Review Article

Tissue engineered vascular grafts for pediatric cardiac surgery

Toshihiro Shoji[1], Toshiharu Shinoka[1,2,3]

[1]The Tissue Engineering Program and Center for Cardiovascular and Pulmonary Research, [2]Department of Cardiothoracic Surgery, Nationwide Children's Hospital, Columbus, OH, USA; [3]Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, USA

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Correspondence to: Toshiharu Shinoka, MD, PhD. Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, USA. Email: toshiharu.shinoka@nationwidechildrens.org.

Abstract: New technologies and science have contributed to improved surgical outcomes in patients with congenital cardiovascular diseases. However, current materials display shortcomings, such as risk of infection and lack of growth capacity when applied to the pediatric patient population. Tissue engineering has the potential to address these limitations as the ideal tissue engineered vascular graft (TEVG) would be durable, biocompatible, nonthrombogenic, and ultimately remodel into native tissue. The traditional TEVG paradigm consists of a scaffold, cell source, and the integration of the scaffold and cells via seeding. The subsequent remodeling process is driven by cellular adhesion and proliferation, as well as, biochemical and mechanical signaling. Clinical trials have displayed encouraging results, but graft stenosis is observed as a frequent complication. Recent investigations have suggested that a host's immune response plays a vital role in neotissue formation. Current and future studies will focus on modulating host immunity as a means of reducing the incidence of stenosis.

Keywords: Stem cells and vascular tissue engineering; tissue-engineered vascular grafts; bone marrow-derived mononuclear cells; cell seeding; cardiac surgery; Fontan

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Introduction

Congenital heart defects are the leading cause of newborn death and affects nearly one percent of all live births (1). Although new technologies and science have contributed to improved patient outcomes, nearly one quarter of these patients will require major reconstructive surgery (2). Current synthetic grafts are typically made out of non-degradable materials such as polytetrafluoroethylene (PTFE, or Gore-Tex®) and polyethylene terephthalate (PET, or Dacron®) (3). While these conduits can be successful in large diameter (>6 mm) operations, they are often susceptible to infection, thrombosis, stenosis, and ectopic calcification (4). Additionally, somatic overgrowth is often times an issue in the pediatric patient population as these grafts lack the capacity to grow, therefore necessitating multiple operations (5). Other alternatives include using autologous tissues, allografts, or xenografts. Unfortunately, all of these substitutes display insufficiencies to varying degrees. Simply put, there is a vast shortage of viable donor tissues and organs, and currently used surgical materials and devices are limited in their efficacy.

Tissue engineering is a relatively new scientific field that could potentially provide solutions to the problems that plague current conduits. Tissue engineering is defined as an interdisciplinary field that combines the principles of engineering and biomedical sciences to create materials that integrate with a patient's native tissue to restore or improve physiologic function (6). The classic paradigm of tissue engineering has three components: (I) a tissue inducing scaffold material; (II) cells or cellular substitutes

and; (III) a means of integrating the scaffold and cells via seeding (7). The three components are interdependent and indispensable to each other if organized neotissue is to be formed. Because the newly formed neotissue is comprised of autologous cells, these constructions would theoretically be more thromboresistant, less susceptible to infection, and have the capacity for growth. While there are many new paradigms and approaches that continue to form, this review will focus on the traditional role of scaffolding and cells in tissue engineered vascular grafts (TEVGs). Additionally, we present the current status of TEVGs utilized for congenital cardiac surgery and arteriovenous applications.

Scaffolding

The ideal scaffold is biocompatible and resistant to thrombosis, stenosis, ectopic calcification, and infection. Surgically, it is important that it is easily handled, sutured, and readily available "off the shelf". Furthermore, it must have adequate mechanical properties to withstand the hemodynamic changes of its designated system. Initially, scaffolds provide a TEVG's structural integrity, as well as the architecture to which cells adhere and remodel (8). Eventually, neotissue will assume the structural and mechanical responsibilities of a TEVG as the original scaffolding degrades. Hundreds of polymers, natural materials, and blends have been investigated in efforts to find the ideal TEVG scaffold. While it is unlikely that there will be one material that will be able to handle the variety of dynamic cases present in pediatric cardiovascular surgery, a select handful are being investigated rigorously. These materials can often be classified based on their synthetic or biological origin.

