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EXPERT OPINION

Bioengineered blood vessels

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Cardiovascular disease (CVD) affecting blood vessel function is a leading cause of death around the world. A common treatment option to replace the diseased blood vessels is vascular grafting using the patient's own blood vessels. However, patients with CVD are usually lacking vessels for grafting. Recent advances in tissue engineering are now providing alternatives to autologous vascular grafts in the form of tissue-engineered blood vessels (TEBVs). In this review, we will describe the use of different scaffolding systems, cell sources and conditioning approaches for creating fully functional blood vessels. Additionally, we will present the methods used for assessing TEBV functions and describe preclinical and clinical trials for TEBV. Although the early results were encouraging, current designs of TEBV still fall short as a viable clinical option. Implementing the current knowledge in vascular development can lead to improved fabrication and function of TEBV and hasten clinical translation.

Keywords: bioreactor, endothelial cells, imaging, preconditioning, stem cell, vascular scaffolds

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1. Introduction

Vascular grafts have wide medical applications in the treatment of cardiovascular disease (CVD), including myocardial infarction and infrainguinal artery occlusive disease [1]. According to statistics provided by the American Heart Association in 2013, one-third of all deaths in the USA were attributable to CVD [2]. Vascular grafting may be necessary in advanced CVD cases, and autologous vascular grafts retrieved from the internal mammary arteries and saphenous veins are commonly used [3]. Availability of these grafts, however, can be limited by the patient's age and pathology. Artificial alternatives, composed of expanded polytetrafluoroethylene and woven/knitted polyethylene terephthalate fibers, are commercially available and have been successfully used as medial and large internal diameter (ID) prosthetics (ID ≥ 6 mm) [1,4]. Unfortunately, when applied to small diameter vessels (ID < 6 mm), these artificial grafts displayed poor patency, largely due to stenosis, myointimal hyperplasia, calcium deposition, infection and thromboembolization [5,6]. Thus, there is an urgent need to identify a reliable source of non-autologous vascular grafts for small diameter blood vessels.

In order for a tissue-engineered blood vessel (TEBV) to perform like a native blood vessel, the following criteria should be met: i) appropriate mechanical properties, which render the structure robust and easily handled during surgery, as well as compliant with the physiological environment; ii) biocompatible, non-immunogenic and low risk of inducing thromboembolic events and intimal hyperplasia; iii) and remodeling capabilities and integration with the native host vessels [7,8]. In our point of view, the TEBV consists of three essential characteristics: i) a scaffolding system that supports cell attachment and proliferation; ii) a variety of cell types, including endothelium, smooth muscle cells (SMCs) and fibroblasts (FB); and iii) and neo-tissue formation following exposure to a sequence of physical and chemical signals during a conditioning phase. In the subsequent sections, we

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describe scaffolding options, cell sources and conditioning used in recent years, as well as a review of preclinical and clinical assessments of TEBVs.

2. Scaffolds

Several techniques are currently being used to create scaffolds for TEBV, including electrospinning, tissue decellularization, self-assembling vessels and others.

2.1 Electrospinning

Electrospinning technology is extensively applied to scaffold fabrication in tissue engineering and has several advantageous properties, which include a highly interconnected porous network, a high surface area:volume ratio and nanofiber structures similar to the native extracellular matrix (ECM) [9]. For vascular applications, electrospinning can create a seamless tubular scaffold with adjustable diameters. As shown in Figure 1A, 4.75 mm diameter of scaffold was fabricated from poly(epsilon-caprolactone) (PCL)/collagen blend, and the scaffold possessed a nano-sized fibrous microstructure. A large number of materials are used in electrospinning, including natural and synthetic polymers and their blend mixtures. ECM-derived natural biopolymers, such as collagen [10], elastin [11-13] and gelatin [14], are used in promoting biocompatibility and enhancing attachment and proliferation of endothelium and SMCs. The synthetic polymers are usually bioabsorbable materials such as PCL, poly(D,L-lactide-*co*-glycolide) and poly-L-lactide that provide initial to long-term strength to accommodate the physiological environment of blood flow. Although various electrospun scaffolds have been fabricated, few of them meet all the requirements of mechanical strength, burst pressure, suture strength and compliance possessed by successful blood vessels. Electrospun scaffolds are easily modified with a number of active molecules: platelet-derived growth factor-BB to stimulate SMCs penetration [14]; heparin to enhance hemocompatibility [15] and arginine-glycine-aspartic acid to improve endothelial cell (EC) attachment inside the vascular grafts [16]. Bilayered or multilayered electrospinning are used to mimic the native vascular structure to facilitate the formation of a confluent monolayer of EC in the lumen and SMC penetration through the scaffold wall [17].

