Double semilunar valve replacement in complex congenital heart disease using decellularized homografts

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Abstract

OBJECTIVES: Patients with complex congenital heart disease often require multiple reoperations, resulting in increased rates of operative morbidity and mortality. Decellularized heart valves (DHVs) have led to reduced reoperation rates compared with current other valve substitutes when used for pulmonary valve replacement and have also shown very auspicious early results in aortic valve replacement. The aim of the work was to analyse the outcome of a single-stage decellularized valve implantation in the aortic and pulmonary position.

METHODS: A prospective follow-up of all patients who received a single-stage double semilunar valve replacement using DHV at our institution.

RESULTS: Since 2011, 5 patients underwent combined semilunar valve replacement with DHV at our institution: two following a Ross procedure (31-year-old man and 38-year-old woman) and 3 after repair of the truncus arteriosus communis (2-year-old boy and 11-year-old and 16-year-old girls). All patients had undergone previous surgery. The Ross patients had preceding valve procedures, and the patients with truncus arteriosus communis had undergone 1 repair and subsequent operative procedures. Despite challenging operations (median bypass time 346 min, range...
275–477 min; median cross-clamp time 229 min, range 140–307 min), there was no perioperative mortality or reoperations. Four of the patients were extubated within 24 h, and the other patient was extubated on postoperative day 2. During follow-up, a good semilunar and biventricular heart function was present in all 5 patients, and the New York Heart Association functional class was I for all the patients at the time of their latest follow-up (median 31 months, range 8–82 months). The mean echocardiographic gradient of decellularized aortic homografts was 5.4 ± 3.2 mmHg and 11.6 ± 4.2 mmHg for the decellularized pulmonary homografts. Valvular regurgitation was 0 or 0–I for all DHVs.

CONCLUSIONS: A single-stage double semilunar valve replacement with DHV has shown promising early results in these 5 very complex cases, providing an additional surgical option after multiple preceding valve procedures in young patients.

Keywords: Congenital heart disease • Semilunar valve replacement • Homograft • Decellularization

INTRODUCTION

With the growing number of patients who have undergone surgical repair for complex congenital heart diseases (CHDs), the prevalence of late aortic root dilatation associated with progressive aortic regurgitation is on the rise, even in cases where repair has been uncomplicated [1, 2].

If surgical repair is required in these patients, aortic valve-sparing procedures or composite aortic valve replacement (AVR) is often performed. However, patients who have undergone several previous surgical procedures are at a considerable operative risk. In particular, patients who previously have received homografts or xenografts in the right ventricular outflow tract (RVOT) frequently develop severe calcification and adhesion of these conduits to the surrounding tissue and the chest, making resternotomy and dissection challenging and dangerous. In these high-risk patients, simultaneous implantation of decellularized homografts in both semilunar positions could present an option or a potential ‘long-life solution of surgical management’ for selected patients, as decellularized homografts have already shown promising results for isolated pulmonary and AVR [3–6]. Decellularized heart valves (DHVs) were approved by the competent authorities for pulmonary valve replacement (PVR) (in 2013, PEI.G.11634.01.1) and AVR (in 2015, PEI.G.11766.01.1).

On the basis of this experience, we performed combined aortic root and PVR using decellularized valve conduits in 5 patients with progressive aortic valve dysfunction after repeated operations for complex CHD who also had degenerated homografts or xenografts in the RVOT position. In the present study, we evaluated the early outcome after these procedures.

PATIENTS AND METHODS

Study population

This study included all consecutive patients undergoing double semilunar valve replacement procedures with DHV at the Hannover Medical School between May 2011 and June 2017. The study was approved by the Institutional Ethics Review Board at the Hannover Medical School. Patients or, where relevant, parents provided written informed consent for inclusion in the study. Perioperative surgical findings and echocardiographic and clinical follow-up data from all patients were collected in 1 database (FileMaker 13, FileMaker Intl., Santa Clara, CA, USA) at the Hannover Medical School.

The indication for double semilunar valve replacement and the decision on the timing of operation were determined in a weekly scheduled heart team meeting between the paediatric cardiologists and congenital heart surgeons in accordance with the current guidelines of the German Society for Paediatric Cardiology [7]. In all cases, the indication was progressive aortic root dilatation, aortic valve regurgitation or aortic valve stenosis combined with the RVOT conduit dysfunction.

The patients had undergone a median of 3 previous operations and were referred to us from other institutions for double-valve replacement using DHV. Two patients had an initial diagnosis of congenital aortic stenosis with a bicuspid aortic valve und underwent a Ross procedure. One of these patients required 2 AVRs following the Ross operation. Three patients underwent repair surgery for truncus arteriosus communis in infancy. The demographic and diagnostic features of the patients are summarized in Tables 1 and 2.