Synthetic biodegradable

The most commonly used synthetic biodegradable materials utilized for TEVGs are polyglycolic acid (PGA), polylactic acid (PLA), and Poly(ε-caprolactone) (PCL). The three materials feature a wide range of properties and have been approved by the FDA for implantation as vascular grafts and other medical applications (9). Their respective degradation rates are dependent on their molecular weight, exposed surface area, and crystallinity. The *in vivo* degradation times of these hydrophobic polymers have been reported to be 2–3 weeks, 6–12 months, and greater than 2–3 years respectively (10,11).

Additionally, combining homopolymers and controlling their ratios can lead to materials that exhibit multiple beneficial properties that otherwise would have been unique to each individual polymer (12). As an example, poly(l-lactide-co-ε-caprolactone) (PLCL), would potentially have the strength of PLA and elasticity of PCL (13). These co-polymers could also include natural materials, which often display better biocompatibility than synthetic polymers *in vivo*. However, it is important to note that linear relationships between the ratio of homopolymers and their physiomechanical properties are nonexistent. For example PGLA, a copolymer comprised of PGA and PLA homopolymers, tends to degrade faster than either individual homopolymers would by itself (14).

Standard processing of these synthetic biodegradable scaffolds include freeze drying, gas foaming, phase separation, salt leaching, three-dimensional printing, and electrospinning. Of these methods, there is considerable attention being paid to electrospun nanofibers. Electrospinning techniques can produce thin fibers that range from 3 nm to 5 μm, and mimic fibril structures found in an extracellular matrix (ECM) (15).

There are a multitude of synthetic biodegradable materials, copolymers, and processing methods that have been investigated for TEVGs. With all these variables, investigators must carefully consider scaffold properties with respect to cellular environments. Generally, slow degrading or small-fiber materials initially give a TEVG better mechanical properties, however they also simultaneously tend to inhibit cell infiltration and proliferation. Minimal cellular proliferation will often lead to poor outcomes later on in a graft's development. Therefore, refining a material's initial mechanical properties is often in conflict with improving cell attachment and differentiation. A balance between the two desired TEVG characteristics must be achieved in order for successful neotissue formation to occur.

Biological

ECM, is a tissue's natural scaffolding. Biological TEVG approaches have centered on obtaining or mimicking this vitally important structure. One approach is to decellularize xenogeneic tissue. Decellularization involves removing most of a tissue's cellular and antigenic components through a washing process that includes physical agitation and chemical removal of surfactants and nucleotides. A decellularized tissue would then theoretically leave behind an intact ECM with mechanical properties similar to that of a human. In fact, xenogenic TEVGs constructed with small intestinal submucosa have been successfully implanted in canine and ovine models with positive results (16,17). However,

concerns over the risk of viral and prion transmission remain. Additionally, the decellularization process can adversely affect the graft's biomechanical properties and make consistent reproducibility difficult. Both of these concerns need to be addressed before this method is fully translated.

The other biological approach is to create an ECM-like scaffold using ECM components such as collagen or fibrin. Weinberg and Bell are credited with reporting the first TEVG, which utilized a collagen gel seeded with smooth muscle cells (SMCs) and endothelial cells (ECs) (18). However, this construct lacked sufficient biomechanical properties and was combined with a Dacron mesh in order to evaluate its efficacy *in vivo*. While technologies and methods utilizing collagen gels have improved, they are yet to display adequate physiomechanical scaffold properties by themselves (19). Fibrin is another ECM component that has been investigated for its potential to induce collagen and elastin production, display high seeding efficiencies, and promote even cellular distribution (20). Moreover, fibrin constructs, supplemented with PLA and autologous arterial-derived cells, have produced positive results following successful implantation in an ovine carotid artery model (21). Both biological approaches have shown encouraging results, but still warrant further investigation before clinical translation.

Cells

SMCs and ECs

The tunica intima and media layers of a blood vessel are mainly composed of ECs and SMCs respectively. ECs, SMCs, and fibroblasts are essential to create a stable intima. Additionally, SMCs make up a large portion of an ECM, which ultimately defines a vessel's mechanical properties. As such, early TEVG investigations looked intently at EC and SMC populations. Early TEVG research showed that seeding SMCs onto a biodegradable graft encouraged rapid neotissue formation (22), and demonstrated physiomechanical properties that were comparable to human vessels (23). However, hyper proliferative SMCs must be controlled in order to avoid neointimal hyperplasia.

