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Current Status of Cardiovascular Tissue Engineering

Review Article

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Abstract

The development of vascular and heart valve surgeries have contributed to improve outcomes in patients with cardiovascular disease. However, there are drawbacks, such as risk of infection and lack of growth potential. Tissue engineered vascular graft (TEVG) and tissue engineered heart valve (TEHV) hold great promise to address these drawbacks as the ideal TEVG and TEHV is easily implanted, biocompatible, non thrombogenic, durable, degradable, and ultimately remodels into native-like tissue. In general, the TEVG and/or TEHV concept consists of scaffold, cells for scaffold seeding, and a subsequent remodeling process driven by cell accumulation and proliferation, and/or biochemical and mechanical signaling. Despite rapid progress in the field over the past decade, small-diameter arterial TEVG and TEHV have not been translated into clinical applications successfully. To successfully utilize TEVGs and TEHVs clinically, further elucidation of the mechanisms for TEVG and TEHV remodeling and further translational research outcome evaluations will be required.

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Introduction

Atherosclerosis is a leading cause of death worldwide and includes coronary artery disease (CAD), aortic disease, peripheral artery disease (PAD), and cerebral vascular disease [1]. Atherosclerotic lesions are treated with either angioplasty or surgery with medication. In the CAD, coronary artery bypass grafting (CABG) is a common surgery, whereas numerous other atherosclerotic diseases require different vascular grafts. For example, vascular grafts are also employed in pediatric heart operations for congenital heart disease. For most CABG procedures, the main source of graft is autologous tissue harvested from either arteries, such as internal mammary artery or the saphenous vein. Autologous tissue grafts or synthetic vascular grafts such as expanded polytetrafluoroethylene (ePTFE; Goretex) or poly (ethylene terephthalate) (PET, Dacron) are also commonly used as vascular grafts [2, 3]. Despite the ready availability and clinical efficacy of these grafts, these materials have some drawbacks. Autologous tissue grafts are in short supply, thus making it difficult to perform multiple or repeat operations. Whereas, small-diameter (< 6mm) synthetic vascular grafts do not have a supply tissue, but display poor patency rates related to thrombosis and stenosis [4]. Another important consideration in these synthetic grafts is their lack of growth capacity, which is of particular concern for pediatric patients. The inability for natural graft growth necessitates reoperation with patient growth, and with it the inherent increased risk for morbidity and mortality. To address these challenges, the concept of tissue engineered vascular graft was generated, and the notion is in the spotlight.

Tissue engineered vascular graft

The definition of tissue engineering is the fabrication of alternative materials for the purpose of restoring biological and physiologic function at the site of defect or injury and eventually become integrated with a patient's native tissue [5]. The basic concept of tissue engineering has 3 components: (1) a tissue-inducing scaffold material, (2) isolation and use of cells or cell substitutes, and (3) the integration of the isolated cells/substitutes and scaffold via a seeding technique [4, 6]. All three factors are interdependent and vital to the formation of highly organized neotissue. With regard to the integration of cells and scaffold, humoral and mechanical biological signaling is an important factor in the scaffold remodeling process. The ideal tissue engineered vascular graft (TEVG) would integrate with the patient's native vessel to restore physiologic function and thus include: the ability to grow, to remodel, to respond to vasoactive hormones, and to rebuild after injury.

Scaffolds

One key factors for successful TEVG fabrication is the choice of biomaterials used for the scaffolds. Currently, either synthetic or biological polymers can be used as scaffold materials for TEVG. These materials should enable neovessel development with less immune response, provide sufficient mechanical support to surrounding tissues, and biodegrade after neovessel formation.