Decellularized homografts

Aortic and pulmonary valve homografts were harvested under sterile conditions from cadavers, brain-dead multiorgan donors or transplant patients (‘domino’ hearts) at our institution. All donors were screened for transmissible diseases and infections.

Decellularization was performed at the corlife oHG, a small biotech spin-off company of the Hannover Medical School, by detergent treatment of the homografts using a solution of 0.5% sodium deoxycholate (Sigma) and 0.5% sodium dodecyl sulphate (Carl Roth, Karlsruhe, Germany) for 48 h, followed by 2 washing cycles (12 h each) in distilled water and 8 washing cycles with Ringer’s lactate solution, as previously described [8]. All

Table 1: Preoperative characteristics of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age at OP (years)</th>
<th>BMI (kg/m2)</th>
<th>Indications for operation</th>
<th>Diameter of the AV (mm)</th>
<th>Diameter of the PV (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>31</td>
<td>24.5</td>
<td>Aorta ascendens 51 mm and PS</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>11</td>
<td>14</td>
<td>AS, aorta ascendens 30 mm and PV degeneration</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>16</td>
<td>23</td>
<td>AS, aorta ascendens 30 mm and PV degeneration</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>38</td>
<td>20.5</td>
<td>AR, aorta ascendens 43 mm and PS</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>3</td>
<td>12</td>
<td>AR and PV degeneration</td>
<td>19</td>
<td>13</td>
</tr>
</tbody>
</table>

decellularization and washing steps were performed under continuous shaking at room temperature. To control for valve sterility, 10 ml of the last washing solution and 3 tissue samples of the DHVs were incubated over 14 days.

**Operative technique**

Each patient was admitted to the hospital once the appropriate homografts were available and following the completion of processing for decellularization and sterility control.

The operations were performed under combined intravenous general anaesthesia via median sternotomy. Venous bicaval and aortic cannulation was used for the cardiopulmonary bypass in all cases. For myocardial protection, antegrade ‘Buckberg’ cold blood cardioplegia was established via combined aortic root cannula in the aorta ascendens and was repeated every 30 min. In cases of aortic regurgitation, the cardioplegia was given selectively via the coronary ostia. For additional protection, the patients were cooled (32–25°C).

Decellularized aortic homografts (DAHs) were implanted using a full root replacement technique with reimplantation of the coronary ostia. The proximal anastomosis was performed using either interrupted 4-0 polypropylene sutures or 3 continuous sutures between commissures. In one 2-year-old patient, we used 5-0 polydioxanone for continuous sutures. The coronary buttons were anastomosed using continuous 6-0 polypropylene sutures. A continuous 4-0 or 5-0 polypropylene suture was used for the distal anastomosis. In all cases, the RVOT was reconstructed with an interposition of the decellularized pulmonary homograft (DPH), with a continuous suture for the proximal anastomosis in the ventriculotomy defect and for the distal anastomosis to the pulmonary artery. In 2 patients, the DPH was bicuspidalized, and thereby downsized, by excising a longitudinal strip containing one of the leaflets and consecutively reapproximating the free edges with 5-0 polypropylene suture (Fig. 1).

At the end of the respective operations, transoesophageal echocardiography was routinely performed to evaluate DHV function. Postoperatively, none of the patients had an aortic valve block. Aspirin was administered 3–6 months postoperatively for 3 children, and Warfarin was given for the adults for 2 months followed by continued aspirin medication (100 mg/day).

**Postoperative evaluation**

All patients were evaluated after surgery, at 6 and 12 months and then every 12 months, including clinical and functional examinations. Clinical follow-up included a regular physical examination of the patients (physical status, measurements of body height and weight, systemic blood pressure, echocardiography (ECG) and New York Heart Association classification). Echocardiographic evaluation (M-mode, 2-dimensional, colour flow, pulsatile and continuous wave Doppler) was performed according to the current guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Cardiac magnetic resonance imaging (MRI) was performed on standard 1.5-T MRI systems (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) by vector ECG-gated balanced cine sequences (steady-state free precession) for volumetric analysis, morphology of the ventricular outflow tracts and semilunar valves. Phase-contrast flow measurements were performed in the ascending aorta and main pulmonary artery. All measurements were performed by the same experienced observer (S.S.) for each patient.