ECs are responsible for a number of physiologic functions and the synthesis of many important regulatory substances and growth factors (24). Unfortunately, ECs are difficult to obtain and have a limited capacity to regenerate. However, the establishment of a confluent EC monolayer on a TEVG's luminal surface is vital in its resistance to neointimal hyperplasia and thrombosis. In one investigation, implantation of ePTFE grafts seeded with ECs produced significantly higher patency rates when compared with an unseeded ePTFE control (25). Interestingly, another study reported that ECs in the pseudointima of a Dacron conduit function at less than 10% of physiologic levels found in native vasculature (26). Additionally, it has been reported that 95% of ECs that are seeded onto grafts are lost within 24 hours (27). Even though the limited number of ECs on a TEVG's lumen confer beneficial resistance to neointimal hyperplasia, and appear to prevent acute thrombosis, several questions remain. "How can endothelialization be improved in quantity and speed?" Also, "where do seeded cells go?" or "what is their purpose?"

Stem cells and bone marrow mononuclear cells (BM-MNCs)

Stems cells are an exciting area of scientific research. Consequently, embryonic stem cells (ESs), induced pluripotent stem cells (iPSs), and mesenchymal stem cells (MSCs) have been recently investigated for TEVG purposes in varying degrees and models. In a mouse model, ECs have been derived from pluripotent ESs, seeded onto a synthetic biodegradable scaffold, and gone on to form a EC monolayer (28). However, there has been limited ES research done in humans as there are political and ethical concerns with obtaining ESs from the inner cell mass of a developing embryo. Fortunately, iPSs do not have to deal with these concerns as they are derived from autologous fibroblasts. However, iPS research is currently limited with respect to traditional TEVG approaches and their potential to form teratomas. MSCs are derived from the mesenchyme of mesodermal connective tissue. They are an intriguing area of TEVG research. Specifically, MSCs are being investigated for their ability to migrate to inflammatory sites, pluripotency, lack of immunogenicity, and secretion of bioactive molecules that can inhibit inflammation and stimulate cell healing (9,29).

Bone marrow contains an abundant amount of stem cells and the use of BM-MNCs has been successfully translated in human TEVG clinical trials. It was previously believed that the stem cell fraction in harvested BM-MNCs went on to eventually differentiate into the mature vascular cells of a TEVG's neotissue. However, it was discovered that the number of seeded BM-MNCs decreases rapidly in the first few days following implantation, and eventually disappear altogether within 1 week (30). Further experiments have led us to the conclusion that seeded BM-MNCs act in a paracrine manner to recruit host cells to remodel via an

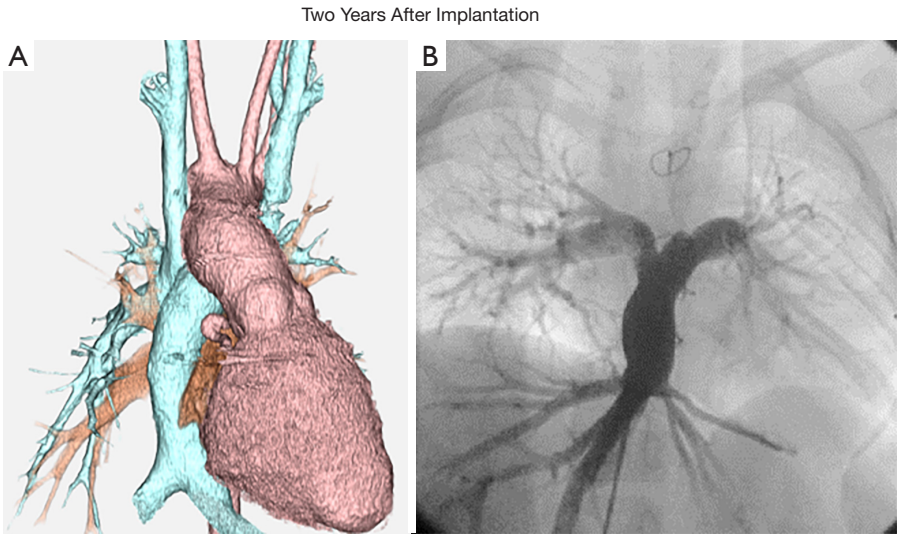


Figure 1 Postoperative images of TEVG. (A) 3D-CT; (B) angiographic image. Adapted with permission from Hibino *et al.* Late-term results of tissue-engineered vascular grafts in humans. *J Thorac Cardiovasc Surg* 2010. TEVG, tissue engineered vascular graft.

inflammation mediated process (31). Investigations have demonstrated that too much inflammation can lead to occluded grafts by thrombosis or stenosis, but on the other hand, an absence of an inflammatory response leads to no neotissue formation. Though BM-MNC seeding has been successfully translated clinically, the precise mechanism of their effect on TEVGs warrants further study.

