Hemodynamic Characteristics of the Matrix P Decellularized Xenograft for Pulmonary Valve Replacement during the Ross Operation

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Background and aim of the study: Aortic valve disease can be treated successfully by means of the Ross operation. Alternatives to pulmonary valve replacement with homografts are needed. The study aim was to demonstrate the performance of a decellularized porcine xenograft valve (Matrix P) in adult patients after the Ross operation.

Methods: Between July 2002 and May 2004, a total of 50 Ross operations was performed with the Matrix P for pulmonary valve replacement. Operative results and postoperative hemodynamics were evaluated.

Results: The median patient age was 46 years (range: 17-70 years). Among patients, 36% underwent additional procedures, most often repair of aneurysms of the ascending aorta or coronary artery bypass grafts.

One patient died from septic multiorgan failure on postoperative day 36. One reoperation on the Matrix P and one reoperation on the aortic valve were necessary; both reoperations were uneventful. Postoperative echocardiography demonstrated low transvalvular gradients that did not tend to increase over time.

Conclusion: In contrast to homografts and other xenografts the Matrix P decellularized xenograft showed, postoperatively, no rise in right ventricular-pulmonary artery pressure gradients. Indeed, the valve was seen to behave similarly to a physiologically normal valve in a healthy subject.

The Journal of Heart Valve Disease 2005;14:78-81

Clinical material and methods

Patients
Between July 18th 2002 and May 3rd 2004, 50 consecutive adult patients (38 males, 12 females; median age 46 years; range: 17 to 70 years) received the Matrix P for pulmonary valve replacement during the course of their Ross operation. All patients provided their written informed consent according to the authors’ protocol for clinical studies (2) and in agreement with the principles of good clinical practice. Approval to conduct the study was obtained from the local ethics committee.

Valve characteristics
The Matrix P is a porcine pulmonary valve, which is decellularized in a proprietary process (AutoTissue GmbH, Berlin, Germany). Basically, complete decellularization is obtained by using sodium deoxycholate, after which a validated sterilizing procedure is used that includes the use of alcohol and antibiotics. Since February 2004 this implant has been CE certified and thus available commercially in Europe.

Surgical approach
All operations were performed in a standardized manner, with normothermic cardiopulmonary bypass and warm blood cardioplegia, by three independent surgeons (W.K., J.L., S.B.) from the authors’ institution. For the autograft, a subcoronary or inclusion cylinder

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implantation technique was preferred, while for pulmonary valve replacement the Matrix P was used (Fig. 1). Postoperative care was conducted according to the authors’ institutional standards.

Follow up
Hemodynamic evaluation was performed according to the protocol by means of transthoracic echocardiography at discharge, at three, six and 12 months postoperatively, and yearly thereafter. The mean velocity across the pulmonary valve was monitored, the mean gradient was calculated by the modified Bernoulli equation, and pulmonary valve regurgitation assessed. Computed tomography imaging of the new valve was performed before discharge and during follow up visits in a few patients, after having obtained their informed consent.

Statistical analysis
Values were expressed as median (range) and mean ± SD. SPSS 10.0 software (SPSS, Inc., Chicago, USA) was used for all calculations.

Results
The underlying disease was aortic stenosis in 17 patients, pure aortic insufficiency in 27, and a mixed lesion in six. Three patients presented with acute or subacute endocarditis, and one patient with prosthetic valve endocarditis and annular abscess. Concomitant cardiac diagnoses were coronary artery disease in seven patients, requiring one or two coronary artery bypass grafts in six cases. Aneurysm (>6 cm) of the ascending aorta was seen in six patients. One of these patients underwent replacement of the ascending aorta, whilst in the remaining five the ascending aorta was tailored to an appropriate size. Four patients with mitral regurgitation >3° underwent mitral valve repair, either by a modified de Vega procedure or implantation of a Carpentier annuloplasty ring. In one patient a ventricular septal defect was closed in combination with the Ross operation, and another patient required size reduction of a giant right atrium.

The surgeons were very satisfied with the good sewing characteristics of the soft and pliable decellularized tissue, the strength of the material, and the good hemostatic properties with a lack of any needle hole bleeding.

One obese patient with steroid-treated chronic obstructive pulmonary disease died 36 days after surgery as result of septic multorgan failure. One patient required temporary right ventricular assist device support for two days postoperatively, but was later weaned and discharged in good condition. One reoperation was required on the aortic valve due to autograft insufficiency; this patient underwent an uneventful implantation of a stentless pericardial valve. During the study period, one reoperation of a
pulmonary valve became necessary due to a false aneurysm at the distal suture line.

Echocardiography at discharge demonstrated a median flow velocity of 0.8 m/s (range: 0.4 to 0.95 m/s). The mean right ventricular-pulmonary artery gradient was 2.9 ± 1.7 mmHg (range: 0.8 to 8.6 mmHg). During the follow up period there were no relevant changes in hemodynamic performance as compared with values at discharge (Table I).