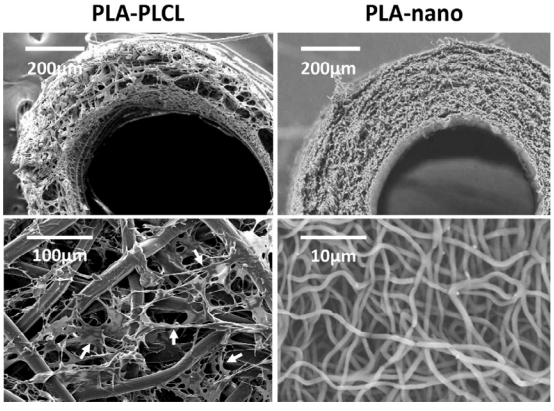
Synthetic scaffold: In pursuit of ideal scaffolds, hundreds of synthetic polymers have been developed for TEVG purposes. Polyglycolic acid (PGA), Polylactic acid (PLA), and Poly (ε-caprolactone) (PCL) are the most widely used synthetic degradable polymers in animal models [7-9]. These polymers have different degradation rates, determined by initial molecular weight, exposed surface area, crystallinity, and ratio of monomers. The degradation periods of PGA, PLA, and PCL are 2-3 weeks, 6-12 months, and 12 weeks respectively [4, 10]. Additionally, combining these materials with other synthetic polymers can provide better mechanical properties and degradation rates. Copolymers, such as poly (L-lactide-co-ε-caprolactone) (PLCL or PCLA) and poly (L-lactic-co-glycolide) (PLGA) have already proposed and investigated by us and other researchers [11, 12]. Besides PLCL and PLGA, Polyhydroxyalkanoates (PHA), and comprising polyethylene glycol and a polycarbonate of dihydroxyacetone (MPEG-PDHA) have been reported for use in synthetic scaffolds [13, 14]. Standard processing methods for these degradable polymer tissue scaffolds have included gas foaming, salt leaching, phase separation, freeze drying, 3D printing, and nanofiber electro spinning. Slow degradation of polymers enables the graft to better retain mechanical properties, but simultaneously make it more difficult for cellular infiltration and proliferation into grafts, therefore causing a delay in tissue remodeling. The electro spinning technique has been proposed as a promising method of fabricating vascular grafts (Figure 1). These ultrathin fibers have diameters in the range of 3 nm to 5 μm, and can be tailored to resemble the ECM structure, which is composed mainly of collagen and elastin fibrils [15]. As such, electro spun small-diameter scaffolds have displayed a high patency rate in addition to having good surgical and mechanical properties in an arterial graft model [8, 16].

Biological scaffold: The two main forms of biological scaffolds are decellularized tissues and ECM or ECM-like components, such as collagen or elastin. Decellularized tissue, often xenogenic, ought to contain an intact and structurally organized ECM. The decellularization process, which removes most cellular antigenic components, can be achieved through a combination of physical agitation, chemical surfactant removal and nucleotide remnants. Decellularized tissues lack cellular components and DNA, but have proper biocompatibilities and mechanical properties, similar to that of natural ECM. A well-known decellularized tissue is the small intestinal submucosa (SIS). The small-diameter SIS grafts implanted to ovine carotid and femoral arteries had similar mechanical properties to normal arteries [17] and SIS-fibrin hybrid scaffold implanted to carotid arteries showed high patency in sheep models [18]. However, the decellularization process can potentially place physical and chemical stress to the ECM, and adversely affect its biomechanical properties causing tissue deterioration which can lead to degenerative structural graft failure [19]. Additionally, further drawbacks of decellularized tissues include the inability to make modification to ECM content and architecture, and risk of viral and prion transmission from donor tissue.

Niklason et al. have reported a unique and interesting method of fabricating decellularized tissue for small-diameter arterial graft using biodegradable PGA scaffold [20, 21]. Allogenic aortic SMCs are cultured onto a PGA scaffold in a bioreactor, the engineered vessels were then decellularized, and seeded with autologous EPCs and ECs on the graft lumen. This engineered vessel had mechanical properties much like the human saphenous vein and gradually remodeled gradually, but a large drawback to this method id that it require long culture times.

ECM and ECM-like components are another biological scaffold type. These biological scaffolds are composed of natural ECM parts. Weinberg and Bell reported the first TEVG, using a collagen gel as a natural-material scaffold seeded with SMC and EC [22]. However, this TEVG lacked sufficient mechanical strength, and had to be integrated with a Dacron mesh to be evaluated *in vivo*. As an alternative to collagen, TEVG based on ovine SMC and EC embedded in fibrin gels have been developed. Similar to collagen, fibrin gels can achieve high seeding efficiency and uniform cell distribution [23]. Furthermore, when fibrin gels are combined with PLA and seeded autologous arterial-derived cells, the resulting endothelialized vessels have been successfully implanted in the carotid arteries of sheep [24].

Figure 1. Representative scanning electron microscopy images of aortic TEVG for mice. Left; PLA-PLCL grafts were constructed using a dual cylinder chamber molding system from a nonwoven 100% Poly(L-lactic acid) (PLA) fiver mesh and a 50:50 poly (L-lactic-co-ε-caprolactone) copolymer (PLCL) sealant. Total Porosity was 60% and pore size was 30μm approximately. Arrows indicate the PLCL sealant between PLA fibers. Right; PLA-nano grafts were composed of PLA nanofibers, which were constructed using electrospinning technology. Total porosity was 70% and pore size was about 5μm.



Cell

TEVG requires viable cells for neotissue formation. The main components of a blood vessel are endothelial cells (ECs) in intima and smooth muscle cells (SMCs) in media. In addition, because of advancements in technology, stem cells have also attracted further attention for their potential use in TEVG. TEVG cellular incorporation can often provide the signals needed for tissue remodeling and rebuilding.

