Decellularization of Aortic Homografts: South American and European Current Experience

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Human Tissue Bank – PUCPR - Brazil
DISCLOSURES

✓ Ownership and patent license of the SDS decellularization technique (d-CELL Allograft)

✓ Consultant and Member of the Advisory Board Tissue Regenix Ltd – England
DECELLULARIZED HEART VALVE

✓ Decellularization Technique
✓ Fresh Allografts, no cryopreservation
✓ Storage at 4°C for up to 6 months
Decellularized Heart Valves Brazilian Experience (2005-2018)

Number of Implants = 1870 cases
Cryolife aortic valve replacement

**BRIEF RESEARCH REPORT**

Late durability of decellularized allografts for aortic valve replacement: A word of caution

Meghana R. K. Helder, MD, Nicholas T. Kouchoukos, MD, Kenton Zehr, MD, Joseph A. Dearani, MD, Joseph J. Malezewski, MD, Charles Leduc, MD, Courtney N. Heins, BS, and Hartzell V. Schaff, MD, Rochester, Minn; St Louis, Mo; and Baltimore, Md

![Graph showing survival rates with different methods]  
**FIGURE 2.** Kaplan-Meier curves for freedom from reoperation. Patients implanted with a DAVA had a 92% (95% CI, 84%-100%) freedom from reoperation at 5 years postimplantation, compared with 100% in the control group. Freedom from reoperation at 10 years postoperatively was 51% (95% CI, 34%-76%) in patients receiving a DAVA, compared with 80% (95% CI, 60%-100%) in the control group (P = .06).
Synergraft aortic homograft study

• Reasons for reoperation in DAVA:
  – endocarditis 26 %
  – aortic stenosis 29 %
  – aortic regurgitation 31 %

• Only 10 DAVA were available for histological analysis
  – in 7 edematous degeneration and calcifications were found
  – in 3 valves mild recellularisation was found
  – adventitial fibrosis and neointimal fibrosis were identified in all 10 specimens
FIGURE 1. Histopathologic findings of DAVAs in tissue sections stained with hematoxylin and eosin (left column) and corresponding Verhoeff-Van Gieson elastic (right column) stains, showing (A and B) full-thickness degeneration of the valve cusp and (C and D) marked calcification of the tubular component of the graft. (Original magnification, 40×.)
CryoLife homograft processing

• Proprietary technique, details unknown such as strength testing after processing

• Homografts in the Helder report have been cryopreserved and radiated before implantation. Both of these procedures have been demonstrated to impact the ultrastructure.

• In contrast, the ARISE trial is evaluating fresh, non-cryopreserved and non-radiated DAH for AVR.

Courtesy of Prof Samir Sarikouch - Hannover
Current status clinical trial

ARISE - Homografts

Calculated sample size - 120 patients

Inclusion stopped

Courtesy of Prof Samir Sarikouch - Hannover
Current status clinical trial

ARISE Trial - implantations per hospital

Courtesy of Prof Samir Sarikouch - Hannover
Decellularized aortic homografts for aortic valve and aorta ascendens replacement†

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Thomas Breymanna, Philipp Beerbaumn, Harald Bertramn, Mechthild Westhoff-Bieckn,
Karolina Theodoridisg, Dmitry Bobyleva, Eduard Cheptanaru,², Anatol Cibotaru,² and Axel Haverichn

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Figure 1: Echocardiographic mean gradient over time in the DAH. Different colours represent different patients; loose-smoothened lines are interpolated between the measurements for each individual. Some individuals show gradients that decrease over time.

I. Tudorache et al. / European J. M.

Figure 2: Valvular regurgitation over time in DAH (0 = none, 0.5 = trace, 1 = mild, 1.5 = mild to moderate, 2 = moderate, 2.5 = moderate to severe and 3 = severe). This figure shows the individual aortic valve insufficiency development and loose-smoothened interpolation lines. The decrease of insufficiency is not uncommon.

Figure 3: Freedom from explantation including the percentage of conduits with degeneration signs for the DAH (peak gradient >49 mmHg and/or at least moderate regurgitation). For 3 Moldavian patients, only clinical follow-up was available.
## Overview cell-free homografts 9/2018