2.2 Decellularized scaffolds

Another approach to prepare scaffolds for tissue engineering is to decellularize native tissues, such as small intestinal submucosa [18-20], canine aorta [3], porcine arteries [21,22], porcine abdominal aortas [23] and human umbilical arteries [24]. Decellularized blood vessels have the advantage of preserving native ECM components that are necessary for cell adhesion, migration and proliferation. These acellular scaffolds possess the mechanical properties to endure normal blood pressure. Different animal species were implanted with TEBV made from decellularized scaffolds to be used as arterial and coronary bypasses, which were patent for several months [21,22,24-26]. Several shortcomings to the decellularized scaffold have been encountered, including the potential transmission of animal pathogens, lack of control over ECM composition and architecture, tissue degradation leading to deteriorating structural graft failure and inadequate migration of cell due to the tight matrix organization [3,27].

2.3 Cell self-assemble vascular graft

Cell self-assembling scaffolds are composed of autologous cell-derived ECM sheets harvested from *in vitro* cultures [28]. Manipulating such cell-derived ECM sheets allows the formation of tubular vascular grafts [29]. Such grafts have shown high patency and have been used in a human clinical trial as arteriovenous (AV) shunts for hemodialysis access [30,31]. Although the cell self-assembling vessels showed promising results in early clinical applications, they require extensive *in vitro* culture (about 6 – 9 months) and high cost (over $15,000/graft) [32]. Self-assemble approach was used in fabricating another type of TEBV, combined with prototyping imprinting technique, in a ‘bottom-up’ approach [33]. Multicellular spheroids were printed into a designed pattern on an agarose mold, and following several days in culture, the spheroids fused together to form an ECM-bound construct. The major drawback of this approach is the difficulty in controlling cell distribution within the vascular construct, especially the formation of a monolayer of EC.

2.4 Biosynthetic vascular graft

To reduce the culture time of the self-assembling method, an alternative method was developed, where allogeneic SMCs were cultured on rapidly degrading polyglycolic acid (PGA) tubular scaffolds over 8 – 10 weeks to form the wall of the bioengineered vessel [34,35]. The bioengineered vessel was subsequently decellularized, leaving only cell-secreted ECM in the scaffold, which was seeded with autologous endothelial progenitor cells (EPCs) to obtain a non-thrombogenic vascular graft that resisted intimal hyperplasia [35]. Preclinical trials of these grafts were successful in canine [34] and porcine [35] models, and clinical trials are pending.

2.5 Other methods to prepare vascular scaffolds

Phase separation and solvent extraction have been used in fabricating porous scaffolds that improved cell penetration into the scaffold [36,37]. Collagen and elastin hydrogels have also been used for vascular scaffold fabrication. Suspensions of collagen and elastin have been freeze-dried in annular molds and have yielded tubular scaffolds with high porosity, small diameter, micron-scaled pores. While these scaffolds were biocompatible, the resultant mechanical properties were poor [38].