Endothelial cells (ECs) and smooth muscle cells (SMCs): ECs possess a variety of physiological functions and synthesize many active substances, such as nitric oxide, fibronectin, heparan sulfate, interleukin-1, tissue plasminogen activator, and various growth-promoting factors [25]. The most important function is promotion of thromboresistance in TEVG. In 1978, Herring et al, introduced a technique for ECs seeding on non-biodegradable prosthetic materials. ECs were harvested from venous tissue by scarping the luminal surface [26]. Furthermore, implantation of EC-seeded ePTFE grafts resulted in significantly better outcomes compared to a non-seeded control group. According to these studies, the presence of a confluent EC monolayer on the luminal surface of a TEVG greatly enhances its thromboresistance and prevents the development of neointimal hyperplasia. On the other hand, the ECs composed pseudointima formed on synthetic TEVG was reported to function less than 10% of physiologic levels as compared with EC of native vessels. Additionally, EC have limited capacity for regeneration [27] and there is significant seeded EC loss that occurs in the first 24 hours of exposure to pulsatile flow, up to 95%, in an animal model [28]. Thus, it is thought that seeded ECs are mainly a means to prevent acute thrombosis. The mechanism for endothelialization of TEVG are proposed as followings; 1) seeded ECs, 2) the migration of ECs inward across the anastomosis from the native vessel, 3) the deposition of circulating endothelial progenitor cell (EPCs) onto the inner surface of synthetic TEVG [20, 29], and 4) ECs coverage from the ingrowth of capillaries through porous grafts (transmural endothelialization) [30]. EPCs are attractive sources of endothelialization, since they have the advantage of easy isolation via non-invasive sampling of peripheral blood. However, it remains controversial that there are adequate amounts of EPCs in peripheral blood to cover the luminal surface of TEVG as an endothelium.

It is widely accepted notion that in addition ECs, SMCs and fibroblasts are also essential to produce a stable intima. The ECM that ultimately defines the mechanical properties of a vessel are predominantly comprised of SMCs. In the 1980s-1990s, researchers reported TEVG seeding with SMCs, showed rapid neotissue formation when compared with unseeded control [31] and displayed physiological and mechanical functions comparable to native human vessels [32].

Stem cells: Recently, researchers have reported on the use of mesenchymal stem cells (MSCs), embryonic stem (ES), and induced pluripotent stem (iPS) cells for TEVG. The theoretical advantage to using stem cells as a cell source is that stem cells can be differentiated into mature cells with proper conditions and make it possible to obtain functional cells for tissue regeneration. Hashi et al, revealed not only that MSCs produced well-organized layers of ECs and SMCs, but also that MSCs have antithrombogenic properties [7], thus opening new possibilities for MSC use in TEVG.

BM-MNCs have undergone the most successful translation in human studies of TEVG. It was previously believed that the stem cell fraction within the seeded BM-MNCs population differentiated into the mature vascular cells of developing neovessel. However, we have revealed that the number of seeded cells in the graft decreased rapidly in the first few days after TEVG implantation, ultimately resulting in the absence of all BM-NMCs within 1 week post-implantation [33]. BM-MNCs contain an abundance of cytokines that can enhance neovessel development. Therefore more recently, it is believed that seeded BM-NMCs likely act in a paracrine manner to recruit additional host cells that work together to form neovessels. Some animal studies have demonstrated that TEVG seeded with BM cells may be a reasonable therapeutic option [34, 35]. We have suggested that BM-MNCs seeded TEVG are safe and effective to use in some arterial animal model and pediatric patients undergoing extracardiac total cavopulmonary connection procedures [36, 37]. Although several studies showed that BM-MNCs contribute to neovessel development and prevents thrombus and stenosis, the precise mechanism remains to be fully elucidated.

ES cells are pluripotent cells derived from early embryos. Shen et al, had developed a TEVG seeded with ECs derived from mouse ES cell. However, research on human ES cells is limited, since there are political and ethical concerns. On the other hand, iPS cell research is promising, because it does not have to consider the political and ethical problems associated with ES cell harvest, nor require immunosuppressive therapy. We have reported experience with iPS cell sheeted TEVG, and the cells also may function in a paracrine manner to induce neovascular formation. However, a number of obstacles must still be overcome prior to the implementation of iPS cells in TEVG applications [38].

Signaling

Both biochemical and biological mechanical signaling are thought to be important factors in the scaffold remodeling process.

