Trileaflet aortic valve reconstruction with a decellularized pericardial patch in a sheep model

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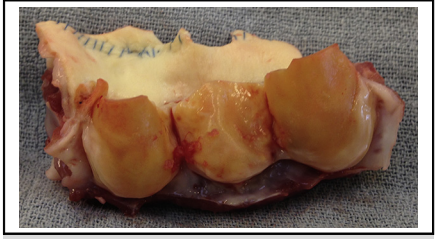
ABSTRACT

Background: The purpose of this study was to provide a preliminary assessment of the performance of a decellularized pericardial patch in a trileaflet aortic valve reconstruction in a long-term juvenile sheep model.

Methods: A sheep surgical model was used to perform a complete trileaflet reconstruction (Ozaki technique) of the aortic valve with 3 separate pericardial patches. Valve function was assessed 1 week, 3 months, and 6 months after surgery via transthoracic echocardiography. Calcification resistance and host cell infiltration of the pericardial material were assessed at 6 months after surgery.

Results: Three of 6 sheep with implanted pericardial neo-cusps survived until the planned time of sacrifice after surgery, whereas 3 animals had a successful implant but died shortly after the procedure as the result of a bad recovery from cardiopulmonary bypass. Echocardiography at 6 months revealed a high coaptation area with only minimal regurgitation. In all explanted leaflets, cusp tissue was soft. There was only minimal calcification in 8 of 9 leaflets.

Conclusions: Aortic valves reconstructed with a decellularized pericardial patch demonstrated adequate diastolic function with minimal regurgitation and resistance to calcification. Combining the Ozaki technique with this decellularized pericardial scaffold showed adequate hemodynamics, sustained mechanical integrity of the patch and limited calcification of the material. These results, together with earlier experimental and clinical data, indicate the potential of this material for aortic valve repair. (J Thorac Cardiovasc Surg 2016;152:1167-74)



Explanted CardioCel neo-cusps after 7 months in aortic position.

Central Message

A trileaflet aortic valve reconstruction in a pericardial scaffold in sheep revealed excellent results. Together with the existing clinical experience, a multicenter clinical trial will start.

Perspective

Aortic valves reconstructed with CardioCel demonstrated excellent function and very low calcification. The results support application of this pericardial scaffold in trileaflet aortic valve reconstruction. The unique combination of optimal hemodynamics of the reconstructed aortic valve, together with the decellularized character of the pericardial material, can offer benefits towards durability.

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Aortic valvular surgery is the most common valvular surgical intervention performed.[1] With the ideal replacement tissue yet to be found, several options, each with their own advantages and disadvantages, are available to candidates for aortic valve repair. Prosthetic valves have been developed with xenograft tissues as leaflets that are surgically implantable and that also are deliverable via catheter. Although these technologies have been an improvement on previous technologies, the prosthetic valves still do not enable full motion of the aortic valve annulus and root and lead to suboptimal hemodynamics.

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Abbreviation and Acronym
TTE = transthoracic echocardiography

The development of stentless valves has alleviated this problem somewhat, but still a great increase in durability has not been reached. Other techniques seek to replace the leaflets all together with autologous pericardium and thus provide superior hemodynamics. In all these instances, limitations still exist in the tissue used to reconstruct the valve leaflets. Autologous pericardium is free from donor-derived pathogens and antigens but requires fixation with glutaraldehyde to avoid resorption and thickening and to improve durability.[2,3] Homologous pericardium also requires fixation to overcome retraction and thickening.[3,4] Xenogeneic pericardium, conventionally fixed with glutaraldehyde for sterilization and to reduce antigenicity, can be made readily available in unlimited supply but is prone to calcification leading to valve deterioration.[5,6] For younger adults and pediatric patients, the inability of prosthetic valves and tissue heart valve substitutes to remodel and grow with the heart is a serious limitation.[7] In addition, glutaraldehyde fixation presents problems with cytotoxicity.[8,9] Thus, the search for a biocompatible material that provides patients with a lifelong solution is still ongoing.[10]

