Decellularization of aortic valves: only time will tell

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Keywords: Tissue engineering • Decellularization • Aortic valve replacement • Regenerative medicine

Which is the best procedure for aortic valve replacement for a 33-year old female patient and which is most suitable for a 15-year old male athlete?

One choice could be a mechanical valve, with the aim of providing lifetime durability. However, the era of purely artificial valve prostheses composed of rigid components is drawing to a close. In Germany, for example, their share of the total of implanted aortic valve prostheses in 2014 amounted to a mere 14%. Glutaraldehyde-fixed xenografts still have limited durability, which precludes their use in very young patients.

(Paediatric) Cardiac surgeons therefore have turned to the concept of tissue engineering, and a number of groups have pursued the idea of decellularizing existing biological valve resources to create a biological aortic valve prosthesis, which, in the best case, would regenerate and be remodelled as the patient’s own valve or, at the very least, would be less prone to degeneration and calcification. Several protocols have been evaluated and decellularization is usually achieved by cell lysis due to changes of osmotic pressure induced using buffer solutions such as tris(hydroxymethyl)-aminomethane [1]. Bile components (sodium deoxycholate, sodium dodecyl sulphate), TRITON-100 (polyethylene glycol p-(1,3,6-tetramethylbutyl)-phenyl ether) [2] or 3-[[3-cholamidopropyl]dimethylammonio]-1-propanesulphonate) [2] are then used to wash out the cell remnants from the collagen, while preserving the basal membrane and scaffold integrity.

Artificial scaffolds created via tissue engineering offer several advantages, such as the possibility of creating custom-made scaffolds with consistent quality and the feasibility of off-the-shelf usage. But despite their comparative strengths in theory, only three protocols [3–5], out of the numerous groups working in the field of tissue-engineered heart valves have been successfully transferred to the clinic, all of which use decellularized allogenic matrices to generate aortic valve substitutes. The use of human aortic valves remains challenging and allograft procurement remains an unsolved problem [6]. Decellularized aortic valves have shown remarkable initial results. Surgical handling resembles that in native aortic valve surgery and leads to superior effective valve areas in comparison with other valve prostheses [7–9], while avoiding the two-valve procedure of a Ross operation. However, on the basis of current preclinical experience, little is known about the factors surrounding the desired recellularization process, which is key to creating an individualized, functioning graft. Cultivated mesenchymal stem cells either derived from bone marrow [10] or de-differentiated from circulating blood [11] cells have been used in conjunction with endothelial cells for in vitro reseeding of the decellularized matrix. Reseeding the scaffold under quasi-physiological conditions in an appropriately equipped pulse duplicator favours and accelerates the reseeding process, which also was shown to take place after direct implantation of the unseeded scaffold [12]. Ex vivo reseeding, however, has the disadvantage of being both time- and resource-intensive, and infections may further reduce the already small number of available conduits, or put the patient at risk if an infection is discovered only after implantation.

In vivo recellularization has been demonstrated in large animal studies on aortic valve replacement [12], and there is evidence for recellularization of decellularized grafts in humans (Fig. 1). Recellularization is crucial and therefore research has also addressed factors which may enhance invasion of recipient’s cell populations. These ‘growth factors’, however, have thus far not shown satisfying results and have therefore not yet been viable for clinical application.

From a surgical point of view, I would emphasize the importance of perfect implantation, even a normal aortic valve may fail in the setting of a relevant subaortic stenosis due to jet-damaged leaflets. Although recellularization may also occur from the adventitial side, as shown by the Padua group [13], recellularization from the luminal side is certainly important for cusps. It seems very clear that this is much more likely if surgery is able to establish a laminar flow across the implanted graft. From my experience, it is of utmost importance to avoid any distortion of the graft, as these cusps are soft and susceptible to mechanical alterations. As we have found no evidence for dilatation using the Hannover protocol for decellularization, full root replacement without any augmentation can maintain graft compliance and possibility of growth. Since individual predispositions (especially in congenital heart defects, e.g. after LeCompte manœuvre in transposition) are prevalent among our patients, it is quite difficult to simulate these factors in animal models, meaning that we will have to wait for the mid-term and long-term results of the first clinical implantation series to fully assess these aspects.

There are numerous technical aspects surrounding the implantation of a decellularized aortic valve which also need to be
analysed during the follow-up of the first patients. What suture material is best? How will decellularized grafts behave in terms of scar formation at anastomosis levels? Is it likely that such grafts will exhibit less stenosis at difficult anastomoses, and does scar formation pose a limitation to any growth potential?

Since 2008, 60 initial implantations of decellularized grafts have been successfully conducted and have shown outstanding haemodynamic performance. A number of questions, however, still exist which only can be answered via carefully performed clinical research by cardiac surgeons. On the basis of over a decade of experience in implanting decellularized pulmonary valves, during which time no explantations have been necessary, we are, however, confident that the use of decellularized valves represents a significant step towards finding the ‘ideal valve replacement’. As to whether decellularized aortic valves can similarly meet all of the initial expectations, only time will tell.

Conflict of interest: none declared.

REFERENCES


Figure 1: A non-valved decellularized aortic homograft 4 months after implantation in a newborn at Hannover Medical School. Biopsy was taken during the second step of a staged palliation. Histology shows an intact elastic matrix and amount of recellularization by recipient cells (Courtesy: Prof. K. Klingel, Tubingen, Germany).