The former includes protein adsorption, complement activation, macrophage adhesion, giant cell formation, and ECM remodeling. It is known that an integrin on inflammatory cells plays a crucial role in the recognition of biomaterials, and absorbed proteins, such as albumin, fibrinogen, and others, modulate host inflammatory cell interactions and adhesion [39]. Macrophage adhesion occurs in response to chemokines and other chemoattractants, especially when wound healing and foreign body reactions are induced [40]. Furthermore, foreign body giant cells can release degradation mediators between the cell membrane and biomaterial surfaces. M-2 macrophages play an important role in ECM remodeling. As synthetic TEVG are implanted into the host, macrophages infiltrate actively formed ECM, and this milieu has shown to stimulate monocyte polarization into the M-2 anti-inflammatory phenotype [41]. M-2 macrophages have the ability to secrete chemotactic cytokines while simultaneously partially degrading ECM material in order to facilitate new tissue in-growth.

Blood vessels remodel in response to continually changing hemodynamic and metabolic conditions. In particular, shear stress and cyclic mechanical loading due to blood flow and pressure are important. Some investigators have demonstrated that ECs alter their production of many substances, expression of adhesion molecules, and growth factors in response to imposed shear stress

both *in vivo* and *in vitro* [42, 43]. SMC growth response correlates with cyclic mechanical loading magnitudes. As a result, cyclic stretch influences both SMC synthetic and contractile phenotypes [44].

Clinical studies for TEVG

Vein and pulmonary artery: We have performed the first human clinical trial evaluating the use of TEVGs in congenital heart surgery [45]. We subsequently implanted 25 TEVGs as conduits for extra-cardiac total cavopulmonary connection with follow-up out through nine years [37] (Figure 2). There was no graft-related mortality and no evidence of aneurysm, graft rupture, graft infection, or ectopic calcification. Approximately 16% of patients had graft stenosis and underwent successful percutaneous angioplasties.

Arteriovenous shunt: L'Heureux et al. reported a new fabrication method called sheet-based tissue engineering in 1998 [46]. Sheets of living fibroblasts grown from cells extracted from patient biopsy samples were wrapped around a stainless steel mandrel and cultured. Subsequently, the inner plies were devitalized by air-drying, and ECs seeded into the lumen. The outer plies were living, and formed an adventitia equivalent. In the first clinical report, they have documented early (0-3 months) safety results for the first six patients implanted with arteriovenous shunt grafts for hemodialysis access [47]. They subsequently reported the 6 month follow-up data of the TEVGs implantation for first 10 patients and patency was 63% (5/8). However, two of the nine implanted grafts experienced early structural failure [48]. Subsequently, they developed an additional TEVG which differed by proactively isolating ECs and fibroblasts and storing it at -80°C for several months. Prior to implant, the TEVG was rehydrated, and its lumen seeded with living autologous endothelial cells to provide an antithrombogenic lining [49]. However, in 3 implants, 2 required interventions for stenosis (both eventually failed) and 1 patient died due to infectious causes [50]. It is clear, that further improvements will be needed in the future to use TEVG for chronic hemodialysis access usage as marketable products.

Artery: There are high hurdles to overcome regarding TEVG usage for arteries. The arterial TEVG must be durable enough to endure the arterial pressure, which differs from low venous pressure. Much research has been conducted in this area and has produced various TEVGs, Here, we introduce some arterial TEVG studies in large animal models.

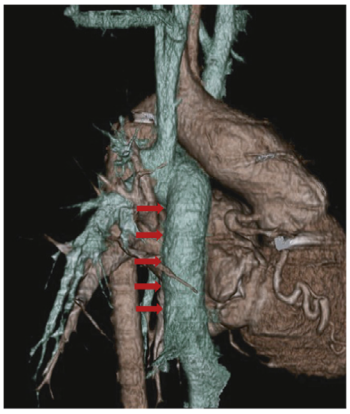
As previously mentioned, electrospinning is promising method for fabricating synthetic TEVG for arteries. Mrowczynski et al. reported results of 22 porcine carotid artery replacements with a biodegradable electrospun PCL TEVG [51]. The one month patency rate was 78% (7/9) for electrospun PCL nanofiber grafts, compared with 67% (4/6) for the ePTFE control graft, but the PCL groups showed higher neo endothelialization percentage than the ePTFE group (86% vs 58%). Long-term follow-up is required, but this simple fabrication method is attractive.

Row et al investigated SMC and EC seeded SIS-Fibrin grafts that were implanted as left common carotid artery conduits in 20 sheep, and the patency was 100% (18/18, 2 died of reasons unrelated to the implants). The surprisingly successful patency rate is valuable in pre-clinical animal model, but the graft's viability in a clinical setting is yet to be determined. Possible limitations to this particular graft are its seemingly expensive costs and the complex fabrication method to create the TEVG is complicated and the cost seems to be expensive.

