Relation between size of prosthesis and valve gradient: comparison of two aortic bioprosthesis

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Abstract

Objectives: The outcome of patients undergoing aortic valve replacement (AVR) may be affected by the influence of prosthesis–patient mismatch on left ventricular mass regression. However, due to the discrepancies in labeled valve size, size of sizer and actual valve dimension, it is difficult to compare different valve types. In order to perform an objective comparison, this study was designed to compare the hemodynamics of the Edwards Lifescience pericardial (ELP) and the Medtronic Mosaic porcine (MM) bioprosthesis between patients receiving the same valve size and between patients with the same aortic annulus diameter. Methods: This prospective, randomized study was performed on 81 hospital survivors out of 86 patients undergoing AVR with either the ELP (n = 39) or the MM (n = 42) bioprosthesis. Intra-operative randomization was performed after the surgeon had excised the aortic valve, measured the size of the aortic annulus with three different sizers (ELP, MM and a set of metric sizers), and decided which size he would implant for either of the valve types. All valves were implanted in supra-annular position with the same implantation technique. Echocardiographic follow-up was performed early postoperatively and 6 months thereafter.

Results: In 12 (31%) of the patients receiving the ELP-valve, as compared to 3 (7.1%) of the patients receiving the MM-valve, the labeled valve size was smaller than the aortic annulus diameter (P < 0.05). Early postoperatively, mean (17.4 ± 3.1 vs 20.3 ± 3.6 mmHg) and peak gradients (30.1 ± 4.8 vs 37.6 ± 9.6 mmHg) for the 21 mm ELP-valve were lower than for the 21 mm MM-valve (P < 0.05). All other hemodynamic parameters did not show significant differences at any time point. When the same aortic annulus diameter was taken as a reference, there were no significant hemodynamic differences between either valve type at any time point, regardless of the valve size implanted. Conclusions: This study demonstrates that the hemodynamic performance of the ELP and the MM bioprosthesis are comparable when the same aortic annulus diameter is taken as a reference. The significant variabilities between different valve types with regard to labeled valve size, valve-sizer size and actual valve size have to be taken into account, when hemodynamic comparisons are performed.

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Keywords: Aortic valve replacement; Biological prosthesis; Aortic annulus diameter; Labeled valve size; Hemodynamic performance

1. Introduction

Due to the increasing number of older patients requiring aortic valve replacement (AVR) and the persistent risk of thromboembolic and bleeding complications in patients with mechanical prosthesis, the use of biological valve substitutes has continuously increased during recent years. Accordingly, there is a renewed interest in the hemodynamic performance of biological valves, because intermediate and long-term survival may be affected by the influence of prosthesis–patient mismatch on left ventricular mass regression especially in patients with small aortic roots [1–3]. Hemodynamic comparison of the various available biological valve types, however, is difficult, since substantial discrepancies between industry-labeled valve sizes, dimensions of valve sizers and actual size of the respective valves exist [4,5]. In order to obtain accurate and clinically relevant data on the hemodynamic performance of different valve types, it is therefore necessary to compare the hemodynamic performance of valve prosthesis in relation to the dimensions of the native
aortic annulus and not on the basis of industry-labeled valve size [6–8]. Since the second generation Edwards Life-science pericardial (ELP) and the third generation Medtronic Mosaic porcine (MM) bioprosthesis are both designed as supra-annular valve substitutes and have gained widespread use as aortic valve prosthesis, a direct comparison of both valves appears justified.

This study was designed to compare the hemodynamics of both valves between patients with the same industry-labeled valve size and between patients with the same diameter of the aortic annulus in a prospective, randomized fashion. The results of this investigation should help surgeons to choose the optimal valve substitute for the individual patient.

