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Tissue-Engineered Heart Valves: A Review

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ABSTRACT

Background: Mechanical heart valves (used in patients under 60 years of age) and Bioprosthetic heart valves (usually used in patients 60 years or above) have their own limitations, advantages, and disadvantages. The life-long necessity of using anticoagulants in mechanical valves and the early structural deterioration of bioprosthetic valves within 10-20 years, difficult to procure appropriately sized valves in children, prompted the need to develop a newer kind of valves that are living, can grow, and have the capability to be modulated according to the changing needs. Tissue-engineered valves are probably a solution to these problems. **Aim:** To construct a tissue-engineered heart valve (TEHV), a scaffold is needed, either a decellularized biological matrix or a nanofiber-made biodegradable material, which acts as a template to support the growth of seeded cells or repopulated cells, and the extracellular matrix. **Current status and Future perspectives**: Tissue-engineered heart valves have passed the laboratory tests, preclinical tests, and are now being implanted in selected patients with promising results. It is a living valve, and some of the defects that are revealed in the animal and human levels are being solved, and very soon, widespread human use will start. Certainly, it will be a milestone development in the field of heart valve surgery.

Keywords: Tissue-engineered Heart Valves, Artificial Heart Valves

BACKGROUND AND RATIONALE

The first mechanical heart valve device was created and implanted by Dr. Charles Hufnagel in 1952, in the descending thoracic aorta in a case of aortic regurgitation [1]. The problem of anti-coagulation surfaced soon. Numerous other designs had been created, but lifelong anti-coagulation could not be avoided. The first successful clinical use of chemically treated autologous or homologous fascia lata and heterologous pericardium in Inescu-Shiley valves in 1971 in the aortic

position prompted the spread of pericardial xenograft patches in valves and other cardiac defects [2]. The use of anticoagulant for a limited period and use of antiplatelet agent popularized these valves. The shorter longevity and Glutaraldehyde (GA) toxicity became evident, later on, limited its use in patients over 60 years of age. Glutaraldehyde was the main chemical substance to treat these tissues, but the cytotoxicity of commercially available GA-crosslinked bovine pericardial patches became evident as time passed by in vitro direct contact and extract assays of murine fibroblast culture [3]. Early calcification of these tissues in the long-term follow-up also becomes a major factor in their durability. Bovine, equine, and murine species have been used, but with the same effect. GA reduces immunogenicity by cross-linking, increases durability, but the residual GA that remains even after rinsing, and the phosphate contents of the patches also imbibe calcium ions to produce early calcification. Anti-calcific treatment can reduce but cannot fully neutralize these effects, and the restenosis, deformity, regurgitation, rupture, dystrophic calcification, aneurysm formation, and cartilaginous degeneration are not uncommon [4]. Aldehyde-treated autologous pericardial patches and commercially available pericardial patches showed some resistance to infection; however, they are prone to the same pathological effects [5]. These patches also prevent endothelialisation because of the cytotoxic effect of the released aldehydes and so remain prone to early degenerative changes, graft failure, and deformity [5]. GA treated patches are non-living and so are not useful in cases where remodeling, regeneration, and integration with the recipient's body is a necessity [4]. To achieve long-term durability, freedom from anti-coagulation, a valve is needed which are living, can grow, and remodel as the patient ages. It will also be suitable for use in children where a small-sized valve is unavailable. Extensive research was going on to get relief from the toxic aldehydes and at the same time, to maintain structural integrity with the development of new anticalcific treatments; however, the commercial applications produced the same result [3], so the decellularization of tissues as an alternative came into the horizon of new research [4]. From that time, numerous GA-free, decellularised patches or implants are available in the market [3]. The problems of infection, aneurysm formation, calcification, and degeneration were gone [5], and, in fact, patches explanted from tissues showed features of endothelialisation, neovascularisation, and evidence of remodeling [6]. A new approach was to use decellularized small intestinal submucosa of porcine small intestine as a source of Extracellular matrix(SIS-ECM) [7]. It contains mainly Type I (90%), Type III, IV, V, and VI collagen (10%), glycosaminoglycans, numerous growth factors, all embedded in a large proteoglycan molecule [8]. Implantation of SIS-ECM in the cardiac tissue causes gradual biodegradation of the scaffold with repopulation of endothelial cells, native fibroblast invasion, and, at the same time, release of growth factors, such as vascular endothelial cell growth factor (VEGF), basic fibroblast growth factor (b-FGF), and transforming growth factor beta (TGF-β), but also has a high biodegradability. This led to neoangiogenesis, endothelialisation, mitogenesis, and release of Fibronectin, Laminin, and other matrix proteins involved in the regenerative schema [9]. This produces unique remodeling with an acceptable cell and matrix array resembling the native tissue [9]. CorMatrix® (CorMatrix Cardiovascular, Inc., Roswell, Atlanta, and Alpharetta, GA, USA) is marketed as a decellularised porcine SIS material which can be folded over to produce a single layer by application of pressure [9]. It also has a lyophilized type, which needs rinsing with normal saline to make it flexible, rehydrated, and easily maneuverable. CoreMatrix has been used extensively in the repair of various cardiac defects, but the initial enthusiasm faded when later follow-up from failed cases showed inflammatory response, incomplete biodegradation, and inadequate regeneration [10-12]. An attempt to repopulate damaged myocardial cells from infarction by seeding it with skeletal myoblasts, hematopoietic stem cells, bone marrow cells, and the initial successes were soon turned into failure [13,14].

