Right Ventricular Outflow Tract Reconstruction with Decellularized Porcine Xenografts in Patients with Congenital Heart Disease

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Background and aim of the study: Decellularized xenogeneic pulmonary valves have been introduced for right ventricular outflow tract (RVOT) reconstruction in congenital heart disease. In the present study, the intermediate-term results from three institutions were analyzed.

Methods: Between January 2006 and September 2008, a total of 61 patients (median age 7 years; range: 9 days to 50 years; median body weight 21 kg; range: 1.9-140 kg) underwent RVOT reconstruction with either the Matrix P® (n = 9) or Matrix P Plus® (n = 52) tissue-engineered conduit. Eighteen patients underwent surgery in infancy, and 31 patients had previously undergone one or more RVOT interventions or operations.

Results: The valve sizes ranged from 11 to 27mm. Five patients died during the hospital stay or within three months, from non-valve-related causes; hence, the early mortality was 8.2%. No deaths occurred during the follow up period. Reoperation due to valve failure became necessary in four patients; three patients underwent RVOT interventions due to distal anastomotic stenosis, and six reinterventions were performed distal to the valve due to hypoplastic branch pulmonary arteries. Patients with valve implantation during infancy showed a composite freedom from valve-related reoperation, catheter intervention or valve dysfunction (defined as dPmax >40 mmHg) of 87% at one and three years postoperatively. Both, computed tomography and magnetic resonance imaging studies demonstrated normal structural features, with no evidence of calcification.

Conclusion: The Matrix P/Matrix Plus conduit represents a viable alternative for RVOT reconstruction in patients with congenital heart disease. The intermediate-term performance of the conduits was favorable compared to that of other currently available implants.

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heart disease, who had undergone surgery between 2006 and 2008 at three institutions.

Clinical material and methods

Patients

Between January 2006 and September 2008, a total of 61 consecutive patients (median age 7 years; range: 9 days to 50 years) underwent primary or repeat reconstruction of the RVOT with the Matrix P or Matrix P Plus valve. Informed consent was obtained for each patient to participate in the study. Of the patients, 18 (30%) were aged ≤1 year, eight were neonates, and 10 (16%) were aged >18 years. The demographic data of patients, underlying diagnoses leading to surgery and details of patient subgroups as infants and those with primary repairs are listed in Table I. Subsequently, 30 patients (49%) underwent primary repair (most often in infancy), and 31 (51%) had undergone one or more prior RVOT procedures (Table II). The complexity of the patient cohort is apparent from the high number of additional surgical measures required, which included reconstruction of the pulmonary artery bifurcation in eight patients and Ross-Konno procedures in three infants. Two patients required mitral valve repair, one patient a tricuspid valve repair, one hypoplastic aortic arch required enlargement, and in two patients the ascending aorta had to be reconstructed. An intraoperative dilatation of a branch pulmonary artery with stent implantation was performed in one patient. In total, 13 patients underwent surgery at Bologna, and 24 patients each at Duisburg and Berlin.

Surgical technique

All operations were performed under cardiopulmonary bypass, with or without hypothermia. The use of circulatory arrest or a cardioplegic technique was performed according to the surgeon’s preference. Special care and diligence were applied during placement of the valve to avoid sternal compression. According to the valve manufacturer’s instructions for use, oversizing was strictly avoided. In most instances, a valve size of $Z \pm 1$ was appropriate; the $Z$-scores were taken as described elsewhere (8). The valve was fitted in an anatomically correct, orthotopic position whenever possible, and the length of the valve was considered to be important to avoid kinking and crimping. A length that allowed the valve to be seated under gentle traction when the circulation was re-established was considered appropriate. Great care was paid to the distal anastomosis, which was always carried out initially with a very fine monofilament sewing material. The valve sizes used are shown in Figure 1, and an operative view following the implantation of a Matrix P Plus valve in Figure 2.

Follow up

All patients were followed up by their attending pediatric cardiologists. The median follow up was 30.5 months (range: 15 to 52 months). The echocardiographic technique and evaluation followed institutional guidelines, and was carried out routinely at discharge, after three months, and annually thereafter.
Additional imaging was performed according to the preference of each center. In Bologna, all patients underwent computed tomography (CT) scans at one year postoperatively as part of the routine follow up, while 18 patients in Berlin and Bologna each underwent magnetic resonance imaging (MRI) studies after one year of follow up.

**Statistical analysis**
All data were presented as median and range. Survival and time-to-event analyses were performed using Kaplan-Meier actuarial methods. The statistical data were analyzed using PASW Statistics, version 18.0.0 (SPSS Inc., Chicago, Illinois, USA).