2. Patients and methods

2.1. Patients

This prospective, randomized study was performed on 86 patients (age range 54–79 years). For data analyses 81 hospital survivors were included. All patients underwent AVR with either the ELP (n = 39) or the MM (n = 42) bioprosthesis. Exclusion criteria included emergency surgery, age <19 and >80 years, left ventricular ejection fraction <25%, reoperative procedures of any type, multiple valve replacement or other concomitant procedures other than coronary artery bypass grafting (CABG), endocarditis, and co-existent illness known to have a high mortality. The study was approved by the hospital ethics committee and written informed consent was obtained from all patients before inclusion.

2.2. Operative technique

All operations were performed by a total of four staff surgeons, using complete or partial median sternotomy and standard cardiopulmonary bypass techniques, including systemic normo- or mild hypothermia and cold ante- and retrograde blood cardioplegia. Distal anastomoses in patients undergoing additional coronary artery bypass grafting were performed before AVR. Intra-operative randomization was performed after the surgeon had excised the aortic valve, decalcified the aortic annulus if necessary, measured the size of the annulus with three different sizers (ELP, MM and a standard set of intra-annular, cylindrical-shaped metric sizers with diameters of 19, 21, 23, 25, 27, and 29 mm), and decided which valve size he would implant for either of both valve types. With regard to sizing with the metric sizers, the surgeons were instructed to determine the largest size that just slips through the annulus without applying any force and without dilating the annulus. All valves were implanted in supra-annular position using the same technique of multiple, vertical mattress sutures, reinforced by subannular polytetrafluoroethylene felts and allowing the prosthesis to sit on top of the annulus.

2.3. Echocardiographic assessment

Transthoracic Doppler echocardiographic evaluation was performed between postoperative days 8–12 and at 6 months postoperatively. Standard parasternal and apical views were obtained. The following parameters were measured: left ventricular end-diastolic and end-systolic diameters, thickness of the posterior wall and the interventricular septum, ejection fraction, ejection time, maximum and mean flow velocities across the valve and in the left ventricular outflow tract. Using standard equations the following calculations were performed: peak and mean transvalvular gradients, prosthetic valve effective orifice area, and left ventricular muscle mass.

2.4. Statistical analysis

All measurements were log transformed because of a right-skewed distribution and an analysis of variance was applied to test differences between the three aortic sizers. Pairwise comparisons were calculated and P-values were adjusted for multiple comparison by the method of Dunnett. The resulting least-square means and corresponding 95% confidence intervals were transformed back on the original scale.

3. Results

The follow-up at 6 months was 100% complete for all 81 hospital survivors included in the study. Demographic and surgical data of those patients are given in Table 1. The number of implanted valves with regard to valve type and labeled valve size is given in Table 2. In 12 (31%) of the patients receiving the ELP-valve, as compared to only 3

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and surgical data of all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELP</td>
<td>MM</td>
</tr>
<tr>
<td>Number of patients</td>
<td>39</td>
</tr>
<tr>
<td>Sex</td>
<td>Male/female</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>72.3 ± 6.2</td>
</tr>
<tr>
<td>Aortic valve lesion (%)</td>
<td>Stenosis</td>
</tr>
<tr>
<td>Insufficiency</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Mixed</td>
<td>10 (26)</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.53 ± 0.10</td>
</tr>
<tr>
<td>Additional procedures (%)</td>
<td>CABG</td>
</tr>
<tr>
<td>Euroscore</td>
<td>7.98 ± 3.06</td>
</tr>
</tbody>
</table>

ELP, Edwards Lifescience pericardial; MM, Medtronic Mosaic; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting.
(7.1%) of the patients receiving the MM-valve, the implanted labeled valve size was smaller than the assessed aortic annulus diameter ($P < 0.05$). All three of the MM-downsized patients, however, were in the 27 mm aortic annulus-group, whereas all 12 ELP-downsized patients belonged to the 21, 23, and 25 mm aortic annulus-group. In addition, 3 (7.1%) of the MM-patients but none of the ELP-patients received valves with labeled valve sizes larger than the aortic annulus diameter.