These failed sole cell therapy led to a novel attempt at Tissue engineering, first described by Langer and Vacanti [15]. In this, a framework is made from different materials like polypropylene, polyester, decellularised biological tissue, nitiolol, etc., and seeded by endothelial cells, fibroblast, etc. to produce a biological equivalent to normal tissue [16]. The decellularisation process involves the release of cells by Trypsin treatment. The degradation of the scaffold gradually releases numerous growth factors suitable for tissue growth and sustenance. Zimmermann and Eschenhagen in 2000 proposed a new technique to prevent core necrosis of the scaffold [17,18]. To train up the new tissues to have functional abilities such as contractility, conductivity, autorhythmicity, etc., they are placed in a Bioreactor where appropriate types of mechanical, electromechanical, biochemical, and biomechanical pressures are applied to achieve the goal. The main purpose of developing a bioengineered tissue valve is to develop a living valve with the potential for growth, remodeling, and sustenance with full functional capabilities.

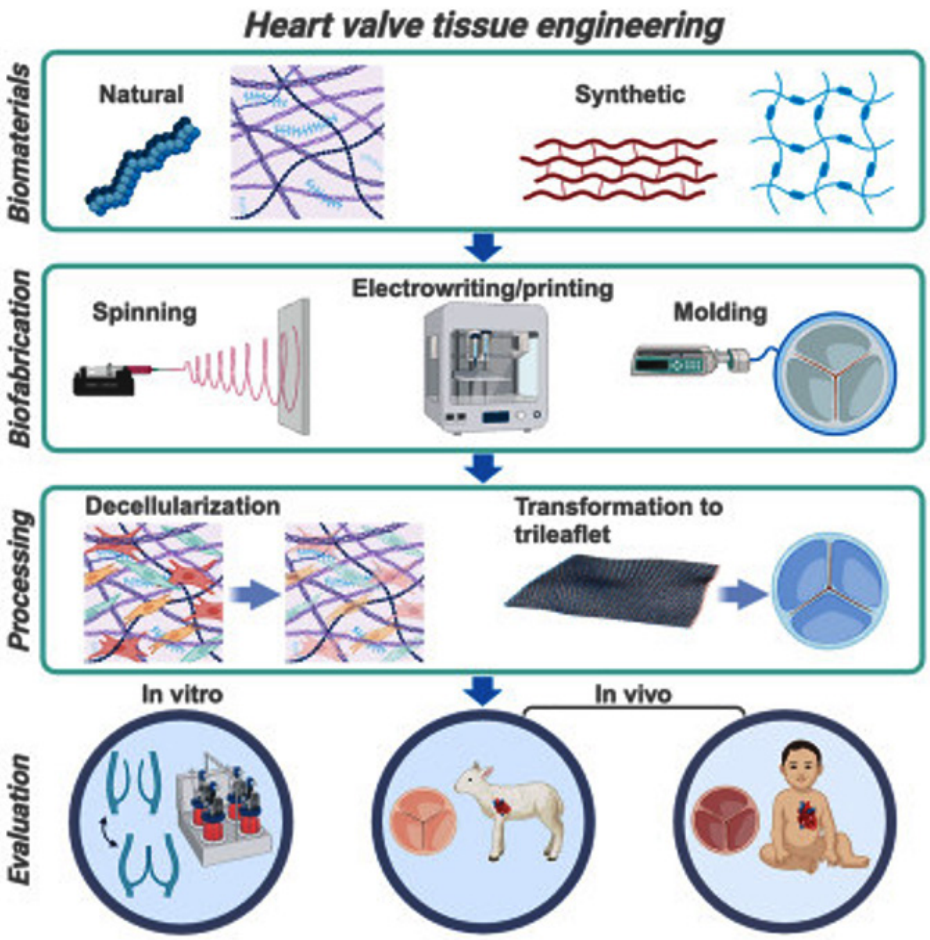

Figure 1: Bioengineered Tissue Valve. (Reproduced with permission from: Mirani B, et al. [19]).

