Prospectively Randomized Evaluation of Stented Xenograft Hemodynamic Function in the Aortic Position

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Background—Standard stented aortic xenograft valves have not yet been compared regarding their hemodynamic function using a stratified intraoperative randomization protocol.

Methods and Results—100 patients were prospectively included after intraoperative metric sizing of the decalcified aortic annulus. They received Mosaic (M) or Perimount (P) aortic valve replacement. Patient age was 73±5 years, 51 were female, and New York Heart Association (NYHA) functional class was 2.8±0.5. The 21-mm annulus group consisted of 5 (M)/7 (P) patients, the 23-mm annulus group of 20 (M)/20 (P), the 25-mm annulus group of 18 (M)/19 (P), and the 27-mm annulus group of 4 (M)/7 (P) patients, respectively. Hemodynamic function was evaluated using transthoracic echocardiography before discharge and at follow-up (438±352 days). Surgery was uncomplicated in all patients. Labeled valve sizes were 0.93 (M) and 1.05 (P) mm smaller than the annulus diameters (p=NS). In-hospital mortality was 5%, all nonvalve-related. Transvalvular blood flow velocities and transvalvular pressure gradients were significantly lower in the 25 P versus the 25 M group at baseline and in the 23 P and 25 P groups at follow-up. There was a significant regression of left ventricular mass index in all patients at follow-up. However, left ventricular mass regression was more pronounced after P aortic valve replacement.

Conclusion—Labeled sizes of prosthetic heart valves implanted are smaller than the true aortic annulus. Both standard aortic xenografts compared in this prospectively randomized trial provide a sufficient hemodynamic and functional outcome. (Circulation. 2004;110[suppl II]:II-74–II-78.)

Key Words: aortic valve replacement ■ stented bioprosthesis ■ aortic annulus diameter ■ hemodynamics

Aortic stenosis is the most common acquired heart valve lesion in the Western societies; it is usually caused by degenerative changes with complex calcification of the native leaflets and the aortic annulus. In symptomatic patients or in the presence of severe stenosis with significant additional left ventricular hypertrophy, aortic valve replacement (AVR) is indicated.

During the past decades, AVR using mechanical valves or stented xenografts has become a routine procedure with low perioperative risk. Prosthetic heart valves have undergone continuous modifications to reach a good level of product quality and to provide an acceptable postoperative hemodynamic performance over the past years. However, an optimal device, possibly mimicking the native physiological valve, is neither available nor in view for AVR.

While facing an aging patient population requiring AVR, there is an increasing interest in xenografts; patients aged 65 years and older are considered suitable candidates. Stented valves usually provide a sufficient functional outcome, as proven by several clinical studies.

During AVR after complete decalcification, sizing is performed to select the largest fitting and thus hemodynamically most suitable valve size. Differences in valve sizes and in sizer dimensions exist between the clinically available stented xenografts. These may lead to misunderstandings, suboptimal valve selection, misinterpretation of clinical results, and significant discrepancies between hemodynamic outcome data. No randomized comparison of different stented xenografts has been published to our knowledge thus far. Furthermore, intraoperative stratified randomization according to the true aortic annulus diameter has not been described in the literature to our knowledge. Aim of the present study was to independently evaluate 2 standard stented aortic xenografts regarding their hemodynamic outcome in relation to metric intraoperative sizing.

Methods
One hundred patients with relevant aortic valve disease received AVR between March 2000 and April 2003. Patients were randomized to receive 1 of 2 standard stented xenografts (Mosaic, Medtronic Inc, Minneapolis, Minn or Perimount, Edwards Lifesciences, Irvine,

Calif), and both were approved for routine clinical implantation (Figure 1). This prospective clinical trial was approved by the local ethical committee; all patients gave informed consent after the study protocol had been outlined in detail. Patients with an indication for xenograft AVR (age older than 65 years or special request or contraindication for anticoagulation) were included.

The 2 devices provide the following features: Mosaic (M) xenograft is a porcine valve mounted on a thin flexible stent. The stent had been originally designed for the Hancock II valve and implies a reduced profile height of 13.5 mm. The xenogenic tissue is processed under physiological pressure fixation, allowing the leaflets to float freely at zero pressure differential using diluted glutaraldehyde. After final rinsing, amino-oleic acid, a surfactant, is applied as additional anticalcification treatment. Hemodynamic data available from the company indicate an effective orifice area of 1.22 cm² for the 21-mm, 1.38 cm² for the 23-mm, and 1.8 cm² for the 25-mm, and 1.8 cm² for the 27-mm prosthesis, respectively.17