All hemodynamic data including mean and peak transvalvular gradient, effective orifice area early postoperative and after 6 months and regression of left ventricular mass after 6 months according to industry-reference, there were no significant hemodynamic differences between either valves early postoperatively or at 6 month follow-up. Since only one patient with a 19 mm annulus was randomized to the MM-valve cohort (receiving a 21 mm valve), no comparison between both valves types was possible in this annulus diameter group. However, the hemodynamic data of this patient were included in the labeled valve size analysis.

None of the investigated valve sizes of either valve type demonstrated any significant difference of hemodynamic parameters between the early and 6 months postoperative evaluation.

### 4. Discussion

Mid- and long-term results of second- and third generation biological bioprosthesis with regard to structural deterioration and need for early reoperation are encouraging. The advantages of biological bioprosthesis compared to mechanical prosthesis also include a lower risk of thromboembolism and anticoagulant-related hemorrhage. Those factors have contributed to the more liberal indications for the use of biological aortic valve substitutes including patients under 70 years of age. Whereas the question of structural durability of currently used biological valves appears to decline as the main factor in the surgeon’s choice for the ideal valve substitue in the individual patient, the issue of hemodynamic performance of the respective prosthesis has gained increased consideration.

Various studies have shown that the hemodynamic performance of aortic valve prosthesis does have a substantial impact on the influence of prosthesis–patient
mismatch on ventricular mass regression and, consequently, mid- and long-term survival especially in patients with small aortic roots [1,3]. Among many other factors, such as stent size and flexibility, compliance characteristics of sinuses, extent of annulus decalcification, positioning of the valve, etc. the most important determinant of postoperative valve hemodynamics is the internal diameter of the implanted valve [7]. However, the surgeon’s goal to implant the largest possible prosthesis in the individual patient is hampered by the fact that there are surprising discrepancies between the industry-labeled valve and valve-size dimensions and the actual internal and external diameter of the respective valves. The internal diameters as reported by the manufacturers of both biological valves used in this study (ELP, MM), i.e., differ by up to 2 mm per industry-labeled valve size, which makes the direct, prosthesis size-related comparison of both valves difficult [9].

The current study evaluated the hemodynamic performance of both valves in relation to the industry-labeled valve size and the actual inner diameter of the aortic annulus. This comparison was possible due to the fact that both valves are designed for supra-annular implantation and, in addition, were implanted with the identical surgical technique, which was used by all four surgeons in the study.

Both valves used in this randomized trial have an impressive track record with regard to valve-related complications such as thromboembolism, hemorrhage or incidence of endocarditis [10–13]. Whereas the ELP-valve has also been demonstrated to have a low incidence of structural deterioration over more than 15 years after implantation, only mid-term follow-up data are available for the MM porcine bioprosthesis [14,15]. However, since its direct predecessor, the Hancock II porcine bioprosthesis, has shown long-term follow-up data comparable to those of the ELP-valve, it appears realistic to assume that the incorporation of new tissue valve technologies such as zero-pressure fixation and alpha amino oleic acid antimineralization treatment to the Mosaic design will provide at least similar long-term outcome [16].

The results of our study indicate that the overall hemodynamic performance of both valves was comparable only when their performance was related to the inner diameter of the aortic annulus and not to the implanted industry-labeled valve size. The clinical relevance of this assessment is also confirmed by the fact that the amount of left ventricular mass reduction after 6 months was similar and substantial in both groups when annulus diameters of 21 mm and more were compared. This comparison was not possible for annulus sizes of 19 mm, since only one patient with a 19 mm annulus size was randomized to the MM-valve group. These data also indicate that the good hemodynamic performance of both valve types avoided a prosthesis–patient mismatch in patients with an aortic annulus diameter of at least 21 mm. The satisfactory hemodynamic performance of both valves also support conclusions from studies by Milano [6] and Rao [8], indicating that biological valves of the second and third generation may even parallel the hemodynamic performance of stentless valves when the comparison of both valve