Mirani B, et al. [18], in a review, have divided the whole process into two components: (1) biomaterial development, (2) biofabrication development. The biomaterials may be natural and synthetic polymers, and the biofabrication strategies utilize molding, electrospinning, melt electrowriting, and 3-D bioprinting and formation of trileaflet geometry [19]. Proper choice of biomaterials and the appropriate and timely application of biomechanical stimulation render these valves viable under changing demands.

The scaffold is very much important for the development of TEHV, the mechanical and biological integrity, maintenance of tissue strength, cell attachment, and incorporation into the matrix; its response to various growth factors is of importance [20]. Two types of scaffolds are in use, namely polymers or decellularized scaffolds.

Polymer Scaffold

The polyglycolic acid polymer(PGA) and later a combination of PGA and PLA (Polylactic acid) were used as the first synthetic polymer [21,22]. It gives more stability to the scaffold, and a gradual hydrolysis rather than proteolysis causes degradation and repopulation by growing endothelial and fibroblast cells in situ or in vivo [23]. The maintenance of trileaflet 3-D structure.

Figure 2: List of polymers (reprinted with permission from ar.inspiredpencil.com).

Macroarchitecture, is still a challenge; however, current research is giving promising results [24-26].

Decellularized Scaffold

Biologically based valve scaffolds, either xenogenic or allogenic origins, are natural valve-shaped scaffolds that can be decellularized to reduce immunogenicity in different techniques to act as mortises. The decellularization techniques include non-ionic and ionic detergents, chelating agents, and enzymatic methods [27]. Four decellularization methods have been clinically used until now, 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 [27]. A comparison among methods for decellularization gave mixed results, but regarding deoxycholic acid (DOA), the cell elimination is quite good, whereas sodium dodecyl sulfate does not preserve the architecture and extracellular matrices very well [23,27-30]. Age of the valve at the time of decellularization, the sterilization process has an important bearing on the longevity of TEHV [24]. Both gamma irradiation, beta-propriolactone treatment are used, although prolonged irradiation more than 25kGy is damaging to the extracellular matrix [31,32].

Comparison between decellularized biomaterial and Synthetic polymer as Scaffold:

Reddy B, et al. [20] have reviewed the differences between the biological and polymeric scaffolds [19]. Biomaterial has been defined as any substance or a blend of natural or synthetic source that could be used to provide functionality to the damaged tissue or organs [20]. The effectiveness biomaterial depends on lot of properties that include its composition, biodegrability versus non-degrability, porosity, potential for cellular or tissue in-growth, biocompatibility, and sometimes composite scaffolds of biological and synthetic polymers give better results [19].

Cellular Elements of TEHV

Initially, vascular endothelial cells from the harvested vein were cultured in tissue culture media. The cells were collected and seeded on the previously procured and processed biological scaffold, and after maturity, were implanted, but the mature cells have limited capacity to grow and cannot effectively cover the remaining immunogenicity of the scaffold even after treatment [33,34]. Also, without vein harvesting the ready availability of endothelial cells cannot be ensured, the time taken by tissue culture, chances of microbial contamination limit its uses. So, new cells were tried, which include umbilical cord stem cells, bone marrow-derived progenitor cells, mesenchymal stem cells, etc., which all gave mixed results [35-41].

***In vitro* versus *In situ* Tissue Engineering**

There are two types of technique in seeding the heart valve, 1) In vitro technique- here the basic design of the heart valve scaffold in made, either from decellularized biological valve or a polymer scaffold, then it is seeded with previously procured and cultured autologus cells, by biofabrication, then trained up in a bioreactor, then implanted in a body. However, in

many cases, in vitro tissue engineering is also expensive, time-consuming, and underdeveloped. It takes time to grow cells and tissue, and there is no guarantee that the cells and tissues grown are viable and not mutated. 2) In the in situ technique, the scaffold is formed in the same way and is implanted in the body; it is then gradually repopulated with autologous cells from the body. The cell populations are autologous, conform to the anatomy and functionality of the valve involved, are cost-effective, do not need regulatory control in trade, and are most likely to overshadow the *in vitro* technique.