**Results**
In the present series, nine Matrix P valves and 52 Matrix P Plus valves were implanted. The follow up was 100% complete. Five patients died during the hospital stay or within three months of surgery, from non-valve-related causes; hence, the early mortality was 8.2%. The cause of death was low cardiac output in three cases: one four-month-old with complex transposition of the great arteries (TGA); one 23-year-old patient after unifocalization; and one neonate with interrupted aortic arch, aortic valve stenosis and ventricular septal defect (VSD) who died from extracorporeal membrane oxygenation complications. One five-month-old boy died from sepsis after complex pulmonary artery reconstruction and valve replacement, and a 12-year-old patient died due to uncontrollable bleeding from the ascending aorta (the post-mortem histology showed a connective tissue disorder). No deaths occurred during the follow up period.

Three patients underwent RVOT interventions due to distal anastomotic stenosis, and two required reoperation as a result of failure of the dilatation. Reoperation due to valve failure or failure of distal anastomotic balloon dilatation became necessary in four patients. In one patient, after Matrix P implantation, reoperation was necessary due to the formation of a large aneurysm proximal to a distal stenosis. Stenoses at the level of the distal anastomosis led to reoperation in two patients (an 11-year-old boy after a Ross operation, and a one-year-old boy at 11 months after the repair of truncus type I). A fourth patient developed prosthetic valve endocarditis at two years after the operation; this patient had dilatation of a branch pulmonary artery stenosis six months after implantation of the first valve. Three of the four patients again received a Matrix P Plus implant. The actuarial freedom from reoperation or reintervention was 96 ± 2.5% and 90 ± 4.1% at three and four years, respectively (Fig. 3).

The exchange of a fully functioning conduit was performed deliberately during reoperation for residual VSD in a patient with complex TGA at 1.5 years after a Rastelli-type operation, at which time a 13 mm valve was replaced with a 15 mm valve. The explanted valve (Fig. 4) showed no signs of stenosis, pannus overgrowth, or degeneration. An histologic evaluation showed repopulation of the specimen, but there were no signs of inflammation on any part of the valve (Fig. 5).

Endothelium-like cells (CD 31- and F VIII-positive)
were seen to line the surfaces of the leaflets and the inner wall of the vessels.

Due to hypoplastic branch pulmonary arteries, six reinterventions distal to the valve or anastomosis were performed during the follow up period. One dilatation of a recurrent coarctation of the descending aorta was also performed. Patients who underwent valve implantation during infancy showed a freedom from valve-related reoperation, catheter intervention or valve dysfunction (dPmax >40 mmHg) of 87% at one and three years postoperatively.

Trace or trivial (< grade I°) transvalvular regurgitation was seen in six patients (10%), and showed no progression during follow up in all but one patient, who required reoperation due to aneurysm formation. No new-onset valve insufficiency developed during the follow up period. The average gradients at discharge were 10 mmHg (range: 2 to 40 mmHg) and 18 mmHg (range: 5 to 45 mmHg) at the latest follow up examination.

Echocardiography performed in infants (n = 15) showed median peak gradients of 6 mmHg at discharge; only two infants had peak flow velocities >2 m/s. At the latest follow up study, the median gradient had risen to 18 mmHg (range: 5 to 45 mmHg), with one infant showing a gradient >40 mmHg. In 46% of cases the flow velocity was <2 m/s.

Thirty-one patients had undergone one or more RVOT procedures before Matrix P/Matrix P Plus implantation. Among these patients, the median peak gradient rose from 13 mmHg at discharge to 21 mmHg at the most recent follow up; two patients showed gradients >40 mmHg. Three of the four reoperations fell into this group with previous RVOT intervention or operation.

The overall performance of the valves of the entire
group, of infants, and also of patients who had undergone previous RVOT interventions or operations are listed in Table III. CT studies performed at one year postoperatively showed no evidence of calcification of either the valve or the patch material. A representative MRI investigation conducted at 32 months after a Rastelli repair for complex TGA is shown in Figure 6.

Discussion

In the present series of 61 consecutive patients operated upon at three institutions, a new valve conduit developed with tissue engineering technology (7) was used for RVOT reconstruction. The Matrix P valve is a decellularized porcine pulmonary valve which can be used ‘off the shelf’ for pulmonary valve replacement, although for more complex situations the Matrix P Plus - a Matrix P valve with proximal and distal patch extensions - has been developed.

As with all valve or conduit procedures, strict adherence to technical details is very important. First, absolutely no touching of the valve leaflets and suturing of the valve to the patch extension is mandatory. In addition, correct sizing, trimming and careful sewing - especially at the distal anastomosis, with very fine monofilament material using an everting sewing technique - must be stressed in order to avoid the inclusion of patch or valve adventitia into the lumen.