### Table 5
Hemodynamic parameters early postoperatively according to aortic annulus diameter

<table>
<thead>
<tr>
<th>AAD (mm)</th>
<th>PSPG (mmHg)</th>
<th>MPG (mmHg)</th>
<th>EAO (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ELP</td>
<td>MM</td>
<td>ELP</td>
</tr>
<tr>
<td>19, n = 8</td>
<td>36.2 ± 5.3</td>
<td>–</td>
<td>18.5 ± 2.7</td>
</tr>
<tr>
<td>21, n = 18</td>
<td>31.6 ± 4.5</td>
<td>35.6 ± 8.5</td>
<td>18.9 ± 3.6</td>
</tr>
<tr>
<td>23, n = 21</td>
<td>28.0 ± 3.8</td>
<td>30.4 ± 4.6</td>
<td>15.5 ± 2.8</td>
</tr>
<tr>
<td>25, n = 23</td>
<td>24.0 ± 4.0</td>
<td>25.4 ± 5.4</td>
<td>15.2 ± 2.8</td>
</tr>
<tr>
<td>27, n = 11</td>
<td>22.2 ± 4.7</td>
<td>23.7 ± 5.0</td>
<td>11.6 ± 2.2</td>
</tr>
</tbody>
</table>

AAD, aortic annulus diameter; ELP, Edwards Lifescience pericardial; MM, Medtronic Mosaic; PSPG, peak systolic pressure gradient; MPG, mean pressure gradient; EAO, effective orifice area.

### Table 6
Hemodynamic parameters at 6 months postoperatively according to aortic annulus diameter

<table>
<thead>
<tr>
<th>AAD (mm)</th>
<th>PSPG (mmHg)</th>
<th>MPG (mmHg)</th>
<th>EAO (cm²)</th>
<th>LVMR (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ELP</td>
<td>MM</td>
<td>ELP</td>
<td>MM</td>
</tr>
<tr>
<td>19, n = 8</td>
<td>36.1 ± 5.1</td>
<td>–</td>
<td>18.4 ± 5</td>
<td>–</td>
</tr>
<tr>
<td>21, n = 18</td>
<td>30.9 ± 4.5</td>
<td>35.7 ± 8.2</td>
<td>19.2 ± 2.7</td>
<td>18.6 ± 2.9</td>
</tr>
<tr>
<td>23, n = 21</td>
<td>27.8 ± 3.6</td>
<td>30.2 ± 4.8</td>
<td>16.0 ± 3.2</td>
<td>16.1 ± 4.8</td>
</tr>
<tr>
<td>25, n = 23</td>
<td>23.9 ± 4.1</td>
<td>24.9 ± 5.2</td>
<td>15.0 ± 3.0</td>
<td>15.3 ± 3.7</td>
</tr>
<tr>
<td>27, n = 11</td>
<td>22.2 ± 4.6</td>
<td>23.4 ± 4.2</td>
<td>1.5 ± 3.7</td>
<td>12.7 ± 2.6</td>
</tr>
</tbody>
</table>

AAD, aortic annulus diameter; ELP, Edwards Lifescience pericardial, MM, Medtronic Mosaic; PSPG, peak systolic pressure gradient; MPG, mean pressure gradient; EAO, effective orifice area.
types is performed between patients with the same aortic annulus diameter. Our data clearly show, however, that the ELP-valve does have a hemodynamic advantage, when industry-labeled sizes of the implanted valves are compared, especially in patients with labeled valve sizes of 21 and 23 mm. This can easily be explained by the fact that the size-matched manufacturer-reported internal diameter of the ELP-valve is between 1.5 and 2 mm larger than the respective manufacturer-reported internal diameter of the MM-valve [9]. However, the surgeon’s decision on the maximum possible implantable valve size entirely depends on the information given to him by sizing the aortic annulus with the sizers provided by the manufacturers. Since the outer diameter of the intra-annular portion of the ELP-sizer is almost 1.5 mm larger than a size-matched MM-sizer (data provided by both companies), it is easy comprehensible that our data demonstrate a significant tendency to implant smaller ELP- than MM-valves in relation to the inner diameter of the aortic annulus. This difference eventually erased the hemodynamic advantage of the size-related larger internal diameter of the ELP-valve.