Bioreactor Training

Biomechanical stimuli have a significant impact on cell behavior, including in vitro differentiation, and physiological hemodynamic conditioning has been found to promote new tissue development. It has effect on cell proliferation and maturation, extracellular matrix deposition and orientation of the fibre deposition. These concepts have led scientists to design bioreactors to mimic the *in vivo* environment of heart valves [37]. In tissue engineering of the heart valves, the bioreactor should give optimal environment as it is present in the human body. It should provide with adequate oxygen supply, optimal removal of CO2, maintenance of PH, appropriate pressure resembling systemic or pulmonary blood pressure according to proposed implantation site, a wavy flow resembling physiologic environment. Various mechanical, Biochemical, electrical forces are applied in the bioreactor according to the need of implantation sites. Modern bioreactor has replaced old bioreactors which were static in function. The dynamic bioreactors have all the mechanisms to ensure physiological functions, sensors for getting information, and automation.

Clinical Implantation

The first successful bioengineered heart valve was implanted in the pulmonary position in a Ross procedure patient in 2000. The result was excellent, and at one-year follow-up showed acceptable hemodynamic performances [38].

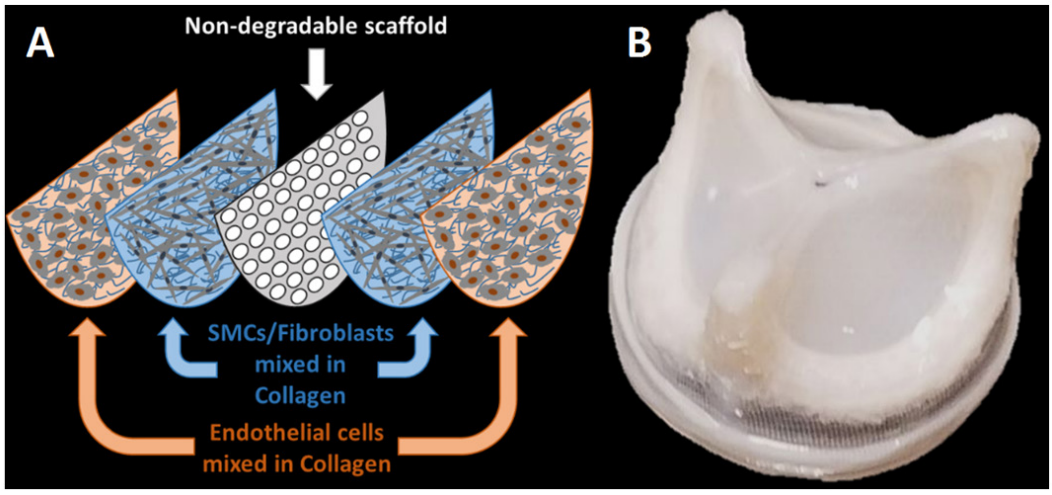

Figure 3: Hybrid tissue engineered heart valve using non-degradable scaffold

A) A schematic of non-degradable scaffold with smooth muscle cells, fibroblast and endothelial cells mixed in collagen **B)** The final tissue engineered heart valve before implantation, published with permission from https://kheradvar.eng.uci.edu/index.php, Kheradvar research group, 2420 engineering hall, University of California, Irvine- CA 92697.

Several operations that followed using tissue-engineered valves in the RVOT showed early success; however, long-term outcomes showed some valve failure. The results of TEHV implantation in low-pressure areas like RVOT were quite good; however, placement of this type of valve in the high-pressure aortic position was also promising [39]. The development of a polymeric heart valve for Transcatheter Aortic Valve Replacement (TAVR) is showing good results. The clinical trial of Foldax® Tria™ valve in the U.S (2019), China's polymer SIKELIA ™ TAVR valve (2022), and the clinical trial of Tria™ mitral valve in India in 2023 are important trials in this field and are showing comparable results [40,41].

Future Challenges

The TEHV should have the dynamic property of adjusting itself to the changing needs of the environment of implantation sites. Ideally, it should be once and for all, the replacement of heart valves. So, a gradual maturation, differentiation, and

response to wear and tear is necessary. Cells have to function both as endothelium, interstitial cells laying down collagen, elastin fibres in proportionate amounts, and extracellular ground substances throughout the long years of duration [42]. Further research to improve cell availability, cell incorporation, and Scaffold development is necessary before embarking on its widespread clinical use.

Conflict of interests

The authors declare no conflicts of interest. Prof. Hoque prepared the manuscript; co-authors contributed to review and editing.

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