Clinical results of implanted tissue engineered heart valves

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ABSTRACT

Since the first heterotopic implantation of a biological heart valve in 1955 by Murray, bioprostheses have been steadily improved. For allografts different methods have been evaluated and modified to stabilize and preserve the available tissue. Xenografts were fixed to cross-link the connective tissue as well as prevent immunogenic reactions. Nevertheless, gluteraldehyde fixation leads to structural deterioration, which could only be partially reduced by different kinds of anti-mineralization treatment. Due to preservation and fixation, allografts and xenografts become non-viable bioprostheses with a lack of remodelling, regeneration and growth. Tissue engineering is a possible key to overcome these disadvantages as it will provide living tissue with remodelling, regeneration and growth potential. This overview will look at the key points to provide such tissue engineered heart valves by creating an appropriate scaffold where cells can grow, either *in vitro* or *in vivo* and remodel a neo-scaffold which will lead to a functional autologous heart valve, and show initial clinical results.

Keywords: *tissue engineering, clinical, remodelling potential.*

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INTRODUCTION

Cardiovascular diseases are the most common reason for morbidity and mortality in western countries.

Treatment of valve diseases is, beside coronary bypass surgery, the most common therapy in cardiac surgery. Worldwide approximately 300,000 heart valve operations are performed and since the introduction of catheter-implantation techniques, transapical and transfemoral, the number has further increased. In Germany each year around 20,000 heart valve procedures are performed (1). If valve reconstruction cannot be performed, valve replacement will be necessary. Today mechanical or biological heart valves are routinely used; however, both types of prosthesis show specific limitations. Mechanical heart valves work satisfactorily over many years after implantation but life-long anticoagulation needs to be taken (2).

With biological heart valves full anticoagulation is not necessary and only low doses of anti-thrombogenic therapy will be sufficient but these valve prostheses are limited due to tissue deterioration (3). Human tissue valves show ideal hemodynamic performance; however their availability is limited and due to immunogenic activity

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these valves degenerate with time (4-9). None of these heart valves show growth potential, which implicates reoperations in young patients (10). Therefore a new generation heart valve is needed to overcome these disadvantages, showing the benefit of a healthy viable tissue valve with remodelling, regeneration and growth potential. Tissue engineering could be able to create such a heart valve with all the advantages of a regular healthy valve (11, 12).
This paper presents a review of the clinical use of different tissue engineered (TE) heart valves, starting with a three-dimensional scaffold, which will be seeded *in vitro* or *in vivo* with autologous cells (13-17).

Concept of tissue engineered heart valve

Tissue engineering was defined by Nerem (18) as the "development of biological substitutes to restore, maintain or improve function".
To create a viable heart valve by tissue engineering, a fundamental understanding of the natural complexity of heart valves is needed. Schoen et al. (19) showed the evolution of the tissue architecture and cell phenotypes in a heart valve through senescence. In the late fetal period, the main components of the extracellular matrix are glycosaminoglycans, whereas during the next period the collagen and elastin start to be organized and finally show a trilaminar structure.
Furthermore the cell component density will change with time, which means that during the early phase of valve development there will be a decrease in the cell components within the valves at adult age. Additionally, valvular interstitial cell phenotype expression will also undergo an evolution, as demonstrated by Aikawa et al. (20), who showed differences in protein expression. This knowledge is essential to create a viable TE heart valve.

Scaffolds

Understanding the natural development of a heart valve is essential to create an appropriate scaffold, based either on a polymer or decellularized origin. In a previous review article we described the importance of different aspects of a scaffold or matrix, which should be fulfilled to allow natural behaviour. The following should be considered: mechanical and biological integrity, providing dynamic and biochemical signals, allowing cell attachment and migration, securing diffusion of vital cell nutrients and expression factor and allowing dynamic changes of the scaffold architecture (21). Two different possibilities are available to create such a scaffold, namely polymers or decellularized scaffolds.
Polymer scaffolds. The first synthetic polymer scaffolds were created with polyglycolic acid (PGA) and later additionally supported by polylactic acid (PLA) (22). The advantages of synthetic scaffolds are the unrestricted availability in each size at any time and that sterility is not an issue. *In vivo* experiments, however, have showed several disadvantages. One major issue was the stability of the scaffold, which was already problematic at low pressure circulation (23). Therefore Sodian et al. (24) modified the PGA scaffold by using thermoplastic polyesters polyhydroxyalkanoates and poly-4-hydroxybutyrate, which allowed better handling to mould a trileaflet heart-valve shape. Hoerstrup et al. (25) combined PLA with poly-4-hydroxybutyrate; however, this modification showed progression of valve regurgitation and stenosis over time. Furthermore DNA levels at 20 weeks were higher than in native heart valve tissue which needs to be observed. This overshoot of valvular interstitial cell ingrowth is probably due to the lack of biochemical signals of the extracellular matrix (26).
Regeneration of biological valve is based on proteolysis, whereas synthetic scaffolds are

degraded through hydrolysis. No answers are yet available on the circulation of reciduals after the hydrolysis of the scaffold is completed (27). At this time, however, degradation will mainly take place *in vitro* and therefore this risk should be limited.

