Review

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Biological heart valves

Abstract: Cardiac valvular pathologies are often caused by rheumatic fever in young adults, atherosclerosis in elderly patients, or by congenital malformation of the heart in children, in effect affecting almost all population ages. Almost 300,000 heart valve operations are performed worldwide annually. Tissue valve prostheses have certain advantages over mechanical valves such as biocompatibility, more physiological hemodynamics, and no need for life-long systemic anticoagulation. However, the major disadvantage of biological valves is related to their durability. Nevertheless, during the Iast decade, the number of patients undergoing biological, rather than mecbanical, valve replacement has increased from half to more than three-quarters for biological implants. Continuous improvement in valve fabrication includes development of new models and shapes, novel methods of tissue treatment, and preservation and implantation techniques. These efforts are focused not only on tbe improvement of morbidity and mortality oftbe patients but also on tbe improvement of tbeir quality of life. Heart valve tissue engineering aims to provide durable, "autologous" valve prostheses. These valves demonstrate adaptive growth, which may avoid the need of repeated operations in growing patients.

Keywords: allografts; biologic heart valves; tissue engineering; xenografts.

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Introduction

Currently, cardiovascular diseases play the most important role in the morbidity and mortality of tbe worldwide population, with 80% of all cases occurring in developing countries and causing more than 19o/o of all deaths [21, 71]. Currently, more than 68 million cases of rheumatic heart disease are reported worldwide, causing 1.4 million deaths each year [67]. Rheumatic fever (young adults), atherosclerosis (elderly patients), and congenital malfor - mations (children) cause cardiac valvular pathologies and so affect almost ali population ages [56].

Most valvular heart diseases cause obstruction of the antegrade flow (stenosis), failure of the retrograde flow (insufficiency), or a combination of both. Severe valvular pathologies are usually addressed surgically by repairing or replacing the affected valve using an artificial valve substitute [1, 52]. Almost 300,000 beart valve operations are performed worldwide annually (55]. Tbere are two principal types of heart valve substitutes, which are widely used in cardiac surgery: mechanical pros - thetic valves from nonbiologic material (polymer, metal, carbon) or biological valves, wbich are created using either buman or animal tissue. Tissue valve substitutes have certain advantages over mechanical valves, such as biocompatibility, more physiological hemodynamics, and no need for life-long systemic anticoagulation [10, 44]. Combined risk of thromboembo lic events and hem - orrhage as a compllcation of anticoagulation treatment represents the principal disadvantage of mechanical prosthetic valves [9]. However, the major disadvantage of biological valves is related to their long-term durability (28]. Nevertheless, during the last decade, the number of patients undergoing biological, rather than mechanical, valve replacement has increased from half to more than three-quarters of biological implants [65].For example, in Germany in 2008, among tbe 12,000 patients who under, went isolated aortic valve replacement, 78% received biological and 21% mecbanical valve prostheses, and in lo/o, the valves were repaired !25].The prevalence ofbiological valves as the substitute of choice may be explained v.rith

severa! reasons. Elderly patients represent a continuously increasing proportion of patients undergoing valve replacement. Also, continuous technological development over the past decades has led to improved durability of biological prostheses [47]. Moreover, the development of surgical techniques over the years resulted in improvement in outcome and survival in redo surgeries. On the other hand, mechanical valves do not confer a significant long-term survival benefit over bioprostheses dueto hemorrhagic and thromboembolic risks [11]. Based on tbese facts, more patients, including tbe younger population, favor implantation of biological valves and prefer a life without anticoagulation, even if it means taking risk of reoperation [11].

Three types of biological heart valve substitutes are known: xenogenic, allogenic, and autologous (Figure 1).