Hymacyte (Hymacyte Incorporated, RTP, NC) developed a TEVG to function as a readily available off-the-shelf access method for large and small diameter graft applications [2]. The tissue manufacturing process of this tissue utilizes cadaveric SMCs to seed a PGA scaffold, cultured under radial strain. Subsequently, the TEVG is chemically decellularized prior to implantation [32]. In a series of large animal experiments, these decellularized TEVGs were implanted as coronary and peripheral arterial bypass in canines, and arteriovenous shunt in baboons. For the bypass procedures, the TEVG was seeded with autologous ECsto avoid acute thrombosis. The Hymacyte TEVG showed good patency (7/8 in baboon arteriovenous shunt and 5/6 in canine bypass model), and is currently undergoing clinical trials for hemodialysis access applications.

Mahara et al. have developed a decellularized, small caliber (2mm inner-diameter), and long (20-30cm) ostrich carotid artery graft modified with a novel heterobifunctional peptide composed of a collagen-binding region and the integrin a4b1 ligand expressed on ECs and EPCs. Subsequently, ECs and EPCs were seeded, and six grafts were transplanted in the femoral-femoral artery crossover bypass method to pigs. At 20 days the patency rate was 80% (5/6) [52].

Figure 2. Three-dimensional CT imaging 1 year after TEVG implantation. This TEVG was implanted into a patient with single ventricle physiology as extracardiac cavopulmonary conduit. This image showed a patent graft and no aneurysmal dilatation. Arrows denote extracardiac total cavopulmonary connection graft.



Despite certain TEVGs showing promising results as arterial grafts, there are limitations regarding their use. Currently, TEVGs are commercially unavailable. Further studies will be required to obtain long-term patency rates and consistently safe outcome. Future arterial TEVGs need to be viable not only technically but also economically. The tissue engineering concept will fail to successfully translate to patients suffering from cardiovascular disease if the cost to utilize arterial TEVG clinically exceeds current medical costs. In addition, many cardiovascular diseases are time sensitive, and it currently takes several months for TEVGs to be produced. Patients requiring hemodialysis access, peripheral revascularization, and coronary artery bypass surgery may not have these valuable weeks or months to spare and wait for a new TEVG to be produced.

Tissue engineered heart valve

Heart valve malfunction constitutes a significant part of heart disease, and results in substantial morbidity and death worldwide [53]. Heart valve malfunction can be due to congenital heart disease (approximately 1% of newborns), or the deposition of mineralized calcium [54-56]. The treatment of heart valve malfunction requires surgical or interventional repair or replacement. Currently, the mechanical and bioprosthetic heart valve are used as clinically state-of-the-art of artificial valves [57, 58]. Mechanical heart valves have excellent durability, but are composed of foreign materials that may cause inflammation, infection and thromboembolic complications. Therefore, it requires anticoagulation therapy to prevent thromboembolism. Bioprosthetic heart valves, primarily composed of fixed porcine leaflets or bovine pericardium, are less thrombogenic, but are prone to calcification and progressive deterioration, particularly when implanted in younger individuals [58, 59]. Additionally, both mechanical and bioprosthetic heart valves share the disadvantage of representing non-viable structures that lack capacity to grow, remodel, regenerate or repair, especially in infant' patients [60, 61]. As an alternative, the tissue engineered heart valve (TEHV) is a promising approach to overcome these drawbacks [6] as tissue engineering is a potential means of providing viable autologous cells or tissue [62].

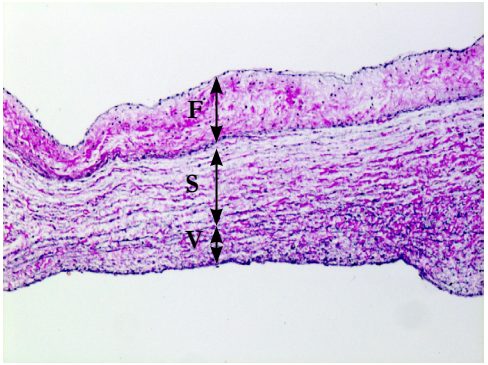
In general, TEHV consists of an unseeded or autologous cell-seeded three-dimensional (3D) biocompatible and/or biodegradable scaffold. The TEHV provides a 3D template for specific tissues to develop into neotissue from their cellular components. The 3D scaffold provides an environment for cell attachment and tissue proliferation like a TEVG [63]. Cells seeded onto a TEHV, *in vitro* or *in vivo*, can develop into neotissue that will eventually replace the scaffold. We first introduced the concept of a TEHV in 1995 [64, 65]. We developed a polyglactin woven mesh, sandwiched between 2 non-woven polyglycolic acid (PGA) mesh sheets, to reconstruct right posterior pulmonary heart valve leaflets by myofibroblast and EC seeding. Subsequently, much ongoing research is being conducted to find the ideal TEHV.