3. Cell sources

Cell-seeded vascular grafts have shown much greater patency compared to unseeded grafts [8,27,39]. ECs are a crucial

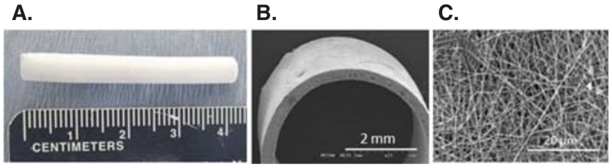

Figure 1. Illustration of tubular scaffold fabricated from poly (epsilon-caprolactone)/collagen using the electrospinning techniques, (**A**) gross appearance; (**B**) cross-section and (**C**) microstructure.

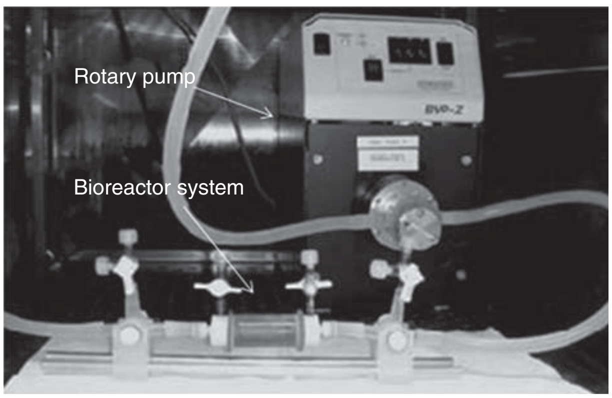

Figure 2. Bioreactor system for tissue-engineered blood vessel is shown. Tubular scaffolds are fitted inside the bioreactor and the flow pattern for conditioning is controlled by rotary pump.

component of the blood vessel that provides an interface between the blood and the blood vessel wall [22]. A confluent and functional monolayer of endothelium is anti-thrombogenic and can prevent the development of pseudointimal hyperplasia and inflammatory response by: i) releasing nitric oxide (NO) and prostacyclin (PGI_2) to regulate platelet adhesion and activation; and ii) producing tissue-type plasminogen activator (t-PA) to degrade fibrin material and dissolve the blood clot [39,40]. ECs can minimize SMC proliferation and prevent intimal hyperplasia by releasing factors such as NO, prostaglandins [41] and heparin-like substances [42]. ECs have limited capacity for regeneration in the elderly and diseased populations [43]. EPCs can be collected from peripheral blood and bone marrow aspirates; moreover, EPCs can be differentiated *in vitro* to mature and functional ECs [22,44]. Kaushal *et al*. seeded sheep EPCs on decellularized porcine arterial segments and implanted the bioengineered blood vessels as a carotid artery interposition graft in sheep [22]. The explanted grafts exhibited contractile activity and NO-mediated vascular relaxation similar to native carotid arteries.

Vascular SMC and FB are essential for the proper function and mechanical strength of a blood vessel. SMC and FB play an important role in maintenance of a stable EC intimal layer [27], while the ECs recruit SMC precursors (pericytes) and induce them to become functional SMCs during vessel maturation [45-47].

Stem cells represent an alternative cell source for TEBV. Examples include bone marrow mononuclear cells (BM-MNC) [48,49], mesenchymal stem cells [50-52] and induced pluripotent stem cells [8]. The advantage of stem cells is their self-renewal and proliferative capabilities. By subjecting stem cells to a differentiation period in culture, all vascular cells needed for a blood vessel can be obtained [48,50,53]. Application of stem cells on TEBV remains in the early stages and is limited by barriers, such as the isolation, enrichment and expansion of fully differentiated stem cell populations and understanding the long-term fate of the stem cells after implantation [54,55].

4. Conditioning approaches

Conditioning of TEBV by applying mechanical stress on the vascular neo-tissue is required for proper blood vessel tissue development and maturation [56-59]. Once implanted, TEBVs face two main types of mechanical forces: i) stretching of the vessel as a result of blood pulsation; ii) shear stress caused by the flow of blood through the vessel. These forces enable the TEBV to achieve the mechanical properties, such as ultimate tensile strength and modulus [60,61], needed to support SMC proliferation, differentiation and ECM remodeling [62]. In addition, shear stress induces ECs to release endothelial NO synthase, prostaglandin 1 [63], thrombomodulin, heparin, and t-PA [64-66] that influences cell morphology and function [63-66] to support blood vessel patency.