Xenogenic heart valves

Xenogenic beart valves of animal origin (usually bovine or porcine) are based either on animal heart valves or animal pericardial tissue, and differ on the nature, type of construction, and cbemical fixation (Table 1). Xenografts fixed with glutaraldehyde are predominantly used in a clinicai practice for heart valve replacement. Their availability and similarity to human valves make them especially attractive for clinicai application. In France, Carpentier found in bis studies (196L1) on tbe anatomy of the valves in various animal species that pig valves were the closest to those of humans [62]. In the same year, Durao and Gunning in England replaced an aortic valve in a patient using a porcine aortic valve. Since then, porcine aortic valves were recognized as suitable biological heart valve substitutes and (in different modifications) have been largely used in recent decades [37].

On the other hand, lonescu designed and developed valves using bovine pericardium treated with glutaraldehyde and mounted on a Dacron-covered titanium frame [33]. This original valve demonstrated excellent hydrodynamic performance with good durability *in vitro.* In March 1971, Ionescu used these xenogenic valves for the first time in patients. After encouraging results, in 1976, the Shiley Laboratory in California began to produce and to distribute this valve worldwide under the name of "Ionescu-Shiley Pericardial Xenograft" [33]. Severa! years after Ionescu's introduction of the pericardial valve, which demonstrated excellent hemodynamic performance and reduced propensity for thromboembolism, other companies began manufacturing and distributing similar pericardial valves. Both porcine aortic and bovine pericardial valve substitutes showed similar outcomes and no need for anticoagulation treatment [37]. However, the major disadvantages remain the gradual degeneration and limited durability of xenogenic valves. The processes responsible for the structural deterioration of biological heart valves are directly linked to the chemical