Generally, these created TE heart valves are simple tubes with leaflets, except for a synthetic scaffold newly developed by Sodian et al. (28) which also offers sinuses. Recent studies on aortic valve reconstruction focus on the sinus function, which supports the valvular function and improves durability (29, 30). Today there are no clinical data available on TE heart valves based on polymer scaffolds.

Decellularized scaffolds. Biological-based scaffolds are an alternative to create a three-dimensional scaffold. Therefore a normally configurated heart valve, either allo- or xenogenic nature, will be decellularized. Several decellularization techniques are available, which are mostly a combination of different elements, namely nonionic and ionic detergents, chelating agents and enzymatic methods (21). Up until now four decellularization methods have been clinically used, following two different concepts. The difference depends on the use of *in vitro* reseeding in which a bioreactor is needed. The second concept is based on the implantation of a decellularized heart valve which will be reseeded *in vivo* by the patient's body. In this case the patient is his or her own bioreactor.

Booth et al. (31) compared different decellularization methods and found that only deoxycholic acid (DOA) and sodium dodecyl sulfate (SDS) were able to completely decellularize tissue. Furthermore there was no destruction of the extracellular matrices seen, which means there was preservation of collagen, elastin and the glycosaminglycans. Rieder et al. (32) showed that SDS might destabilize the triple helical domain of collagen and lead to tissue deterioration. Bodnar et al. (33) noted that the extracellular matrix swells by the use of SDS due to destruction of extracellular proteaglycans and glycosaminglycans. Additional studies performed by Caamano et al. (34) showed cytotoxicity of SDS which will have an influence on the ingrowth of host valvular endothelial and interstitial cells. Kasimir et al. (35) also showed highly variable efficiency of different decellularization treatments in which Triton-X100 and DOA showed the best preservation of the extracellular structures.

Another important issue is the age of the heart valve at the time of decellularization. Stephens et al. (36) showed the different habits of the matrix during maturation. The extensibility differed significantly over time, as a result of age-related shift of material properties of the heart valve with an increase of collagen throughout the valve layer, particularly at the fibrosa and ventricularis layers, as well as an increased density of myofibroblasts.

These findings are in correlation with the previously mentioned study by Schoen et al. (19). Sterilization of decellularized matrices is another important issue, which has been discussed in a previous paper (17). Most of these tissue engineered heart valves have been implanted so far in the low pressure system; however, limited experience is available of implantation into the systemic circulation (17).

Valvular cells

To construct a TE heart valve, autologous valvular cells are needed to be seeded on the three-dimensional scaffold. The cell types needed for seeding are endothelial and interstitial valvular cells, which cannot be harvested, and therefore alternative cell populations are needed.

During the early days, vascular endothelial cells were harvested and multiplied *in vitro* to be seeded later on a prepared ma-

trix. Dohmen et al. (37, 38) used venous endothelial cells, for which an additional intervention or operation is necessary. The advantage of this strategy is the use of end-differentiation cell types in which all cell functions are preserved; however the growth potential is limited. Endothelial cell seeding prior to implantation creates an anti-thrombotic surface and on the other hand covers the collagen against possible immunogenic reactions (39). Although the presented results are excellent, there are limitations as harvesting and cultivation are delicate procedures. The risk of contamination by interstitial cells is always present, which will overgrow endothelial cells. If cell cultures are contaminated, another piece of vein needs to be harvested. Sometimes endothelial growth *in vitro* is limited due to the quality of autologous serum. Therefore controlled pooled serum is needed to overcome lack of endothelial cell growth. Meinhart et al. (40) studied the impact of serum lipid content, which is crucial for endothelial cell proliferation. Schaefermeier et al. (41) investigated the complexity of endothelial cells. Depending on the position of the endothelial cells, a different marker will be expressed. Similar results were found for interstitial specific expression makers but remodelling processes of the extracellular matrix differed. Therefore additional studies are needed to evaluate the possibility of reprogramming endothelial cells at other locations.

New cell sources with increased growth potential need to be evaluated. Progenitor cells could be a good alternative for creating endothelial cells, for example human umbilical-cord-derived progenitor cells (42). The disadvantage with these potential cells will be the need to establish a cell bank in which these cells need to be stored for every individual patient. In addition, the influence of long-term storage on growth and multiplying capacity is still unknown.