<table>
<thead>
<tr>
<th></th>
<th>Aortic valve</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Period</strong></td>
<td>02/2008-09/2018</td>
</tr>
<tr>
<td><strong>Diameter</strong></td>
<td>22.4 ± 3.0 mm</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>180 (210 total)</td>
</tr>
<tr>
<td><strong>Mean age</strong></td>
<td>27.0 ± 20.0 yrs., (in &gt;40 % as a redo operation)</td>
</tr>
<tr>
<td><strong>Age range</strong></td>
<td>0.2-74.4 yrs.</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>100% (1313 exams)</td>
</tr>
<tr>
<td><strong>Patient years total</strong></td>
<td>348.0</td>
</tr>
<tr>
<td><strong>Mean follow-up years</strong></td>
<td>2.0 ± 2.1 (max. 9.5)</td>
</tr>
<tr>
<td><strong>Max. gradient (mmHg)</strong></td>
<td>16.2 ± 18.0</td>
</tr>
<tr>
<td><strong>Regurgitation (Grad 0-3)</strong></td>
<td>0.5 ± 0.6</td>
</tr>
<tr>
<td><strong>Freedom from explantation</strong></td>
<td>94.3 % (n=12/210)</td>
</tr>
</tbody>
</table>

Courtesy of Prof Samir Sarikouch - Hannover
### Freedom from explantation

![Graph showing freedom from explantation over time with different age groups.](image)

#### Number at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Age Group</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
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<tbody>
<tr>
<td>Group 1</td>
<td>&lt;10</td>
<td>40</td>
<td>23</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>10-20</td>
<td>52</td>
<td>36</td>
<td>15</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Group 3</td>
<td>&gt;20</td>
<td>88</td>
<td>32</td>
<td>20</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Courtesy of Prof Samir Sarikouch - Hannover*
The Early and Midterm Function of Decellularized Aortic Valve Allografts

Francisco D. A. da Costa, MD, Ana Claudia B. A. Costa, Roberta Prestes, Ana Carolina Domanski, MD, Eduardo Mendel Balbi, MD, Andreia D. A. Ferreira, MD, and Sergio Veiga Lopes, MD

Department of Cardiac Surgery, Santa Casa de Curitiba, Pontificia Universidade Catolica do Parana, and Institute of Neurology and Cardiology of Curitiba, Curitiba, Paraná, Brazil

Conclusions. The early and midterm results with DAVA demonstrated stable structural integrity, low rate of calcification, and adequate hemodynamics. Although longer periods of observation are necessary, DAVA appears to be a promising alternative for aortic valve replacement in selected patients.

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CLINICAL DATA

• Study Period: Nov 2005 – Sep 2018

• Patients: n= 125 (High Risk Profile]

• Age: 47 ± 18,6 (min=0,1 – max=81)

• Sex: Males = 82, Females =43

  • 27 Concomitant Mitral Valve Disease ( Multiple Reoperations]
  • 20 Ascending Aorta / Hemiarch Aneurysm
  • 27 Bacterial Endocarditis
  • 8 Coronary Artery Disease
<table>
<thead>
<tr>
<th>Data</th>
<th>n</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Valvular Lesion</td>
<td></td>
<td></td>
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<tr>
<td>Aortic Stenosis</td>
<td>46</td>
<td>36,8</td>
</tr>
<tr>
<td>Aortic Insufficiency</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>Mixed Lesion</td>
<td>29</td>
<td>23,2</td>
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<tr>
<td>Etiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatic</td>
<td>18</td>
<td>14,4</td>
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<tr>
<td>Congenital</td>
<td>32</td>
<td>25,6</td>
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<tr>
<td>Degenerative</td>
<td>24</td>
<td>19,2</td>
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<tr>
<td>Prosthetic Valve Dysfunction</td>
<td>21</td>
<td>16,8</td>
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<tr>
<td>Endocarditis</td>
<td>28</td>
<td>22,4</td>
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<tr>
<td>Acute Aortic Dissection</td>
<td>1</td>
<td>0,8</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>0,8</td>
</tr>
<tr>
<td>NYHA Classe Funcional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>9</td>
<td>7,2</td>
</tr>
<tr>
<td>II</td>
<td>69</td>
<td>55,2</td>
</tr>
<tr>
<td>III</td>
<td>39</td>
<td>31,2</td>
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<tr>
<td>IV</td>
<td>8</td>
<td>6,4</td>
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<tr>
<td>Operation</td>
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<td></td>
</tr>
<tr>
<td>Primary</td>
<td>70</td>
<td>56</td>
</tr>
<tr>
<td>Reoperation</td>
<td>55</td>
<td>44</td>
</tr>
</tbody>
</table>
OPERATIVE DATA

• **Surgical Technique**  
  Aortic Root Replacement in all patients

• **Allograft Diameter**  
  21.6 ± 2.5 mm (min=6, max=28)

• **Cross-Clamp Time**  
  110.7±26.1min (min=60, max=215)

• **Extracorporeal Circulation Time**  
  141.4±45.4min (min=80, max=270)
POSTOPERATIVE EVALUATION

Clinical Examination

Echocardiography
- Before hospital discharge
- 6/12 months PO, annually thereafter
- CT Scan
- MRI