TEBV conditioning is a complex process, and recent extensive research has led to the design of *in vitro* flow systems, collectively called bioreactors, which has enhanced TEBV development and function. For example, Yazdani *et al*. manipulated TEBV functions through the delivery of adjustable flow rates and pressure profiles [63,67]. More advanced bioreactor systems allow implementation of further adjustments, such as incremental flow changes in the outer layer compartment [68] and dynamic seeding of cells [69]. **Figure 2** shows our bioreactor system, where the flow pattern is controlled by a rotary pump, while the medium outside of scaffold remains static. This system mimics blood flow *in vivo* and supports the conditioning of the TEBV in a dynamic environment.

Conditioning may not be a necessary step to construct a TEBV, as evidenced by two clinical trials in which TEBV were developed and did not require mechanical preconditioning [8,31]. Mechanical stress applied during the conditioning phase has been demonstrated to support the maturation of TEBV and may reduce the potential risk of failure *in vivo*. Vessel stretching through pulsation improves mechanical properties, such as ultimate tensile strength and modulus [56-61], as well as enhances SMC proliferation and ECM remodeling [62,70,71].

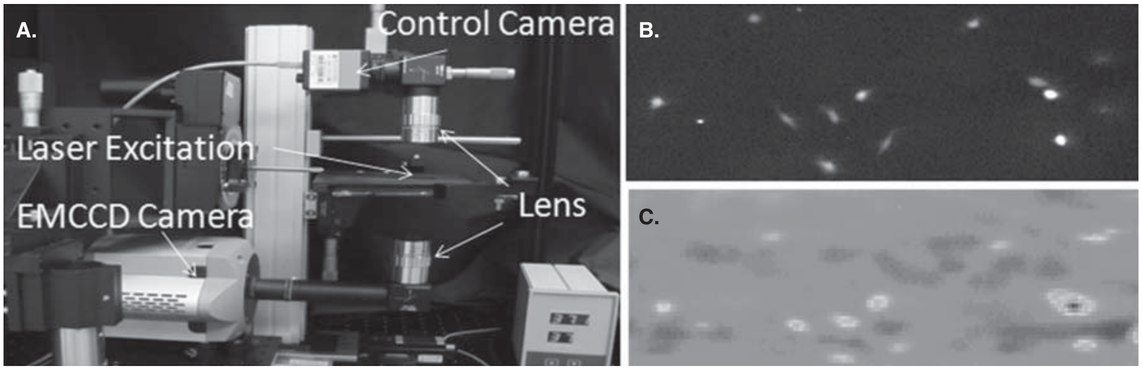

Figure 3. A. A picture of the assembled optical fiber-based imaging system is shown. Fluorescently labeled cells were imaged. **B.** Fluorescently labeled cells, seeded on a PCL/collagen scaffold, are imaged from the top camera (control image). **C.** Reconstructed image of the fluorescently labeled cells through a 600 μm thick PCL/collagen scaffold.
PCL: Poly(epsilon-caprolactone).

5. TEBV assessment

Before TEBV can be used clinically, more testing is needed to evaluate safety and efficacy. Several criteria are used to determine TEBV function: i) mechanical compatibility, including elasticity, suture retention, burst pressure and compliance, to ensure graft endurance of dynamic changes, while avoiding mechanical mismatch that could lead to graft failure [72,73]; ii) cell distribution to achieve a monolayer of EC in the intimal layer, SMC in the medial layer [60] and FB in the adventitial layer, as well as appropriate cellular response to external stimulation [64,74]; iii) functional compatibility, including patency and flow profile to avoid hyperplasia, aneurism or plaque formation after implantation [31,44,75].

