Results With Decellularized Xenografts

To the Editor:

We have read the review article by Vesely¹ regarding heart valve tissue engineering with great attention. The Vesely article describes recent state-of-the-art approaches to the creation of an optimal heart valve prosthesis. We feel, however, that some additional information needs to be added, as the reader could be misled by some statements made in the Vesely article.

The development of decellularized xenogenic scaffolds began in 1984, which is correctly stated by the author. Several enzymes and detergents have been investigated to eliminate interstitial cells. The author describes different techniques for decellularization and correctly concludes that most of these treatments are ineffective. Leyh et al² showed the effective elimination of endothelial and interstitial cells. This method, however, interferes with the extracellular matrix and results in severe structural degeneration and hemodynamic instability of the decellularized tissue in the sheep model. Simon et al³ showed in a clinical study the ineffectiveness of a complex treatment—the “SynerGraft technology”—by using a combination of enzymes (DNAase and RNAase), detergents, cryopreservation, and radiation. Early results showed catastrophic failures of these decellularized xenogenic heart valves. This valve was subsequently eliminated from the market. This method of decellularization seems to be aggressive, and not only eliminates cells, but also destroys extracellular matrix structures, resulting in structural deterioration as well as early calcification. Consequently, decellularization of xenogeneic heart valves, according to the “SynerGraft technology” should be avoided.

We reported the experimental results of a different decellularization technique, based on deoxycholic acid, which was not mentioned in the Vesely article. This detergent allows decellularization of biological tissues, without destroying the integrity of the extracellular matrix. In the juvenile sheep model we were able to show the long-term function of this decellularized valve matrix. Extracellular integrity was maintained, and the potential for regeneration, remodelling, and growth was shown.⁴ During follow-up, excellent hemodynamic behavior was observed in decellularized xenogeneic valve matrices, with the absence of structural deterioration as well as tissue calcification.

Other investigators also evaluated this decellularization technique. Booth et al⁵ showed that deoxycholic acid is able to completely decellularize heart valves, and histological analysis showed that the structural proteins had been retained and appeared to be intact. Similar results were found by Kasimir et al.⁶ This group showed the importance of the particular decellularization technique, which can be highly variable in efficiency and matrix preservation. Again deoxycholic acid was superior, as compared with other methods.

A recent article from our group shows an overview, not only regarding the effectiveness of preservation and mechanical integrity, but also the sterilization of the extracellular matrix, according to ISO EN 1174-1-3:2000, which is essential in heart valve prostheses.⁷

Since 2002, 221 patients have had their right ventricular outflow tract reconstructed with our decellularized xenograft. Early in the series we had several explants with prototypes of the valve, mostly because of distal anastomotic narrowing. All have been successfully reoperated on, and after adequate modifications of the valve, no further explants occurred.

The results of the first 50 consecutive patients, operated on between July 2002 and May 2004, have been reported showing positive results similar to those we found in the juvenile sheep model during previous studies. There was no increase in pressure gradient across the valve, nor was any relevant valve regurgitation reported.⁸

To date 171 more patients received a Ross operation with reconstruction of the right ventricular outflow tract with decellularized xenografts. Our complex patient cohort showed an estimated operative risk according to the logistic EuroSCORE of 5.1±5.2%. The observed mortality in 2005 was 2.7% with no valve related morbidity or mortality in those 75 patients operated on in 2005. We have also not observed any late valve related mortality. In our whole series, 5 late deaths occurred attributable to aortic valve endocarditis, pulmonary embolus from deep vein thrombosis, pancreatitis, cancer, and sudden death. Six patients were reoperated because of early distal anastomotic narrowing. Since we began using a pericardial patch at the distal anastomosis more than one year ago (n=124), this problem has been eliminated.

We believe that this information is of great importance to the readers of Circulation Research. We hope that we were able to clarify the reason why we and others are increasingly using properly decellularized xenogeneic valve matrices in our patients.

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