Echocardiographically, no calcification and no shortening of the graft was detected. At discharge, trivial (<1°) pulmonary valve regurgitation was noted in 11% of the patients, but this did not progress during the follow up period.

The Matrix P, in a three-dimensional reconstruction from a multislice CT investigation, is illustrated in Figure 2.

**Discussion**

The Ross operation delivers unparalleled hemodynamic results after aortic valve replacement, and no currently available implant device provides performance which is comparable to that of the native pulmonary valve in the aortic position (3). This is why the Ross operation is used in younger patients with increasing acceptance. The complexity of the operation involves replacement of the pulmonary valve, which is traditionally performed with pulmonary homografts. However, these carry several disadvantages. In addition to a shortage of supply and a probability of transmitting communicable diseases, up to 30% of patients show a form of possible immunological reaction after homograft implantation. This was demonstrated clearly by Carr-White et al. (4), who reported that 17% of patients developed pressure gradients >30 mmHg across the homograft within the first three years after the operation. Similar observations were made by groups in Austria (5) and Germany (6). Common to all reports has been a significant increase in transpulmonary gradient during the first one to three years after surgery, although fortunately very few patients required reoperation.

In order to overcome the shortage of homografts and their infectious and immunogenic potential, the present authors and others have used stentless xenografts for pulmonary valve replacement (7,8). It was possible to show that after five years no calcification occurred in glutaraldehyde-treated porcine stentless xenografts (9). The hemodynamic performance, however, has been less satisfactory and there was a tendency to develop insufficiency over time. Moreover, in some recent publications the gradients have been higher as compared to those achieved with pulmonary valve performance (8,10,11). The most striking facet of the Matrix P hemodynamic performance - as compared to homografts or xenografts - is that the hemodynamics were normal, as in healthy human subjects, and remained unchanged during follow up periods of one year in eleven patients and two years in one patient. Not a single patient developed a gradient across the Matrix P, and the small range and standard deviations in echocardiographic measurements of pulmonary valve performance support this finding. In contrast to results reported for the Synergraft™ decellularization technique (12,13), the Matrix P is decellularized only with detergents such as deoxycholic acid. This preserves structural integrity (14), and recellularization with collagen-producing fibroblasts was reported in animal experiments (15). In addition, the lack of any calcification of the vessel wall and valve leaflets, which could be demonstrated in the juvenile sheep model, underlined the superiority of this decellularization method (16). The identical technology has been used since May 2000 by the present authors for the tissue engineering of heart valves with autologous seeding of the valvular implants (17,18).

The process of decellularization includes real-time polymerase chain reaction-proven freedom from porcine endogenous retroviruses, whilst the validated

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### Table I: Echocardiographic measurements of right ventricular (RV)-pulmonary artery (PA) mean flow velocities and calculation of mean gradients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Discharge (n = 43)</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean flow velocity</td>
<td>Mean RV-PA gradient</td>
</tr>
<tr>
<td></td>
<td>(m/s)</td>
<td>(mmHg)</td>
</tr>
<tr>
<td></td>
<td>0.8 ± 0.2</td>
<td>3.0 ± 1.7</td>
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<tr>
<td></td>
<td>0.8 ± 0.3</td>
<td>2.6 ± 1.0</td>
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<td></td>
<td>0.7 ± 0.2</td>
<td>2.2 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>0.8 ± 0.2</td>
<td>2.8 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*Values are mean ± SD.

Only 43 patients were discharged (one patient died perioperatively, while in six patients the pulmonary valve could not be visualized adequately during transthoracic echocardiography).
sterilization procedure provides a safety level which cannot be achieved with homografts. The advantage over glutaraldehyde-treated stentless xenograft valves is that those implants have some (albeit small) gradients inherent to their stiffness after glutaraldehyde treatment, and they tend to develop regurgitation in some patients (8-11). Currently, no implant device shows a performance as close to the normal physiological state as does the Matrix P. By using this device, it could be shown that the Ross operation, which impresses with unsurpassed hemodynamic performance of the neoaortic valve, can be performed with physiological hemodynamics also on the right ventricular side.

**Study limitations**

It might be argued that the present study was not randomized but rather was only observational in nature. In fact, a randomized study today would pose ethical problems in the light of the performance characteristics of the Matrix P. An additional limitation was the relatively short follow up period, though it should be noted that this novel technology only became available in summer 2002.

In conclusion, after the Ross operation in adult patients, the Matrix P decellularized xenograft showed a hemodynamic performance which was close to normal human pulmonary valve performance. Most impressively, postoperative elevation of pulmonary pressure did not occur in any patient.

**Acknowledgement**

Dr. Wolfgang Konertz and Dr. Pascal M. Dohmen are shareholders in AutoTissue GmbH, and acting as advisors to the company.

**References**