et al. [12]</td>
<td>Pericardial</td>
<td>43</td>
<td>6.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Porcine</td>
<td>41</td>
<td>26.8</td>
<td></td>
</tr>
<tr>
<td>Borger et al. [15]</td>
<td>Pericardial</td>
<td>57</td>
<td>30</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Porcine</td>
<td>57</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Wagner et al. [22]</td>
<td>Pericardial</td>
<td>110</td>
<td>18</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Porcine</td>
<td>32</td>
<td>69</td>
<td></td>
</tr>
</tbody>
</table>

Criteria for moderate and severe PPM are as follows: moderate PPM <0.85 cm²/m² and severe PPM <0.65 cm²/m². Suri et al. [13] and Ruzicka et al. [18] presented data regarding the PPM; however, the method of presentation did not allow us to incorporate their data into this table. Suri et al. found no difference in the PPM among studied valves; Ruzicka et al. found a higher incidence of PPM with porcine valves of all sizes.

Comment

Aortic valve replacement is one of the most common procedures performed by cardiac surgeons. A gradual improvement in tissue valve design has resulted in better results [2]. However, valve-related problems still arise from time to time in our clinical practice and there is an ongoing endeavour to produce the ideal bioprosthesis, which would have a low profile, a large EOA and be relatively resistant to structural degeneration.

We have pooled together data from 13 studies published since 2000. They have all implanted either second or third generation commercially available tissue valves. Thus, we present data regarding bioprostheses relevant to our daily surgical practice. Our meta-analysis of 2136 patients (48% from RCTs) demonstrates that pericardial valves have a superior haemodynamic profile when compared with porcine valves, even in the small sizes. They demonstrate a larger orifice area with a lower predilection for PPM.

The haemodynamic superiority of pericardial valves may be explained by the increased internal diameter of the recent generation pericardial valves when compared with porcine valves [12, 16]. Implantation of these valves with larger internal diameters naturally leads to lower mean pressure gradients and a larger EOA. Data regarding in vitro testing support also our clinical conclusion.
[27]. Wagner et al. [22] have further demonstrated that mild-moderate exercise exacerbates the difference in gradients between pericardial and porcine valves.

PPM occurs when the EOA of the prosthesis is too small in relation to the patient’s body size, thus resulting in abnormally high postoperative gradients, either at rest or with exercise. The negative effect of PPM on LV mass regression, ventricular function, New York Heart Association functional class, quality of life and valve durability is well documented [28]. A recent meta-analysis of 34 studies [28] with 27,186 patients demonstrated a significant increase in all-cause and cardiac-related mortality in patients suffering from PPM after aortic valve replacement. Our study demonstrated that pericardial valves had a larger EOA/EOAi when compared with porcine valves. While not demonstrated by all studies, we presume that a higher EOA/EOAi would lead to a lower incidence of PPM.

Authors have also reported the long-term outcome after aortic valve replacement using these bioprostheses [29, 30]. The overall consensus appears to be that pericardial valves have lower re-operation rates and a lower risk of degeneration when compared with porcine valves. As these data are primarily from retrospective observational studies, we have chosen not to analyse this aspect in our present study. Although not noted in any of our articles, Brown et al. [31] recently reported the incidence of early tissue valve thrombosis. From 4568 patients, eight needed reoperation for valve thrombosis. All patients were initially implanted with porcine valves. The authors believe that this may be related to the design of the porcine valve stent, which promotes blood stasis between the leaflet and the belly of the leaflet [31].

Our systematic review has some specific limitations. By broadly comparing stented pericardial and porcine valves, we have naturally pooled together valves of different brands, each having their own proprietary leaflet preservation/anti-calciﬁcation techniques. Criteria for valve selection and the technique of valve implantation (intrannular versus supra-annular) would differ as per the implanting surgeon. Considering these factors, which may introduce a bias, we have implemented a random-effect model in our analysis.

However, we believe that our study has some important merits. It is a pooled analysis of more than 2000 well-matched patients comparing the haemodynamic outcome of stented pericardial and porcine aortic prostheses. Moreover, our analysis also contains six RCTs. The pooled analysis signiﬁcantly increases the power of our study, which would be practically difficult to achieve in any single RCT or retrospective analysis.

Clinical relevance

Our meta-analysis demonstrates that pericardial valves demonstrate better haemodynamic performance when compared with porcine valves at early follow-up. At present, long-term data comparing clinical end-points with these two types of valves are limited. Hence, we believe that further studies with longer follow-up duration are needed before clinically relevant differences in these two types of stented bioprostheses may be determined.

CONCLUSIONS

When compared with porcine valves, stented pericardial aortic valves have lower mean transvalvular gradients early after implant. Even pericardial valves in smaller sizes (19 and 21 mm) have a better haemodynamic proﬁle when compared with their porcine counterparts. Further studies are needed to determine if this translates into differences in long-term clinical outcome.

Funding

The study was self-funded. No Government or private agency funded this study.

Conflicts of interest: none declared.