CardioCel (Admedus, Perth, Western Australia) is a pericardial scaffold manufactured from bovine spongiform encephalopathy-free pericardium. The manufacturing consists of several processes, which include steps to remove lipids, cells and cell remnants, nucleic acids (DNA, RNA) and α-Gal epitopes, resulting in a completely decellularized and α-Gal–free pericardial scaffold. In addition, cross-linking is achieved with a low and monomeric glutaraldehyde concentration to minimize glutaraldehyde cytotoxicity levels and to prevent the formation of long chains of polymerized glutaraldehyde. Cytotoxicity is further reduced by a proprietary anticalcification process and a nonglutaraldehyde sterilization and storage solution.

Improved biostability and durability and reduced cytotoxicity and calcification potential were demonstrated compared with autologous pericardium.[10-14] This pericardial scaffold has demonstrated comparable strength and durability to conventional fixed bovine pericardium, with less potential for calcification and lower capacity to evoke an immune response in a rat subcutaneous model.[13] A comparison of the performance of CardioCel versus conventionally fixed autologous pericardium in a juvenile sheep model of mitral and pulmonary valve repair showed that the mechanical properties of CardioCel were preserved at 8 months follow-up, with evidence of a more controlled healing process and a resistance to calcification.[14]

CardioCel has shown adaptive growth potential in preclinical models. Host cell infiltration of the scaffold has been demonstrated in a rat subcutaneous model and in jugular vein implants in juvenile sheep.[11,12] Development of neocapillaries within the scaffold also has been observed in a rat subcutaneous model.[11]

Congenital cardiac defects including valve reconstruction have been corrected in pediatric and adult patients with this material.[15-17] The scaffold performed well at 6-48 months' follow-up, with no signs of device calcification, infection, thromboembolic events, or device failure based on echocardiographic and magnetic resonance imaging data.[15-17] Although the longest-term follow-up data are now out to 7 years and longer-term data still are required, clinical experience with CardioCel thus far is promising.

Previously, the pulmonary and mitral valves of juvenile sheep have been repaired successfully with CardioCel, but the performance of this material in the aortic valve position has not been studied in sheep. The aim of this study was to develop a juvenile sheep model whereby the performance of this scaffold could be evaluated in trileaflet repair of the aortic valve. The handling properties, valve function, calcification, and recellularization potential of aortic valve cusps reconstructed with CardioCel are described.

MATERIALS AND METHODS

Animals

All animals were cared for by a veterinarian in accordance with the "Guide for the Care and Use of Laboratory Animals," published by the National Institutes of Health (NIH publication 85-23, revised 1985). The study was approved by the Ethics Committee of the Katholieke Universiteit Leuven. Six female juvenile sheep, between 6 and 8 months of age and weighing between 37 and 45 kg, were obtained from the Zoötechnical Center of the Katholieke Universiteit Leuven and were quarantined at the animal facility before undergoing surgery.

Patch Description

An aortic valve reconstruction was performed with CardioCel pericardial patches.[13-15] The manufacturing of this patch involves several processes: complete decellularization and removal of the α-Gal epitope is performed, cross-linking is achieved with a low monomeric glutaraldehyde concentration, and cytotoxicity is further reduced by a proprietary anticalcification process.[10-14]

Surgical Procedures

The animals were operated on under general anesthesia. After premedication with ketamine (10-20 mg/kg body weight, intramuscular), anesthesia was induced with increasing concentrations of isoflurane (2.5%; Isoba, Schering-Plough Animal Health, Middlesex, United Kingdom) in oxygen and was maintained with halothane and N20. After endotracheal intubation, mechanical ventilation (11-13/min; tidal volume 0.7 times body weight; positive end-expiratory pressure at 4 cm water after chest opening) was started. A large bore oro-gastric tube was placed in the rumen and allowed to drain by gravity to prevent rumenal distention. Electrocardiogram limb leads were