The hemodynamic analysis of both valve types, however, also indicates that although patients receiving a 19 mm ELP-valve do have reasonable low valve gradients, there is only a small reduction in left ventricular muscle mass after 6 months. It cannot be concluded from our data whether these observations are due to a prosthesis–patient mismatch or may be explained by the relatively short follow-up period of 6 months [17]. The lack of left ventricular muscle mass reduction, however, did not translate in any obvious functional disadvantage, as is demonstrated by the fact that the analysis of the NYHA-class functional status at 6 months postoperatively did not reveal any significant differences when compared to patients receiving larger valve sizes. Nevertheless, since comparable data for 19 mm MM-valves are not available, the possible advantage of aortic root enlargement rather than implantation of a 19 mm ELP-valve should be considered.

This study was designed to evaluate possible hemodynamic differences of often-used biological valves under realistic clinical conditions. Consequently, the design of the study is certainly not free of shortcomings that may have affected study results and the interpretation of those results. The fact that we used the identical implantation technique for both valves may or may not have benefitted one of the valve types used. However, since there are no conclusive data available that may prove a hemodynamic advantage of a certain implant technique for either valve, this decision was based on the fact that both valves were designed for supra-annular implantation and, consequently, can be implanted by the same technique without an obvious disadvantage for one of them. The fact that the operations were performed by four different surgeons also might have influenced the outcome of the study. It does, however, reflect the every day practice in most cardiac centers, where the same valve prosthesis are implanted by different surgeons. In our study, all surgeons had to perform the valve sizing before they knew which prosthesis they had to implant, thereby minimizing the influence of possible valve preferences of the individual surgeon. However, valve sizing itself is a mechanical event that depends on many factors including issues that may vary from surgeon to surgeon such as extent of annulus decalcification, sizing experience or bias. The design of this study certainly cannot totally exclude the influence of those surgeon-related factors on choosing the maximal possible valve size.

In conclusion, our study clearly demonstrates that the hemodynamic performance of prosthetic valve substitutes cannot be compared on the basis of industry-labeled valve sizes but should always be related to the inner diameter of the aortic annulus, a parameter that can easily be assessed intra-operatively. Each surgeon must be aware of significant variabilities with regard to the relation of labeled valve size, valve-sizer size and actual internal and external valve diameters not only between different valves but also within the same valve type. With regard to the ELP and MM prosthesis tested in this study, however, the significant discrepancies of those parameters in both valves erased each other at least when their hemodynamics were related to the diameter of the aortic annulus. In this respect, implantation of either valve provides relatively low gradients and significant reduction of left ventricular muscle mass when labeled valve sizes of 21 mm or more are used.

References


Appendix A. Conference discussion

Mr B. Keogh (Birmingham, UK): I think almost everybody in this audience would be frustrated by the fact that, in the valve world, 19 mm is not 19 mm, and it just depends where you are, who you are, and what box you are looking at.

I see Bob Frater in the audience, who has got a lot of experience with valves over the years, and I would just like to pick your brain, Bob, and see what the view is on the other side of the Atlantic.

Dr R. Frater (Brussels, New York): I wouldn’t pretend for one minute to give the views of the other side of the Atlantic, and I have a connection with St Jude which you need to obviously know about when I talk, but let me talk now with an academic hat on.

I think what the manufacturers face is trying to avoid the most difficult immediate problem that a surgeon may encounter, which is that he has chosen a valve that is too big and he has got it three-quarters in and he knows he has to start again. And when the manufacturers fiddle with the size of the dimension versus the actual dimension of a valve, what they are mostly trying to do is to protect against that danger because they are not sufficiently confident that the surgeons will have the good sense not to pick too big a valve.