To mimic heart valve organization, we must understand the structure of native heart valve. Semilunar valves in human (pulmonic and aortic valves) consist of three semicircular leaflets (cusps) attached to a fibrous annulus called the root [66]. The aortic valve cusps are supported by the aortic valve annulus and commissures. Cusp thickness is generally less than 1mm, and is typically thicker at the base and tip. The flexible valve leaflets (cusps) are composed of three distinct layers of the extracellular matrix (ECM): the fibrosa, spongiosa, and ventricularis [67, 68] (Figure 3). The fibrosa is located nearest the aorta and is composed of circumferentially oriented fibrillary collagens (Type I and III), which is associated with mechanical properties such as stiffness and strength of the cusp [69]. The spongiosa middle layer, consists of proteoglycans interspersed with collagen fibers. The layer works as a cushioned interface between fibrosa and ventricularis layers and has two functions; to provide valve integrity and facilitate its movement. The ventricularis, composed of aligned elastic fibers interspersed with short collagen fiber, enables valve extension and recoil under diastolic and systolic pressures. These layers are composed of valvular interstitial cells (VIC) within a collagen, elastin and glycosaminoglycan (GAG) matrix. The VICs that have features of both SMCs and fibroblasts are called myofibroblast [70]. The cusps are covered with a layer of ECs [71]. To date, several TEHVs that mimic the native valve have been developed. However, TEHVs that display sufficient mechanical performance, biological integrity, less inflammatory and immunogenic responses, encouragement of cell attachment and migration, and long-term durability have yet to be developed.

The source of scaffold for TEHV

Scaffold design, which includes material selection, goes a long way to define a TEHV's success. Native heart valve structure consists of a spongy middle layer sandwiched between two laminar anisotropic fibrous layers. To mimic native heart valve structure, many scaffold designs have been proposed. Mainly two types of scaffold designs have been developed and evaluated; 1) biological and 2) synthetic-based materials. The former are decellularized native heart valve scaffolds from allogeneic/xenogeneic sources, and

Figure 3. Tissue image of tri layered structure of an aortic leaflet in sheep. The three layers consist of fibrosa (F), spongiosa (S), and ventricularis (V).



are fabricated with biological materials such as collagen, elastin, fibrin, alginate or chitosan, etc. The latter are artificial scaffolds fabricated from synthetic polymers [66, 72].

Biological-based materials: The main sources of decellularized heart valve are xenogeneic valves from pigs, sheep, and cows, as allogeneic valves are in short supply. The advantage to using decellularized heart valves is being able to keep native valve structure and while preserving natural ECM complexity and integrity. ECM serves as heart valve structural support and a receiver for signaling factors, such as cell attachment, migration, and proliferation. With this in mind, ECM may be the appropriate scaffold choice for tissue repair and reconstruction [73]. There have been many different approaches to decellurize valve tissues and the list includes; chemical reagents, ionic detergents and chelating agents, biological reagents, and physical methods, such as temperature, force, pressure, and non-thermal irreversible electroporation [74-85]. However, xenogenic material are prone to problems such as potential immunogenic reactions and the transmission of disease from animal to human [86, 87]. In particular, donor' collagen may potentially have immunogenic response to recipient [88]. Moreover, the best known transmitted xenogenic diseases are caused by the porcine endogenous retrovirus (PERV) [89] and bovine spongiform encephalopathy (BSE) [90] which can cause Creutzfeld-Jakob disease. Decellularized tissue scaffolds modified by crosslinkers, such as glutaraldehyde or pentagalloyl glucose, to sterilize xenogenic valves minimize disease transmission, and reduce immunogenicity. Alternative fixation procedures such as dye-mediated photo-oxidation [91], carbodiimide/hydroxysuccinimide treatment [92], or ethanol/glycerol treatments followed by freeze-drying [93] are currently being investigated. In general, decellularization performed with a combination of reagents has shown advantages over single-agent treatments. Despite the many decellularization approaches, the clinical outcomes of decellularized xenogenic heart valves have been disastrous. According to the SynerGraft trial, 4 decellularized porcine heart valves were implanted as right ventricular outflow tract in four children. However, all four grafts failed due to a lack of durability and strong inflammatory response [19]. Contrastingly, favorable results have been reported with decellularized allogenic valves with respect to immunological responses, durability and overall clinical performance [94]. With regard to decellularized scaffolds relying on host recellularization, allogenic heart valves have proven to be far superior to xenogenic heart valves. However, the xenogenic heart valves have the distinct advantage of being in plentiful supply and research on its development continues.