**RESULTS**

The intraoperative dates are presented in Table 3. In 1 patient (Patient 3), a single venous coronary artery bypass graft was performed on the proximal right coronary artery due to a reduced right ventricular contractility. This had been agreed upon preoperatively in light of the complex coronary morphology. Both weaning from bypass and the subsequent postoperative course were uneventful. In this child, a resection of a subpulmonary stenosis was also performed through the defect in the right ventricle. There were no further intraoperative complications, reoperations or reinterventions.

All patients survived these complex procedures. For 4 of the 5 patients, the postoperative course was uneventful and the patients were extubated on the day of the operation. One patient, who had previously known bronchial stenosis, was extubated on Day 2.

The median observation time was 31 months, and the maximum observation time was 82 months. Figures 2, 3 and 4 demonstrate the postoperative MRI and computed tomography images of Patients 1, 2 and 4. At the last follow-up, the mean gradient of DAHs was 5.4 ± 3.2 mmHg and 11.6 ± 4.2 mmHg for the DPHs. Valvular regurgitation was 0 or 0–I for all DHVs. No calcification of the leaflets was seen in all patients. Table 4 summarizes the results of the latest follow-up for all patients.

**DISCUSSION**

Late development of aortic root dilatation leading to aortic valve incompetence with risk of dissection has been observed after
repair of CHD for pathologies such as truncus arteriosus communis [1] and tetralogy of Fallot [2, 9]. Progressive dilatation of the autograft in the aortic position leading to aortic valve regurgitation has also been described following the Ross procedure [10, 11].

In addition, valved conduits are required for the RVOT reconstruction and PVR inpatient groups described above. These cryopreserved homografts or xenografts require regular reoperations due to patient growth and/or graft degeneration [12] which leads to a high number of surgical procedures, e.g. the case of an 11-year-old female truncus arteriosus patient, who underwent 5 operations including 6 heart valve replacement procedures before she was referred to our centre for DHV therapy (Procedure 1: truncus arteriosus communis repair with PVR, homograft; Procedure 2: AVR, Carbomedics 16 mm, Re-PVR, Shelhigh; Procedure 3: Re-Re PVR homograft; Procedure 4: Re-Re-Re PVR, homograft and Procedure 5: Re-AVR, Carbomedics 16 mm).

In such a setting, singular replacement of the aortic root is not a good option, as moderate RVOT graft dysfunction often should be addressed simultaneously to avoid later additional procedures. If biological grafts are selected for simultaneous aortic and PVR, reoperations on both outflow tracts are preprogrammed. On the other hand, double mechanical valve replacement is not an ideal strategy for young patients in view of the medication requirement for blood thinning and the inherent risks. Moreover, mechanical prostheses do not always offer a ‘life-long’ solution, as their use is known to elicit complications such as endocarditis, thrombosis and pannus formation, which all require reoperations [13].

Thus, a combined aortic root and RVOT replacement using decellularized homografts may present an alternative option. The rationale for this approach is to limit the number of future operations in this patient population to the greatest extent based on the currently available evidence that DHV can outlast biological or mechanical valves in these young patients, thus minimizing the cycle of reoperations.

The intraoperative handling of DHV in view of the multiple previous procedures performed in these patients was very favourable as the pliable decellularized homografts are perfectly suited to adapt to difficult anatomical situations. Long DHVs allow for extended aortic root replacement in associated dilatation of the ascending aorta or simultaneous reconstruction of the pulmonary artery bifurcation. Low postoperative gradients highlight the potential of DHV for reconstruction in such complex procedures.

### Table 3: Intraoperative and postoperative data

<table>
<thead>
<tr>
<th>Patient</th>
<th>CPB time (min)</th>
<th>AXC time (min)</th>
<th>Temperature (°C)</th>
<th>Concomitant procedures</th>
<th>Intraoperative complications</th>
<th>Extubation (days)</th>
<th>ICU stay (days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>275</td>
<td>140</td>
<td>32</td>
<td>None</td>
<td>None</td>
<td>1</td>
<td>3</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>477</td>
<td>307</td>
<td>29</td>
<td>Pulmonary artery plastic</td>
<td>None</td>
<td>2</td>
<td>3</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>466</td>
<td>273</td>
<td>25</td>
<td>Subpulmonary SR</td>
<td>None</td>
<td>1</td>
<td>4</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>275</td>
<td>176</td>
<td>32</td>
<td>None</td>
<td>None</td>
<td>1</td>
<td>2</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>346</td>
<td>229</td>
<td>26</td>
<td>None</td>
<td>None</td>
<td>1</td>
<td>9</td>
<td>Alive</td>
</tr>
</tbody>
</table>

AXC: aortic cross-clamp; CPB: cardiopulmonary bypass; ICU: intensive care unit; SR: stenose resection.