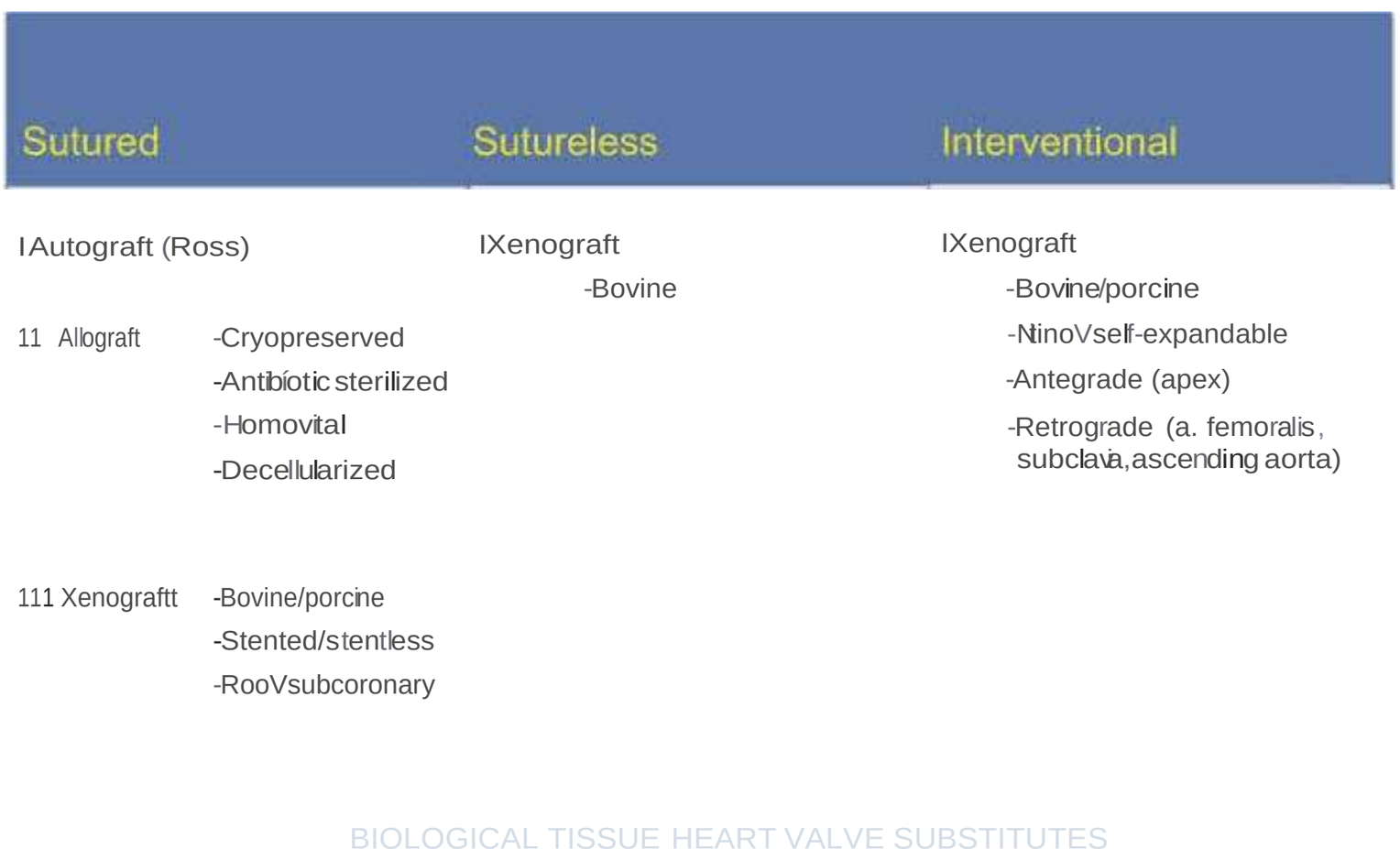

Figure 1 Classification of biological tissue heart valve substitutes according to implantation procedure.

Table 1 Biological heart valve substitutes currently used in clinicai practice.

Valve substitutes	Type	Material	Advantages (according to company information)
Medtronic Hancock 11, Hancock 11 Ultra	Stented Mitral/aortic	Porcine	>25 Years clinicai experience
Medtronic Mosaic Mosaic Ultra	Stented Mitral/aortic	Porcine	Flexible stent "Cinch" implant system
Medtronic Freesyle	Stentless "Root"	Porcine	Full-root configuration, implant versatility
Edwards Aortic porcine Mitral porcine	Stented Mitral/aortic	Porcine	Flexible stent minimizes tissue stress
Edwards S.A.V.	Stented Mitral/aortic	Porcine	Low-pressure fixation, tissue flexibility Supraannular implantation
Edwards Perimount	Stented Mitral/aortic	Bovine pericardium	Up to 20 years proven performance in the aortic position
Edwards Perimount Magna	Stented Mitral/aortic	Bovine pericardium	ThermaFix treatment advanced tissue process – removes both major calcium binding sites
Edwards Perimount Theon	Stented Mitral/aortic	Bovine pericardium	Optimized annular conformity and suturability
Edwards Perimount Magna Ease	Stented Mitral/aortic	Bovine pericardium	Magna valve platform - setting the new valve performance
Edwards Prima Plus	Stentless aortic	Porcine	Low-pressure fixation, low gradient
Terumo Vascutec Aspire	Stented Mitral/aortic	Porcine	Valve is fixed in glutaraldehyde only after tests for optimal function - maintain correct flexion
Terumo Vascutec Elan	Stentless aortic	Porcine	Only natural materiais, apart from sutures, are used in the elan valve, thus, potentially reducing the propensity for endocarditis
Terumo Vascutec BioValsalva	Stentless aortic Valved conduit	Porcine	Self-sealing trilaminate graft material; closely matches aortic root anatomy
St Jude Epic valve	Stented Mitral/aortic	Porcine	Triple composite design: features three separate porcine leaflets matched to optimize leaflet coaptation
St Jude Trifecta	Stented aortic	Bovine pericardium	Superior hemodynamic performance; low risk of PV leak
St Jude Biocor	Stented mitral	Bovine pericardium	Low profile, easy positioning within the cardiac anatomy
St.]ude Toronto SPV	Stentless aortic	Porcine	Excellent durability, free from valve replacement· related deaths 95% after 9 years
Sorin Mitroflow and Soprano	Stented aortic	Bovine pericardium	Maximized flow area, optimized hemodynamic performance
Sorin MORE	Stented mitral	Bovine pericardium	Synchronous leaflet action,PRT treatment-improve performance
Sorin Soprano Armonia	Stented aortic	Bovine pericardium	Low profile and scalloped stent, soft and easy-fitting carbofilm-coated sewing ring, allows blood flow maximization for excellent hemodynamic performance
Sorin Freedom Freedom Solo	Stentless aortic	Bovine pericardium	Excellent hemodynamic performance like a homogr.aft Exclusive detoxification treatment aimed at reducing calcium intake
ATS 3F	Stentless aortic	Equines pericard	Satisfactory hemodynamic, excellent intermediate· term clinicai results
Labcor TIPB	Stented Mitral/aortic	Porcine	Low-profile stent-reduced interference from the coronary ostea or rupture of the (eft ventricle; allows supra-annular implantation
Labcor Dokimos plus	Stented Mitral/ aortic	Bovine pericardium	Special reducer treatment optimized the crosslink and increases the tissue's biological stability, as well as reducing antigenicity
Cryolife O'Brien stentless	Stentless aortic	Porcine	Good midterm hemodynamic performance, satisfactory durability, easy implantation