Ozaki et al. recently showed that an original aortic valve reconstruction method using autologous pericardium had favorable mid-term results [95, 96]. They treated pericardium with a 0.6% glutaraldehyde solution for 10 minutes, implanted the pericardium, and the tissue reformed manually as leaflets. The advantages of allogenic materials are their smaller immunogenic reactions and the absence of potential xenogenic disease transmission. In addition, the method demonstrated by Ozaki, may be able to overcome the general supply disadvantage that allogenic materials typically present.

Decellularized heart valve and heart valve scaffolds fabricated with biological materials share characteristics in that they both contain biological materials such collagen, elastin, fibrin, alginate or chitosan, etc. Thus, they have advantages in terms of cell adhesion, migration, proliferation and differentiation, but their drawbacks are the same as decellularized scaffolds and display vulnerable mechanical properties.

Synthetic-based materials: The advantages of synthetic-based scaffold include less immunogenicity and thrombogenicity [97]. Additionally scaffold absorbability, durability, and mechanical properties are controlled more easily. However, the disadvantages are that we cannot fully mimic the native tissues's complex structure and function. Polyglycolic acid (PGA) and polylactic acid (PLA) synthetic polymer scaffolds were among the first investigated [65, 98]. After that, various synthetic materials have been proposed and reported, such as; poly-hydroxyalkanoates (PHAs) and poly-4-hydroxybutyrate (P4HB) [99, 100], poly-hydroxyoctanoate (PHO; member of the PHA family) [101], PGA and P4HB [102], poly (D, L-lactide-co-caprolactone) (PLCL) and poly (D, L-lactide-co-glycolide) (PLGA) [103], and polyglycerol sebacate (PGS) [104]. In general, there are 3 TEHV scaffold types, and they include; 3D porous scaffolds, fibrous scaffolds, and hydrogels. The techniques to fabricate 3D porous scaffolds include particulate leaching, solvent casting, gas foaming, high internal phase emulsion, microfabrication, solid free-form (SFF) and 3D printing [105-107]. Currently, these techniques enable the fabrication of a variety of porous 3D scaffolds, with differing properties such as interconnectedness, homogeneity, and varying pore sizes. These pores allow nutrients and water to reach vascular cells and enable TEHV growth. Fibrous scaffolds fabrication techniques include electrospinning, phase separation, and self-assembly. Electrospinning is the most commonly used technique to fabricate tissue-engineered scaffolds due to its versatility, polymer applicability, easy handling, and cost-effectiveness. Structurally similar to ECM, hydrogels are hydrophilic polymer chain networks with high water contents, and generally show high permeability to oxygen, nutrients and water-soluble metabolites. Tesng et al. explored trilayer poly (ethylene glycol) diacrylate (PEGDA) hydrogel quasilaminates that corresponded to the three layers of a native heart valve [108]. However, hydrogels have weak mechanical properties and their stiffness further decreases with cell seeding.

A combination of synthetic and biological scaffolds have also been investigated. Chitosan-modified PCL porous scaffolds were fabricated to improve attachment of fibroblast cells to a TEHV [109]. A composite scaffold composed of PLCL, PLGA and type 1 collagen has been tested to determine their efficacy in a TEHV. Other investigators have applied P4HA to mold PGA mesh into valve-shaped scaffolds [102, 110]. Additionally, PGA/PLLA composite fibrous scaffolds were studied to evaluate post-implant characteristics in heart valves [111], whereas PGS-PCL hybrid scaffolds have been studied to evaluate biodegradation and mechanical properties [112]. However to date, synthetic heart valves have yet to be applied in clinical setting.

Table 1 shows the recent large animal and clinical TEHV data. Although some TEHVs, based on decellularized biological-based materials are widely and commercially available, synthetic-based material TEHVs are not yet clinically available.

Cell sources and drug delivery

Since we investigated the TEHV seeded with fibroblast and ECs in 1995 [65], cells of various origins have been used for tissue engineered heart valves, such as adipose-derived cells [113], valve interstitial cells [114], peripheral vascular cells [65, 115], bone marrow stem cells, progenitor cells from blood or amniotic fluid, and

Table 1. Recent large animal and clinical TEHV data.

Reference	Material	Cells	Animal	Valve	Year
Synthetic-based materials					
Shinoka et al	Polyglactin, PGA	Myofibroblast, endothelial cell	Lamb	PV	1995
Sodian et al	PHA	Vascular cell	Lamb	PV	2000
Hoerstrup et al	PGA, P4HB	Myofibroblast, endothelial cell	Lamb	PV	2000
Stock et al	PHO, PGA	Endothelial cell, vascular medial cell	Sheep	PV	2000
Weber et al	PGA, P4HB	BM-MNC	Primate	PV	2011
Biological-based materials					
Matrix P® and P Plus®	Xenograft (porcine)	-	Human	PV	2004
Brown et al	Allograft	-	Human	PV	2011
(Cryo Valve SyneGraft®)				(Ross AVR)	
Ozaki et al	Autologous pericardium	-	Human	AV	2014