Vincentelli et al. (43) showed that the use of autologous bone marrow mononuclear cells showed extensive tissue deterioration and calcification after application to a decellularized valve scaffold in a juvenile sheep model. Mesenchymal stem cells showed excellent hemodynamic and histological results but may enhance inflammatory and thrombotic reactions. Rotmans et al. (44) investigated the potential of bone-marrow-derived endothelial progenitor cells, which are a subset of anti-CD34 cells with excellent in-vitro proliferation and the potential to differentiate into mature endothelial cells. Their results with cell seeding, however, showed a strong increase of intimal hyperplasia in the anti-CD34 seeded grafts compared with the bare grafts.

Therefore additional studies are needed to improve the reprogramming of valvular progenitor or stem cells.

Clinical studies of tissue engineered heart valves

The first clinical implantation of a tissue engineered heart valve was performed in 2000, as published by Dohmen et al. (37), showing the results of an *in vitro* seeded decellularized pulmonary allograft implanted during a Ross operation in an adult patient. Further patients were treated with these heart valves. Ten year clinical results of these tissue engineered heart valves are promising; however, only a limited number of patients were included (14).

In another study decellularized xenogenic pulmonary valves were seeded *in vitro* and implanted. The mid-term results of these tissue engineered heart valves are also promising (38).

Cebotari et al. (45) published initial results on tissue engineered heart valves in which autologous progenitor cells were seeded on an alternative decellularization treated scaffold. The follow-up was 40 months, showing respectable pressure gradients

and only mild to moderate regurgitation. *In vitro* seeding of decellularized heart valves is time consuming and demanding and alternatives have been introduced in clinical application after extensive experimental studies performed on the use of non *in vitro* seeded tissue engineered heart valves. Da Costa et al. (13) were able to show excellent hemodynamic behaviour of decellularized allografts compared with standard allografts. Furthermore they showed in this study a statistically significant decrease in HLA class I and II antigens in decellularized allografts compared with standard allografts: respectively 1.22 ± 1.69 and 5.37 ± 2.25 ($p < 0.01$) and 1.04 ± 1.59 and 5.92 ± 1.66, respectively ($p < 0.001$). Konertz et al. (46) showed in a consecutive study the results of 50 adult patients receiving a decellularized xenogenic heart valve during the Ross procedure. With a maximal follow up of 2 years, this study showed encouraging data on the use of this concept.

Brown et al. (16) found that the Synergraft technology in allografts showed similar freedom from reoperation rates in 342 patients with cryopreserved and synergraft pulmonary valves who underwent Ross operation as well as right ventricular outflow tract reconstruction. Pressure gradients at the latest follow up were also similar in the two groups; however, valve regurgitation differed between the groups, in favour of the cryopreserved valve using the Synergraft technology.

Nevertheless negative results have also been found in clinical practice, as shown by Simon et al. (47). They showed that the Synergraft technology failed in 4 grafts after 2 days and 1 year post-implantation. Using decellularization techniques no recellularization of the decellularized grafts was seen at up to 1 year of follow up. Rüffer et al. (48) published an article about early failure of decellularized pulmonary valves in congenital cardiac surgery, which was probably due to inflammatory response of the extended pericardial patch which was used and not neutralized. Interestingly, in this study the failure was mainly seen in the larger sizes than in the smaller sizes. Oversizing of implanted heart valves is a delicate issue in congenital cardiac surgery and should be avoided as it can lead to early graft failure. Cebotari et al. (49) were able to show improvement of freedom from explantation of fresh decellularized allografts compared with gluteraldehyde-fixed bovine jugular vein valves and cryopreserved allografts of 100 %, 86 ± 8 % and 88 ± 7 %, respectively, at 5 years of follow-up. The mean pressure gradient of the fresh decellularized allograft was significantly lower than that of the gluteraldehyde-fixed bovine jugular vein valves: 11 mm Hg versus 23 mm Hg, respectively ($p = 0.001$). In a recently published article Konertz et al. (15) showed in infants freedom from reoperation or reintervention due to valve dysfunction of 94 % at one year and 84 % at 3 years in patients undergoing complex congenital cardiac surgery. Compared to other available studies with regular heart valves these results are promising.

Zehr et al. (50) showed favourable results of decellularized cryopreserved aortic homografts in 22 patients using this graft for root replacement. Low panel reactive antibody response was seen, which may enhance durability by reducing immunogenicity of these allografts.

Da Costa et al. (51) showed results for decellularized aortic homograft implants as a root replacement in 41 patients. No reoperations were performed due to aortic valve dysfunction with a maximal follow-up of 53 months. One patient, however, needed reoperation on the mitral valve. After approval by the ethics board and patient, a tiny biopsy of the aortic wall was performed showing that it was partially recel-

lularized at 18 months, without distortion of the extracellular matrix.

In summary, first clinical implantations of tissue engineered heart valves seeded either *in vitro* or *in vivo* have been performed. Several studies have been conducted of reconstruction of the right ventricular outflow tract and now initial studies have been initiated to implant these heart valves into the systemic circulation.

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