Among the present patients, reoperation or reintervention due to graft failure occurred only rarely. Indeed, only three reoperations were required in the first year, one of them in an infant. One reoperation became necessary in the third year. During the first year, three reinterventions due to stenosis at the distal anastomosis were performed. Although a large number of neonates and infants were included in the present study, valve degeneration occurred only once during the follow up period. The fact that distal anastomotic stenosis led to reoperation or reintervention most commonly during the first year suggests an early hazard of the development of distal anastomotic stenosis, though this may be due to the presence of residual glutaraldehyde in the patch of the Matrix P Plus. Mild distal anastomotic stenosis may also lead to the slight pressure rise, which occurs over time (see Table III). None of the patients in the present series received any anti-inflammatory medication, although recently the protocol has been changed to include the routine postoperative administration of aspirin (5 mg/kg). Another measure was to develop a patch completely free from glutaraldehyde, and a Matrix P Plus valve equipped with a decellularized equine pericardial patch received the CE mark in April 2010 and is currently available in Europe (the 'Matrix P Plus N'). For this valve, equine pericardium was selected due to its greater strength and flexibility as compared to bovine pericardium; this also avoids the possible transmission of slow virus disease from bovine material.

In general, the performance of the Matrix P and Matrix P Plus can at least match results with allografts or xenografts reported elsewhere. Brown et al. (9) described 117 non-Ross patients who received allografts for pulmonary valve replacement, and found dysfunction in 79% of patients who had received an allograft at infant age after only five years.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Interval</th>
<th>All patients (n = 56)</th>
<th>Infants (n = 15)</th>
<th>Previous RVOT (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve peak velocity (m/s)</td>
<td>Discharge</td>
<td>39 (70)</td>
<td>13 (87)</td>
<td>19 (63)</td>
</tr>
<tr>
<td></td>
<td>Follow up</td>
<td>22 (40)</td>
<td>5 (33)</td>
<td>11 (37)</td>
</tr>
<tr>
<td>Valve peak gradient (mmHg)</td>
<td>Discharge</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Follow up</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Valve regurgitation &gt;2+</td>
<td>Discharge</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Follow up</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Valve reoperation</td>
<td>1 year</td>
<td>3 (5)</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>2 years</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>3 years</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<tr>
<td></td>
<td>4 years</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Valve reintervention</td>
<td>1 year</td>
<td>3 (5)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>0</td>
<td>0</td>
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<td>3 years</td>
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<td>4 years</td>
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Values in parentheses are percentages.
Breymann et al. (10) reported 68% freedom from explantation after 2.2 years for allografts, and 25% for xenograft valves. A review of the literature (11) showed explant rates of between 11% and 46% for allografts between 3.2 and 6.1 years postoperatively. Rastan et al. (12) reported data from 72 consecutive patients with Contegra® implants, and described one- and four-year freedoms from reintervention of 86% and 70%, respectively; for infants, the freedom from reoperation was 78% at one year and 60% at four years. A subsequent risk factor analysis showed that the repair of truncus arteriosus and Contegra size 12 were risk factors for early reoperation. In the present series, five valves sized 11 mm were used and, until now, no reoperation has became necessary. Shebani and coworkers (3) found that a small size and a high right ventricular pressure were risk factors for adverse performance of the bovine jugular vein conduit.

When Bechtel et al. (13) presented results with decellularized allografts (SynerGraft™) in adult Ross patients, they were unable to show any benefit in terms of hemodynamics. Rather, they described a reduced immunologic response to the graft, with no clinical or functional changes when compared to conventional allografts (14). The SynerGraft xenografts showed an extremely poor performance, as noted by Simon et al. (15), which clearly emphasizes the importance of a correct decellularization technology. In the case of the SynerGraft, the authors described severe inflammation leading to structural failure as early as seven days postoperatively. Moreover, calcific deposits were identified at all stages and, surprisingly, were already present in pre-implant samples.

Early calcification, which can occur with allografts and xenografts in the setting of neonatal surgery, was not found with either the Matrix P or Matrix P Plus valve; likewise, neither CT scans, catheterization nor echocardiographic findings showed any signs of calcification in patients. These findings were underlined by experimental data reported by Dohmen and colleagues (6,16), who were unable to demonstrate the calcification of decellularized porcine valves in a juvenile sheep model.

Valve or conduit dilatation and subsequent progressive valve regurgitation has been described for the bovine jugular vein conduit (11,17). However, this was not observed in the present series with the Matrix P Plus. Six patients showed trace or trivial mitral valve regurgitation that was not progressive, while one patient showed grade 2+ regurgitation at one and three years postoperatively, with no deterioration.

Study limitations
The primary limitations of the present study were the lack of randomization and the small patient numbers, with a mixed patient cohort, which precluded an in-depth statistical analysis. In addition, as the echocardiographic follow up was conducted at three different institutions with several investigators in each case, the data acquired should be interpreted with caution. Although a central core laboratory would have improved the quality of the echocardiographic follow up, this procedure was unavailable during the course of the study.

In conclusion, the Matrix P and Matrix P Plus valves demonstrated very satisfying short- and mid-term performance in both neonates and infants. This matched well with the alternatives in current clinical use as allografts and stentless xenograft valves, including the bovine jugular vein conduit.

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References