The Perimount (P) xenograft is manufactured from bovine pericardium. A neutralogic stress-free fixation process in which the tissue is fixed in a bath of glutaraldehyde solution with no applied pressure is used. The stent profile height is 15 mm. The proprietary Xenologix treatment consisting of a cumulative, multistep process that begins after glutaraldehyde fixation and implies exposure to a combination of agents, including ethanol and Tween-80, is used as anticalcification treatment. Hemodynamic data available from the company indicate an effective orifice area of 1.3 cm² for the 21-mm, 1.5 cm² for the 23-mm, 1.8 cm² for the 25-mm, and 1.8 cm² for the 27-mm prosthesis, respectively.17 A significant reduction of tissue calcification has been shown on animal experiments for the amino-oleic acid and Xenologix treatments.18,19

Surgery was performed by experienced surgeons only via standard median sternotomy. Extracorporeal circulation was initiated by right atrial and ascending aorta cannulation. A left atrial vent was inserted via the right upper pulmonary vein. Antegrade cold crystalloid (Bretschneider HTK solution, Köhler Chemie) or warm blood cardioplegia according to surgeon personal preference and moderate hypothermia were applied. After transverse aortotomy, the diseased aortic valve was completely excised, including removal of calcification from the aortic annulus and eventually the anterior mitral leaflet. Then the stratified randomization process was applied: The aortic annulus diameter was carefully measured using metric sizers. Then the patient was assigned to the individual annulus diameter group according to the metric annulus diameter. The type of prosthesis to be implanted was then selected from a by-chance randomization list. Then the prosthesis related sizer was used for valve size selection. Valve implantation was performed using standard horizontal mattress sutures supported by Teflon felt. This resulted in a slightly supra annular position of the valve.

Hemodynamic evaluation was solely performed according to the intraoperatively measured annulus diameter groups. Follow-up was performed at the hospitals outpatient clinic. Mean follow-up is 438±352 days (range, 180 to 1133), 77 patients were seen in hospital. Total follow-up consists of 124 patient-years. Transthoracic echocardiographic examinations were performed preoperatively, before discharge, and at follow-up. Multiplane transesophageal echocardiography was used intraoperatively or whenever additional information besides transthoracic echocardiographic examinations measurements was required. Cardiac morphology and function as well as valve hemodynamics were assessed using standard measurements. Echocardiograms were performed according to standard guidelines and were interpreted by a single physician. Maximum pressure gradients were calculated according to the complete Bernoulli equation and left ventricular mass index according to the Devereux formula.20,21 All measurements were performed according to the Penn convention.

Valve-related morbidity and mortality were evaluated according to standard guidelines.22 Absolute and relative frequencies were calculated. Results are given as mean±SD. After assessing for normal distribution, the Student t test for matched pairs was applied. P<0.05 was considered significant.

Results

From the 100 patients, 51 were female and mean age was 72.8±4.7 years. Predominant aortic valve disease was stenosis in 96 and severe incompetence in 4 patients, respectively. Preoperative New York Heart Association (NYHA) functional class was 2.5±0.6 and body surface area 1.8±0.2 m². Preoperatively, 83 patients were in sinus rhythm, 15 were in atrial fibrillation, and 2 had permanent pacemaker. The additive Euroscore was 5±1.9, and there were no significant differences between the annulus size groups. Preoperative hemodynamic measurements at cardiac catheterization were as follows: left ventricular ejection fraction 61±14%; left ventricular end-diastolic pressure 23±13 mmHg, mixed venous oxygen saturation 66±7%; and cardiac index 2.2±0.5 l/min per m².

Intraoperatively cross-clamp duration was 57±14 minutes, with no relevant differences between the prostheses. All patients had uneventful primary valve implantation. Additional procedures were as follows: myocardial revascularization in 18, replacement of the ascending aorta in 2, mitral valve repair in 1, and left atrial ablation therapy in 2 patients, respectively. Repeat exploration for bleeding had to be performed in 2 patients.

Five patients died in hospital because of sudden cardiac death on postoperative day (POD) 7, multiple organ failure on POD 11, sepsis on POD 15, stroke on POD 30, and pneumonia on POD 45. Patients had received 21-mm (3), 23-mm (1), and 25-mm (1) valves, respectively. Effective orifice area divided by body surface area was 0.74 (3), 0.78 (1), and 0.93...
(1) cm²/m² in these 5 patients, with no significant difference to the other 95 patients.

During follow-up, 3 patients died because of lung cancer (2) after 9 and 24 months, and because of heart failure after 30 months, respectively. Effective orifice area divided by body surface area was 0.68 (1), 0.96 (1), and 0.8 (1) cm²/m² in these 3 patients.