Figure 1: Intraoperative photographs of Patient 5. (A) DPH after resection one of the leaflets of the valve is tested by filling with saline to demonstrate its competence. (B) Operative site from the surgeon’s view. (C) DAH and DPH after implantation. AV: aortic valve; DAH: decellularized aortic homograft; DPH: decellularized pulmonary homograft; PV: pulmonary valve.
Figure 2: Postoperative cardiac magnetic resonance imaging of Patient 2, 18 months after implantation of DHV. (A) Decellularized aortic homograft and (B) decellularized pulmonary homograft. DHV: decellularized heart valve.

Figure 3: Preoperative CT imaging of Patient 1 showing (A) severe calcification of a dilated ascending aorta (cryopreserved homograft) and the pulmonary homograft following a complicated Ross procedure; (B) DPH 5 years after implantation without signs of cusp degeneration; (C) DAH 5 years postoperatively without any dilatation of the long homograft used for AVR (poor CMR quality in the upper aorta ascendens) and (D) DAH detail showing unobstructed opening and pliable cusps. AVR: aortic valve replacement; CMR: cardiovascular magnetic resonance; CT: computed tomography; DAH: decellularized aortic homograft; DPH: decellularized pulmonary homograft.
these are less likely to be achievable using mechanical prostheses or stented bioprostheses. Furthermore, using DHV minimizes the need for extra artificial material, such as Gore-Tex patches or vascular grafts, thereby reducing the risk of infective endocarditis. The long-term performance of DHV is thought to depend on the amount of recellularization by recipient cell populations, which is more likely to occur in non-turbulent flow conditions. This could limit the use of DHV in very poor anatomical situations where residual defects are likely to occur. In such situations, a double mechanical valve replacement may present a better option.

Table 4: Follow-up data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Follow-up (m)</th>
<th>AV-DHV peak gradient (mmHg)</th>
<th>AV-DHV mean gradient (mmHg)</th>
<th>PV-DHV peak gradient (mmHg)</th>
<th>PV-DHV mean gradient (mmHg)</th>
<th>AV-DHV regurgitation (grade)</th>
<th>PV-DHV regurgitation (grade)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>3</td>
<td>2</td>
<td>22</td>
<td>13</td>
<td>0–1</td>
<td>0–1</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>16</td>
<td>2</td>
<td>32</td>
<td>17</td>
<td>0–1</td>
<td>0–1</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>15</td>
<td>8</td>
<td>25</td>
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<td>2</td>
<td>13</td>
<td>6</td>
<td>0–1</td>
<td>0</td>
</tr>
</tbody>
</table>

AV: aortic valve; DHV: decellularized heart valve; PV: pulmonary valve.

Figure 4: Postoperative cardiac magnetic resonance imaging of Patient 4, 31 months after implantation of decellularized heart valve. (A) Decellularized aortic homograft; (B) decellularized pulmonary homograft; (C) EOA of the aortic valve and (D) EOA of the pulmonary valve. EOA: effective orifice area.
The availability of small-sized DPHs, as well as conventional cryopreserved homografts, is rather limited. This prompted us to use a bicuspidalization technique for downsizing of DPHs in 2 cases. We observed no differences to the tricuspid DHV results in our study, in line with the literature for bicuspidized cryopreserved homografts [14, 15], suggesting that this technique may be especially suited for procedures in young children.

Limitations

The main limitation of the present study is the small number of patients who received DHV simultaneously in the aortic and pulmonary position and the degree of heterogeneity between them. Because of the small size of the patient cohort, advanced statistical analyses were not performed. Moreover, the follow-up period is still quite short. However, as the patients continue to be followed up, more data on the mid-term results will become available in the near future. Following the recent approval of DAH by the German authorities (www.pei.de, ARISE AV PEI.G.11766.01.1), it can be expected that the use of DAH will increase in the future and allow a matched comparison to conventional biological prostheses, mechanical valves and Ross procedures in young patients. The scarcity of donors remains another limiting factor for routine use of decellularized homografts in clinical practice.

CONCLUSION

DPHs have shown superior mid-term results in children and young adults for PVR. For AVR, DAHs have performed well in the withstanding systemic circulation with good initial results. In this article, we report on the first patients, in whom we have used decellularized grafts for double semilunar valve replacement, and who have displayed excellent perioperative and early follow-up results. While further evidence is still needed from the pending mid-term results, DHV could present a promising alternative strategy for the treatment of complex CHD in young patients.

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Conflict of interest: Axel Haverich holds shares in Corlife oHG, the company responsible for the processing of decellularized allografts used in this study. All other authors declared no conflict of interest.

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