and morphological changes that occur during tissue processing and valve fabrication followed by mechanical damage due to increased hemodynamic shear stress on the valve after implantation . In particular, valve durability depends on numerous factors such as the nature of the tissue, art of chemical fixation, preservation method, age and medicai condition of the patient, immunological relationship between donor and recipient tissue, hemodynamic stress during the cardiac cycle ...[54, 55].

Chemical fixation

Clinically used xenograft valve tissue is usually preserved by using chemical crosslinking with aldehydes. Preservation using chemical crosslinking diminishes antigenicity of the xenograft, inhibits autolysis, and improves material stability. lt also preserves resistance to thrombus formation and sterility of the valve [55].At the beginning of xenograft development, formaldehyde solution was used for chemical fixation of the tissue. Owing to the high degeneration rate of these valves in the first severa! years after implantation, Carpentier and his colleagues did intensive research work in the field of xenogenic tissue fixation. Carpentier, being 35 years old and an associate professor in surgery, started to follow a teaching program in chemistry in order to improve bis background in chemistry. During this period, he started to investigate numerous crosslinking-inducing factors and found that glutaraldehyde solution was able to efficiently eliminate an inflammatory response [5]. Glutaraldehyde was later proposed for xenogenic tissue valve fixation and provided better clinicai outcomes for these valves [27]. It was also demonstrated that glutaraldehyde efficiently crosslinks collagen. In contrast, formaldehyde induces less stable protein crosslinks, which may be an explanation for premature failure of formaldehyde-fixed xenografts [3].

However, the weakness of chemical fixation represents the alteration of interstitial or fibroblast cells' viability, thus, excluding from the beginning the *in vivo* remodeling of collagen in valve tissue, and therefore, the mechanical properties and durability of the tissue depend primarily on the quality of the collagen in the fabricated valve . Moreover, the fragments of the devitalized cells remaining in the tissue serve as nuclei for calcification [55]. Thiene et al. descrtbed a cascade of events following glutaraldehyde fixation and leading to graft mineralization and valve failure. Gluteraldebyde, being a killer of xenograft cells leads, to ao increased calcium influx into the cytoplasmatic compartment. Subsequently, augmented intracellular calcium combined with phosphorus from the phospholipid membrane fragments of cell debris, triggers the onset of caleium phosphate formation. Thereafter, collagen mineralization also occurs inducing progressive xenograft valve failure and dysfunction l65j. Different preparation steps have been reviewed and changed in order to improve the durability of xenografts. In new generations of tissue valves, a chemical treatment at very low or net zero pressure is provided, including surfactant and heat treatments, together with modifications in stent design. All these improvements are aimed at further reducing the rate of structural deterioration [11].