Mean aortic annulus diameter was 23.9±1.7 mm and mean implanted aortic valve prosthesis size (as labeled) was 23.0±1.8 mm. A total of 12 patients had a 21-mm annulus (5 of those received M and 7 received P prosthesis); 40 patients had a 23-mm annulus (M=20 and P=20); 37 had a 25-mm annulus (M=18 and P=19), and 11 patients had a 27-mm annulus (M=4 and P=7), respectively.

Within those annulus size groups of 21, 23, 25, and 27 mm, patients received differently labeled valve sizes. Details are given in Table 1. However, there were no significant differences in labeled valve sizes in relation to annulus diameters between the 2 (M versus P) prostheses. Results on indicated effective valve orifice area divided by body surface area and on the patient annulus index are given in Table 2.

Further evaluations are purely performed between the different annulus diameter groups. Because of the fact that a small number of patients had a 21-mm or a 27-mm annulus,
Both stented xenografts compared in this study have been evaluated thoroughly and have a reliable short-term and long-term clinical function.\textsuperscript{17,23–27} Furthermore, good postoperative hemodynamic function has been shown. However, as yet, no prospectively randomized comparison of hemodynamic function has been published.

There are several important findings. This is the first prospective study comparing different standard stented xenografts using intraoperative metric sizing and a stratified randomization protocol. Intraoperative stratified randomization according to true aortic annulus diameter measured after complete decalcification is the only measure allowing for objective comparison between different aortic valve implants.

### TABLE 4. Hemodynamic Function Given for the 23-mm and the 25-mm Annulus Groups for Mosaic (M) vs Perimount (P) Aortic Valve Implants

<table>
<thead>
<tr>
<th>Aortic Annulus Diameter, mm</th>
<th>Maximum Blood Flow Velocity, m/s</th>
<th>Maximum Pressure Gradient, mm Hg</th>
<th>Mean Pressure Gradient, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>M 23</td>
<td>2.58±0.6</td>
<td>23.8±11</td>
<td>16.4±6.6</td>
</tr>
<tr>
<td>P 23</td>
<td>2.41±0.5</td>
<td>19.6±9</td>
<td>13.9±4.9</td>
</tr>
<tr>
<td>M 25</td>
<td>2.54±0.5</td>
<td>22.5±10</td>
<td>14.9±7.1</td>
</tr>
<tr>
<td>P 25</td>
<td>2.05±0.4*</td>
<td>13.2±6*</td>
<td>11.3±3.7*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aortic Annulus Diameter, mm</th>
<th>Maximum Blood Flow Velocity, m/s</th>
<th>Maximum Pressure Gradient, mm Hg</th>
<th>Mean Pressure Gradient, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>M 23</td>
<td>2.66±0.5</td>
<td>25±10</td>
<td>17.2±5.4</td>
</tr>
<tr>
<td>P 23</td>
<td>2.31±0.4*</td>
<td>18.4±8*</td>
<td>12.1±4.7*</td>
</tr>
<tr>
<td>M 25</td>
<td>2.45±0.6</td>
<td>21.6±11</td>
<td>14.3±6.7</td>
</tr>
</tbody>
</table>
| P 25                        | 2.18±0.3†                        | 15.7±5*                         | 11.2±3.9†                   | $*P<0.05$ between M and P groups.  
†$P<0.05$ between M and P groups.  
‡$P=0.08$.

Thus it should become a standard approach for future comparative clinical trials.

From the results it became obvious that there are discrepancies between the true metric aortic annulus diameter and the labeled diameter of the prosthetic valve finally implanted. Differences in metric versus product-related sizer dimensions have been described previously without any subsequent adjustments to clinical practice.\textsuperscript{11–16} Now, for the first time to our knowledge, a prospective comparison of true metric aortic annulus diameters to labeled aortic valve diameters becomes available. Not surprisingly there were no significant differences between the 2 xenograft valve types regarding labeled valve diameters implanted in the different aortic annulus diameter groups (Table 1). Neither the superstructure nor the size of the coronary sinuses dictated any downsizing of the prostheses in relation to the measured sizes of the prostheses and the intra-annular diameter.

Results in Table 2 indicate that patients with 21- and 23-mm annuli are at risk for moderate patient prosthesis mismatch. The finding of moderate patient prosthesis mismatch has been associated with slightly increased mortality of 2.1-fold in a larger patient population.\textsuperscript{17} The more frequent occurrence of moderate patient prosthesis mismatch in the smaller size annulus groups may be an explanation for the increased mortality observed throughout this study. However, only 1 patient died primarily because of a cardiac cause. A more frequent use of stentless aortic valves would probably be a useful strategy to avoid or at least decrease the incidence of moderate patient prosthesis mismatch.