Now the other side of that is if a valve is well designed and for a given dimension has lower gradients at a given output than another valve, if you know that, then you can make your choice appropriately and not try to oversize. I think that is as much as I am going to say.

Dr T. David (Toronto, Canada): Your method of study is the best way to answer the question that you have raised on valve size versus hemodynamic outcome after aortic valve replacement. Because your trial was randomized, I think it would be appropriate for you to give the gradients in all patients together as opposed to size by size. Size is irrelevant because we implant the largest possible aortic valve prosthesis in a given patient, and since you had 81 patients available to study, you should have showed us the mean gradient for all 39 Carpenter Edwards Perimount and all 42 Mosaic valves. My bet is there is no difference. Am I correct?

Dr Seitelberger: Yes, you are absolutely right. When you look at the data with regard to the metric sizer, this actually shows that there is no difference. Our goal was to look at the day-to-day surgical problem of the individual patient, what is the best valve you put in the individual patient with relation to his internal annulus diameter, and when you look at those data, even when they are not compiled in the way you just mentioned, it is the same outcome; both valves show actually the same outcome for the individual patient with the same aortic annulus diameter.

Dr David: It has been my experience that any patient who would take a 19 mm Perimount, I can often implant a 21 Hancock II or a 21 Mosaic. Thus, the hemodynamic of a 21 Mosaic is comparable to that of 19 Perimount. Isn’t that the case?

Dr Seitelberger: Well, that is true. We did not implant a single Medtronic 19 mm valve, but there certainly is a bias in the study with respect to the fact that we really put in valves according to the sizers. So we didn’t even try to oversize the valves. And when we would not put these patients into the study, in those patients that received a 19 mm Edwards Life Sciences valve, not least because we know that sometimes the aortic annulus has a pericardial strip. So there is a certain bias in this respect, because I personally pray whenever it is possible not to put in a 19 mm valve. This is my personal strategy. But this strategy was not applied in this study.

Dr David: Thank you for examining this issue correctly.

Dr J. Laos (Bad Bevensen, Germany): In swine, like in human, the valve is not trisymmetrical. You have a small left coronary leaflet, a median right coronary leaflet and a larger noncoronary leaflet. When you implanted the Mosaic valve did you take care of this orientation or did you just implant it, because we have the impression when you implant the valve anatomically, which means that you orient the largest leaflet towards the noncoronary sinus, you get better hemodynamic results, and this might account for the difference between the Edwards and the Mosaic valve?

Dr Seitelberger: That is a good suggestion. We have put in I think more than 200 Mosaics so far, and I haven’t done this, so maybe the next one will be better when we go along with the suggestions.

Dr G. Rizzoli (Padova, Italy): I don’t know if I got your message right, but you compared the echocardiographic data according to the LV size and to the actual measurement of the annulus. Didn’t you normalize your echo data for the body surface area of the patient?

Dr Seitelberger: We did not on purpose because we did not want to do a prosthesis mismatch study. We just wanted to document the surgical problems in the everyday practice of a surgeon. So with regard to a possible prosthesis–patient mismatch, for example, for the small ELP valves, I can’t even give you the data right now because it was not our goal to go for the relation with regard to body size. We were just looking for the aortic annulus, that was our goal, because that is the problem you face during surgery. You are not looking at the patient in terms of weight and fat and so on and so on. You are just trying to put in the largest valve possible, and that was the goal of our study, to answer those questions.

Mr Keogh: Having done this study, what information would you like to see published on the box that the valve comes in to help you make the correct decision in the future?

Dr Seitelberger: Certainly it would be great if all companies would agree on some type of measurement where you can actually really compare the size of the valves, and in my opinion they should do it in relation to the inner aortic annulus diameter, if that is possible. And if they should also design not only the valves but also the sizers with respect to that, that would be perfect for all of us. And then it would also become much more easier to do a good scientific comparison of products. Most of the publications that are out in this respect, they have no scientific value because they always compare the same valve sizes, the industry-labeled valve sizes. So that would also help the surgical community in terms of better scientific output.