Valve design

Stented valves

Most commercially produced tissue valves are mounted into a metal ora plastic stent with three posts (typical semi· lunar valve sbape) and surrounded by a sewing ring at the base. This sewing ring, on the one hand, facilitates secure fixation of the implanted graft in valve annulus, but on the other hand, the valve ring díminishes the opening valve area ofthe graft [55]. Depending on differences in the forro and shape of the ring prosthesis, these substitutes provide increased gradients through the valves and increased stress at the attachment of the stent [35]. These facts may influence both cardiac function and durability of the valve [34].

Stentless valves

ln order to prevent patient-prosthetic mismatch and to optimize bemodynamics, the use of stentless valves was revived in the early 1990s [35]. These valves are sewn directly into a surgically prepared aortic valve site either as a root or in subcoronary technique. Both methods are more difficult due to surgical insertion and may produce more complications such as bleeding or valve incompetence . Moreover, stentless semilunar valve configuration does not readily permit mitral or tricuspid valve replacement [55].

Sutureless valves

Sutureless valves have been recently introduced into clinicai practice [22, 59]. These valves are mounted on an expandable stent, which may be delivered *in situ* after excision of the diseased valve and can be deployed without being sutured. Some of these valve prostheses require

placement of a few guiding sutures for precise positioning of the valve. The major advantage of these valves is the simplicity of implantation, resulting in time savings in the procedure and also lowering transvalvular gradients in even those grafts with small-sized annuli. Reduction of cross-clamp time in patients with aortic valve stenosis and impaired ventricular function may substantially increase early postoperative outcomes. On the other hand, so far, no long-term durability data are available, and therefore, these valves are predominantly implanted in octogenarians [58).

Transcatheter valves

Transcatheter valve implantation is a new method enabling tbe truly minimally .invasive implantation of pulmonary and aortic valves without the use of the beart-lung machine. Antegrade transapical or retrograde transvascular implantation methods (througb the ascending aorta, subclavian, carotid, femoral artery) can be used [66]. In this case, implantation is performed on a beating heart, and the new prosthesis is placed orthotopically, while the calcified native valve leaflets are being squeezed aside. In recent years, several prostbeses have become available for transcatheter valve implantation [14, 66). In order to reduce the size of the delivery system, some companies reoriented their valve production from bovine to thinner porcine pericardium [4j. Because ofthe important mortality rate (3-11o/o), high risk of stroke (2-7o/o) and also because of the absence of long-term durability results, implantation of transcatheter aortic valves is mostly oriented toward elderly and high-risk patients [66]. The "PARTNER" Trial data showed the same rates of survival at 1year in high-risk patients with severe aortic stenosis, comparing transcatbeter and surgical procedures for aortic valve replacement, although tbere were important differences in periprocedural risks [61}. Two years' follow-up data showed more frequent paravalvular regurgitation after the transcatheter approach, which was associated witb increased late mortality in this group of patients [36]. On tbe otber hand, improving the tecbnology and gaining longer follow-up data may potentially expand tbe indications for transcatheter valve implantation toward younger popu lation.

Human allograft valves

Human allograft valves provide severa! advantages compared to existing valves [39]. These valves, harvested from cadavers or heart transplant recipients ("domino" hearts), prove to have significant resistance to infection and have enhanced physiologic hemodynamical properties. Moreover, in severe valve endocarditis, homografts are preferred to other grafts because of a perfect conformation to a recipient's damaged valve annulus [19, 68, 69]. Many factors, such as method of barvesting, preservation protocol, technique of irnplantation, or selection of the patients, are controversially discussed in terms of their influence on bomograft durability after implantation .The first clinicai implantations of an aortic homograft valve were performed by Heimbecker and colleagues witb poor outcomes [26]. Ross reported on tbe first successful aortic valve replacement with an aortic valve homograft [49]. At the beginning of the bomograft era, antibiotic-sterilized and wet-stored valves were largely used in the clinicai praxis, but due to poor durability, these valves were subsequently replaced by cryopreserved allografts. Tbese days, homografts are usually frozen in dimethyl sulfoxide, followed by storage at -196°C. These valves contain viable cells, can be stored for years, and provi de enhanced durability [24]. Another preservation method has been developed by Yacoub. Fresb allograft valves stored at 4°C ("homovital") showed good long-term results with 97o/o of patients 30 years of age or older remaining free from valve degeneration after 10 years [68]. These results suggest that preserved cellular viability in unprocessed valves represent an advantage, and the rate of degeneration is relatively slow.