Follow-up
- Clinical Follow-up – 106 patients (90.1% complete)
- Mean clinical follow-up time = 4.9 years (0.1 – 12.4)
DECELLULARIZED AORTIC VALVE ALLOGRAFTS RESULTS

Early Mortality = 6.4% (8/125)

- Low Cardiac Output ...........................................4
- Sepsis and Multiorgan Failure...............................2
- Cardiogenic Shock ...........................................2
AVR WITH DECELLULARIZED AORTIC VALVE ALLOGRAFTS LATE SURVIVAL

Survival (%)

0 20 40 60 80 100

Time (Years)

0 2 4 6 8 10 12 14

79.3% at 10 Years
CI95% = (66.9% - 87.4%)

Patients at Risk (117) (93) (68) (50) (31) (13) (1)

Early Death = 8
Late Death = 16
<table>
<thead>
<tr>
<th>Cause</th>
<th>Count</th>
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</thead>
<tbody>
<tr>
<td>Sudden Death</td>
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<tr>
<td>Pneumonia</td>
<td>2</td>
</tr>
<tr>
<td>Cancer</td>
<td>2</td>
</tr>
<tr>
<td>Brain Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Acute Myocardial Infarction</td>
<td>2</td>
</tr>
<tr>
<td>Reoperation for CABG</td>
<td>2</td>
</tr>
<tr>
<td>DVP– Pulmonary Embolism</td>
<td>1</td>
</tr>
<tr>
<td>Trauma</td>
<td>1</td>
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<tr>
<td>Unknown</td>
<td>3</td>
</tr>
</tbody>
</table>
RESULTS

CLINICAL FOLLOW-UP

правлено функционального статус

- NYHA I - 91 пациент
- NYHA II - 14 пациент
- NYHA III - 1 пациент
- NYHA IV - 0 пациент

- 2 случая тромбоэмболии
- Нет случаев кровотечения
- 1 случай бактериальной эндокардитис
DECELLULARIZED AORTIC VALVE ALLOGRAFTS
EARLY AND LATE MAX INSTANTANEOUS GRADIENTS

Mean Early Peak Gradients
11.6 ± 10.3

Mean Late Peak Gradients
9.6 ± 7.21
DECELLULARIZED AORTIC VALVE ALLOGRAFTS
AORTIC REGURGITATION

Aortic Regurgitation
(Number of Observations)

Time (Years)

None/Trivial
Mild
Moderate
Severe
DECELLULARIZED AORTIC VALVE ALLOGRAFTS
FREEDOM FROM ≥ MODERATE AR

92.4% at 10 Years
CI95% = (64.4% - 98.6%)

4 Events
1 Bacterial Endocardites
3 Cusps Prolapse *

Patients at Risk (108) (93) (68) (50) (31) (13) (1)
DECELLULARIZED AORTIC VALVE ALLOGRAFTS REOPERATIONS (N=5)

AR due to Healed Bacterial Endocarditis ............ 1
Primary Cusp Prolapse * .............................................. 3
Patient Outgrowth ............................................ 1

* 1 PATIENT REOPERATED ELSEWHERE – NO ECHO AVAILABLE – SURGEON REPORT ONLY
DECELLULARIZED AORTIC VALVE ALLOGRAFTS

FREEDOM FROM REOPERATION ON THE ALLOGRAFT

91.1% at 10 Years
CI95% = (75.9% - 96.9%)
EXPLANTED AORTIC ALLOGRAFT
8 YEARS OF FOLLOW-UP

AORTIC WALL

- Well preserved aortic wall
- Elastic fibers intact
- "in vivo" repopulation
- Endothelization
- Minimal Intimal Hyperplasia
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CT SCAN EVALUATION – CALCIUM SCORES -

ABSENT OR MINIMAL CALCIFICATION ON CUSPS AND CONDUITS AT 8 YEARS OF FOLLOW-UP !!!!!!
CT SCAN EVALUATION – CALCIUM SCORES -

ABSENT OR MINIMAL CALCIFICATION ON CUSPS AND CONDUITS AT 7 YEARS OF FOLLOW-UP !!!!!!
CT SCAN EVALUATION – CALCIUM SCORES -

More Intense Calcification on the Aortic Wall Only at 9Years of Follow-up
Decellularized Allografts have shown very promising results up to 12 years of follow-up. They are well incorporated to the host, with minimal inflammation and negligible immune reaction. They do not retract in the pulmonary circulation and do not dilate in the systemic side. Occasional biopsies have demonstrated partial repopulation of these grafts and minimal or absent calcification, even in children under the age of 12 years. These data demonstrate that decellularized allografts have, at least up to 10 years, better performance than conventional cryopreserved allografts and they are currently our graft of choice for patients at any age.
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