The maturation of TEBV *in vivo* is a complex process that requires a set of chemical and physical stimulations to control scaffold degradation and reorganization of ECs and SMCs [76,77]. Monitoring the maturation of TEBV may be achieved through destructive and nondestructive (noninvasive) manners. Methods that require the 'sacrifice' of the samples include histology and molecular analyses, whereas noninvasive methods, such as MRI [78,79], ultrasound, X-ray CT imaging and optical imaging, allow real-time and repetitive measurements of a single sample [78,80]. Ultrasound has a relatively low resolution (sub-millimeter) and is commonly used for macroscopic imaging to determine vessel graft patency and flow patterns or to grossly monitor ECM production [80], whereas X-ray CT scans provide greater resolution but may require longer scanning time to visualize at the cellular level [80]. Since TEBV maturation involves complex interplays between cells and their changing environment, a noninvasive imaging system that provides information at a cellular level would allow for optimization of TEBV preparations. MRI can provide cellular-level imaging with the proper labeling but is limited by depth of penetration and the unknown effect of labeling agents [78]. Optical coherence tomography can provide information about ECM changes in vascular graft but is limited in resolution [81]. Optical imaging techniques, including multiphoton imaging [82], two photon and confocal microscopy, have the potential to monitor individual fluorescently labeled cells [83]; however, these techniques have a limited penetration depth, which limits their application in TEBV monitoring. Our laboratory has recently developed an optical fiber-based fluorescence imaging system (**Figure 3A**) [84,85], which decouples the excitation from the optical fiber and the detection. This approach has the potential to achieve deeper penetration and longer working distance than standard microscopy; further, this technology yields real-time information regarding cell morphology and function and could be applied to both *in vitro* and *in vivo* systems **Figure 3B-C**.

6. Preclinical and clinical studies with TEBV

Although great advances have been made over the past three decades, many TEBV prototypes remain at the preclinical stage in mouse [86], rat [49,50], rabbit [87], ovine [22,47], canine [34,35,48] and porcine [23,88] models. To date, two clinical trials have been initiated for venous and pulmonary circulation and for AV shunt. In the first trial, vascular grafts composed of PGA and ε-caprolactone or L-lactide were seeded with autologous BM-MNCs and resulted in less than one-fifth developing stenosis failure within 7 years of implantation [8]. In the second trial, the TEBVs were fabricated using the cell self-assembling method [31]. The grafts were implanted as a shunt between the brachial artery and the axillary vein in 10 patients with end-stage renal disease, and 50% of patients had a graft functioning for hemodialysis 6 – 20 months after implantation. Comparing the two trials, one may conclude that partial success can be achieved with different types of TEBV. It is possible that based on patient classification and the specific graft application, different types of vascular grafts should be considered and tailored to specific clinical requirements.

7. Conclusion

TEBV provides an alternative to synthetic vascular grafts, which currently yield unsatisfactory results, in the treatment of CVD. The requirements for both cell compatibility and mechanical properties have yielded a variety of scaffold types and cell sources that can be considered as a biologically responsive vascular graft replacement [89]. While each type of scaffold provides advantages, meaningful progress will require integration of multiple fabrication approaches, such as electrospinning of PGA combined with self-assembly of cells and decellularization [90]. Leveraging the potentials of vascular progenitor and stem cells could provide a solution to the repopulation of the scaffold in achieving proper function. Modifications such as mechanical preconditioning and controlled release of cytokines are a valuable approach to further improve TEBV function. Further, better understanding of cellular responses to environmental changes will aid optimization of the fabrication process in achieving long-term functional TEBVs. Recent clinical studies have shown a great promise for the use of TEBV as a treatment option for a variety of vascular disease conditions. Widespread clinical use of TEBVs to treat vascular diseases might gain approval following multicenter safety and efficacy trials that utilize 'off-the-shelf' (short preparation time) products that would reduce manufacturing costs and could be mass-produced.

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Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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