Integrity and function of the cells within the bomograft as well as maintenance of the matrix components have been shown to be important determinants for long-term function of allograft heart valves [70]. On the other hand, endothelial cells express tbe major bistocompatibility complex (MHC) class I and Ii molecules, representing a potential immunogenic surface and stimuJate a donor-specific immune response that can cause the degeneration of the implanted valve [17]. Owing to high immunological competence in children, early allograft failure occurs frequently in pediatric patients [13). Another drawback of allograft valve substitutes is the inability to grow concomitantlywith the growth of tbe patient body, requiring repeated valve replacement in pediatric patients.

Autograft valves

Using of an autologous pulmonary valve to reconstruct the diseased aortic or mitral valve bas been proposed by Ross in 1967 [50]. In this case, the patient's own pulmonary valve is replaced with a cryopreserved allograft or

with a glutaraldehyde-fixed xenograft valved conduit. In pulmonary position, implanted allo- or xenografts degenerate slowly because of the lower shear-stress environment. Moreover, any dysfunction of the graft in pulmonary position is tolerated better and longer on the right side of the heart. The advantages of this method are that patients do not need any anticoagulation treatment, the autograft provides excellent hemodynamic properties, it is resistant to infections, and it grows (dilates?) as the patient grows [64]. Tbis represents an enormous advantage especially for the treatment of aortic valve failure in pediatric patients [45}. However, the major disadvantage is that the surgeon addresses two valves during the operation in order to treat a single valve disease, and in the case of autograft failure, patients develop two valve diseases instead of one l46].

In order to overcome the disadvantages of allo- and xenografts, Ionescu created an artificial valve based on autologous fascia lata tissue procured from the patient. During the same procedure, he constructed the valve during the operation by mounting the living fascia on a Dacron -covered titanium frame in the shape of a three-cusp valve [29]. He began the clinicai implantation of these valves in April1969 [31, 32]. Thís procedure of valve construction and implantation was used in many centers worldwide for about 3years. Unfortunately, the fascia lata did not perform well over longer periods of time in tbe high-pressure environment of the left heart, and this procedure was later abandoned [30]. Based on the Ionescu studies, another Romanian surgeon, Deac, introduced a novel biological valve substitute for mitral surgery by concocting it from the patient's own pericardium during surgery [16]. However, the complexity of the procedure and unsatisfactory long-term outcome prevented the implementation ofthis method in routine valve surgery. Nevertheless, these days, autologous pericardium is routinely used in reconstructive valve surgery for the reconstruction of leaflet defects or as a partia! cusp replacement [2, 63].

Tissue engineering

During the last decade, efforts were made to develop cardiac valve prostheses by means of tissue engineering and use of autologous cells [23]. The main concept of tissue engineering is the usage of biological or artificial scaffolds with the shape and function of the concerned organ for the subsequentreplacement of damaged tissue. For heart valve substitutes, tissue engineering represents an upcoming alternative source for the creation of viable and biologically active grafts [23]. Two different concepts are followed: the valvular grafts are either reseeded in *vitro* before implantation [6, 38, 57]. or the cell-free scaffolds are implanted in order to provide a substrate for reseeding with autologous cells *in vivo* [18, 42]. Tissue-engineered valves should contain a specific population of autologous cells. Currently, interstitial and/or endothelial cells are seeded on decellularized biological scaffolds or biodegradable matrices [7, 53]. Cells ou three-dimensional scaffolds start to produce their own matrix proteins, gradually constructing and replacing the preseeded matrix. This process can be initiated *in vitro* (tissue engineering) and continuéd or initiated *in vivo* (guided tissue regeneration). It can be assumed that viable tissue engineered grafts should provide absolute biocompatibility, no thrombogenicity, no teratogenicity, long-term durability, and nature-like biomechanical properties and, moreover, should posses the normal biological ability to grow. There is great expectation for tissue-engineered heart valves with regenerative properties from the pediatric and young adult population, in whicb results ofvalve replacement are notas favorable as those in the older adult [20, 40].