PGA; Polyglycolic acid, PHA; poly-hydroxyalkanoate, PHO; polyhydroxyoctanoate, P4HB; poly-4-hydroxybutyrate, BM-MNC; bone marrow-mononuclear cell, PV; pulmonary valve, AVR; aortic valve replacement, AV, aortic valve

umbilical cord vascular cells. These cells have been researched for their potential ability to recellularize, proliferate, or construct new heart valve tissue indirectly through chemical mediators, such as growth factors. However some cell sources, such as valve interstitial cells and peripheral vascular cells, necessitate the sacrifice of intact structures of donor organisms. Additionally, cell sources, such as progenitor cells from amniotic fluid and umbilical cord vascular cells, have low clinical feasibility due to their extremely limited supply. In contrast, bone marrow stem cells are an attractive alternative, as they are a source of hematopoietic cells and cells that can differentiate into non-hematopoietic cells, such as those of adipocytic, chondrocytic, or osteocytic lineages. These stem-like cells are currently referred to as marrow stromal cells (MSCs) and have several advantages; 1) It is easy to obtain as they can be collected by a simple puncture of the iliac crest under local anesthesia, 2) they show an extensive proliferation capacity *in vitro*, and 3) they have the potential to differentiate into various tissues [72]. Indeed, MSC derived human cells differentiate into a myofibroblast-like phenotype [116]. As such, the tissue engineering concept suggests that a favorable microenvironment will guide cellular differentiation towards phenotypes that are appropriate for autologous tissue replacement.

In the TEHV development process, growth factors are crucial for regulating cell migration and differentiation into the scaffold. In decellularized aortic heart valves, heparin-vascular endothelial growth factor (VEGF) coatings had an antithrombotic effect and induced adhesion, proliferation and migration of EPCs onto the scaffold [117]. When compared to unmodified decellularized scaffolds, decellularized valves modified with TGF-β loaded polyethylene glycol (PEG) nanoparticules, showed superior biocompatibility, biomechanical properties, and ECM microenvironments [118]. On the other hand, granulocyte colony-stimulating factor administration accelerated heart valve deterioration similar to that of observed in non-decellularized xenogenic biological valves [119]. Therefore, further research for additional growth factors will be needed to obtain desirable results.

Summary and future perspective

Patients with cardiovascular disease often require various vascular graft implantations and/or heart valve replacements. With regards to TEVGs, patients utilize autologous grafts and non-biodegradable synthetic grafts, but suitable donor tissue for autologous graft is in short supply and synthetic grafts (particularly, small-diameter grafts) display lower patency rates, higher risks of infection, and the inability to grow or remodel. TEVGs hold great promise to resolve these problems. The rapid rise and development of tissue engineering for the past decade has enhanced the clinical feasibility of TEVGs. Investigators have focused on electrospinning technology because it enables scaffold constructs to be composed of either biodegradable synthetic polymers or biological polymers that resemble vascular tubes or flat sheets, and produced in a rapid, reliable, and cost effective manner [120, 121]. However, electrospun arterial TEVGs for artery have yet to be implanted in clinical trials.

On the other hand, using mechanical or biological hearts valves as state-of-the-art heart valve treatments are common worldwide and have improved life expectancies. However, there are some negative side effects in both types of heart valves. Mechanical heart valves require long-term anticoagulation treatment and biological heart valves lack durability and are potentially prone to calcification. In pediatric patients, both valves lack growth potential. To overcome these drawbacks, different TEHV concepts have been developed, which have the potential to remodel, regenerate, and grow into functional tissue constructs. Fabricated scaffolds should have appropriate three-layered structure/morphology, mechanical properties, and be able to regenerate functional ECM. Both biological-based and synthetic-based materials have good TEHV concepts, but each have their respective disadvantages. Biological-based materials have small pore sizes and low porosity, thus limiting cell survivability. Synthetic-based materials cannot fully mimic the trilayered structure of native heart valves, and to date have not display sufficient mechanical properties. Therefore, more research is needed to develop optimal scaffolds that can be applied in clinically.

To be widely accepted, TEVGs and TEHVs should be less invasive, cost effective, time saving, and readily available off-the-shelf. Although scaffold technology has progressed rapidly toward clinical use, cell culturing and seeding processes have several limitations, as they are technically complicated and have high costs. Bone marrow cells are a promising and attractive cell source as they are technically convenient to obtain. Patients must wait several weeks or months for TEVG and TEHV implantations

requiring cell harvests, as approaches to collect cultured and conditioned cells requires time. Therefore, to successfully and safely utilize TEVGs and TEHVs clinically, more multidisciplinary, translational research will be have to be conducted.

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