Circulatory function was comparable between groups and within normal limits at postoperative baseline as well as at follow-up evaluations. Predischarge baseline echocardiographic examinations should be the common standard for the evaluation of valve implants in the short-term and the long-term.

Hemodynamic function was assessed by comparing the standard measure of maximum transvalvular blood flow

### TABLE 5. Left Ventricular End-Diastolic Internal Diameter (LVDd) and Left Ventricular Mass Index (LVMI) Given for the 23-mm and the 25-mm annulus Mosaic (M) vs Perimount (P) Groups at Baseline and at Follow-Up Measurement

<table>
<thead>
<tr>
<th>LVMI</th>
<th>LVDd, Baseline, mm</th>
<th>LVDd, Follow-up, mm</th>
<th>P, Baseline Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic Annulus Diameter, mm</td>
<td>M 23</td>
<td>5.0±1.1</td>
<td>4.9±0.9</td>
</tr>
<tr>
<td></td>
<td>P 23</td>
<td>4.8±0.9</td>
<td>4.4±0.6†</td>
</tr>
<tr>
<td></td>
<td>M 25</td>
<td>4.8±0.4</td>
<td>4.6±0.7</td>
</tr>
<tr>
<td></td>
<td>P 25</td>
<td>5.1±0.8</td>
<td>4.8±0.8†</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LVMI</th>
<th>LVDd, Baseline, g/m²</th>
<th>LVDd, Follow-up, g/m²</th>
<th>P, Baseline Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic Annulus Diameter, mm</td>
<td>M 23</td>
<td>196±43</td>
<td>187±31</td>
</tr>
<tr>
<td></td>
<td>P 23</td>
<td>204±89</td>
<td>156±52*</td>
</tr>
<tr>
<td></td>
<td>M 25</td>
<td>212±72</td>
<td>199±50</td>
</tr>
<tr>
<td></td>
<td>P 25</td>
<td>208±82</td>
<td>178±49</td>
</tr>
</tbody>
</table>

$*P<0.05$ between M and P groups at follow-up.  
†$P=NS$ between M and P groups at follow-up.
velocity. This allowed for further calculation of transvalvular pressure gradients given in Table 4. The observed results indicate the hemodynamic advantage of the P aortic xenograft versus the M valve.

Postoperative left ventricular mass regression can be regarded as one of the most important parameters to define a normally functioning prosthetic aortic valve. As such, significant left ventricular mass regression was observed in all patients, as shown in Table 5. This indicates that all xenografts provided sufficient hemodynamic function for myocardial reverse remodeling and thus functional recovery in the long-term. However, differences were observed between the 2 prostheses, yielding a more pronounced left ventricular mass regression after P xenograft implantation.

Are there any explanations for the differences in hemodynamic function between the 2 xenografts examined? The most striking difference of the 2 xenografts, their construction from porcine valves in comparison to bovine pericardium, may be 1 factor, but usually both should provide comparable hemodynamic features. Differences definitively exist in the stent design. The M prosthesis is mounted on a stent originating from the Hancock II valve. The profile inherent to this stent may cause the comparably worse hemodynamic outcome.

All operations were performed using a similar surgical technique. Most importantly, horizontal mattress sutures were used with Teflon felts below the annulus, bringing all xenografts into a slightly supra-anular position. Thus no relevant hemodynamic differences should arise from the implantation technique.

In the future, use of supra annular prostheses may lead to further improvement in hemodynamic function after AVR. Upsizing of the prosthesis can be safely performed in most patients, leading to a larger effective orifice area. Further studies on this interesting aspect are necessary.

There are some limitations of the present study that need to be addressed. Sufficient numbers of implants to perform reliable statistical comparison were available in the 23- and 25-mm annulus groups only. However, the study results presented are based on sufficient data in those 2 groups. In-hospital follow-up was only complete in 77 of 92 patients. To achieve comparable results, we decided to include in-hospital echocardiographic follow-up for comparative analyses. The data presented were clearly sufficient to answer the most important question of this study and to define whether there was a hemodynamically different outcome between the different prostheses. Follow-up included >12 months on average, thus covering the period of most dramatic regression of left ventricular mass after AVR.

In summary, both xenografts provide acceptable hemodynamic function with significant left ventricular mass regression in all patients at follow-up. However, the hemodynamic profile was significantly better in the most frequently implanted aortic annulus diameter groups for the P aortic valve.

References


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