Decellularized valvular grafts possess the forro and similar biomecbanical properties of native buman beart valves. Different methods were described to produce completely acellular allogeneic or xenogeneic matrices by removing cellular components, which are believed to raise a residual immunological response and subsequent early graft degeneration [41, 55]. Decellularization techniques include mechanical, enzymatical, detergent-based, or combined removal of the cells, leaving a scaffold composed essentially of extracellular components. The complete elimination of the cells from the xenogeneic tissue should diminish Hs antigeuic properties. However, Rieder et al. documented a remaining strong potential of decellularized porcine scaffolds to attract monocytic cells in comparison with human scaffolds [48].

Altbough the results of animal experiments in the implantation of decellularized xenograft scaffolds bave been promising, the clinicai applications of these valves were largely unsuccessful [60]. Simon et ai. used SynerGraft decellularized porcine valves for valve replacement in the right ventricular outflow tract of children and showed a high rate of failure. Histological examination of these valves revealed incomplete initial decellularization, lack of cell repopulation, severe inflammation, calcification, and degeneration of the valves [60].

The Konnertz group provided promising preclinical results as well after implantation of xenografts in growing sheep models. Nevertheless, the clinical usage of

decellularized porcine "Matrix P" valve substitutes for pulmonary valve replacement in children and young adults resulted in poor clinicai outcomes [12, 43, 51]. Probably, human immune reaction to nonfixed xenogenic tissue played a decisive role in valve degeneration. Perhaps, the discrepancies between "good" preclinical results in sheep and poor clinicai results may be explained by the cboice of the wrong animal model. Transplantation of nonfixed porcine decellularized tissue to primates would be a more appropriate and representative model for the human system and could better reflect the mechanisms of immunologic deterioration of xenogenic tissue.

In contrast, the usage of decellularized scaffolds based on human tissue provided satisfactory early and midterm results. Costa et al. reported an important reduction in the immunogenic response to decellularized human allografts compared with the cryopreserved valves and their normal function *in vivo* up to 18 months follow-up {15].

Our group reported in 2006 its first clinicai experience of tissue-engineered valves using progenitor endothelial cells isolated from the peripheral blood of the patients, and the results of 3.5 years of follow-up in pediatric patients with pulmonary valve pathology. These valves showed, during the entire follow-up period, no signs of graft stenosis, valve degeneration, progression of valve regurgitation, cusp thickness, or a reduction of the cusp's mobility. We documented an increase of valve annulus diameter with simultaneous diminution of valve regurgitation during normal growth of the patients at 3.5 years follow-up. This phenomenon has been interpreted as normal physiological growth of the TE valve [6].

Our two-center experience of implantation of decellularized pulmonary homografts in children and young adults showed better performance compared to cryopreserved homografts and glutaraldehyde-fixed xenograft valves. Implantation of these valves in young patients showed enhanced durability and adaptive growth capaci · ties. These valves provided better performance and reintervention-free survival [8].

Summary

Biological heart valve substitutes represent an important component in the surgical treatment of advanced valvular diseases, providing good hemodynamics and no need for anticoagulation therapy. However, limited durability of these valves still remains a problem that has been continuously addressed by physicians and researchers over the decades. lmprovement in valve fabrication including development of new models, new shapes, novel treatment methods witb different biological tissues, enhanced preservation, and implantation techniques is still actively pursued. These efforts are focused not only on improve - ment of morbidity and mortality of the patients but also on improvement of postoperative quality of life.

Tissue engineering represents a promising approach to create "autologous" valve prostbeses with important properties of adaptive growth and may prevent the need of repeated operations in young patients.

Received October 26, 2012; accepted May 13, 2013

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