Studies and clinical trials

Arteriovenous

While going against the conventional tissue engineering paradigm, L'Heureux *et al.* pioneered the tissue engineering by self-assembly approach (TESA). This approach utilized cultured human skin fibroblast sheets wrapped and fused around a mandrel. Subsequently, the resulting construct's lumen was then seeded with autologous ECs (32). Following promising animal studies, these constructs were implanted as arteriovenous grafts in end-stage renal disease (ESRD) patients. Preliminary results from human trials were reported in 2007, and followed by expanded results in 2009. Out of 9 patients, 1 died due to non-graft related complications and 3 patients experienced graft failure due to either dilation, thrombosis, or aneurysm. The remaining 5 patients were able to continue dialysis treatment past 6 months (33). In comparison to conventional ePTFE grafts, the TESA grafts displayed a 4.2 fold decrease in interventions required. However, it should be noted that the TESA approach involves complicated production methods, extensive fabrication times of greater than six months, and faces challenges with respect to costs (34).

In 2011, Niklason *et al.* in a baboon model, reported successful implantation of a TEVG which utilized human cadaveric SMCs seeded onto a PGA scaffold that was subsequently cultured for 8 weeks, and then decellularized of potentially antigenic components (35). These readily available "off the shelf" conduits are produced by Humacyte Inc. Phase II clinical trial results were recently published for their human acellular construct implanted as arteriovenous grafts into 60 ESRD patients. At 18 months, their constructs had a primary patency of 18% and secondary patency of 81% compared to 33% and 55% respectively in ePTFE grafts (36,37). The human acellular graft is currently in a phase III clinical trial and could potentially be a new viable option for dialysis patients in the near future.

Vein and pulmonary

Following successful TEVG implantations in large animal models, in 2001 we proceeded with the first human TEVG clinical trial focused on children with congenital heart disease in Japan (38). Between 2001 and 2004, a cohort of 25 Japanese patients underwent extracardiac total cavopulmonary connection procedures utilizing an autologous BM-MNC seeded TEVG made from PCL/PLLA polymer mixtures on a PGA or PLA backbone (*Figure 1*). Mindful of the challenges

Table 1 Patient status after TEVG implantation, as of August 2016 [all grafts are patent, but seven (28%) were complicated by stenosis]

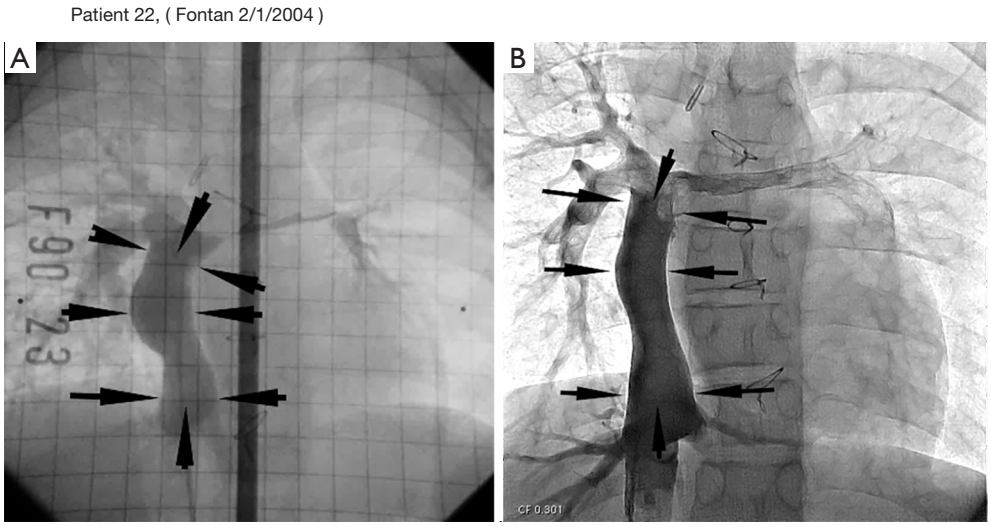
Patient ID #	Age at surgery (years)	Graft type	Graft diameter (mm)	Patient status	Graft patency	Graft-related complications
1	2	PLA	16	Alive	Patent	None
2	1	PLA	20	Alive	Patent	None
3	8	PLA	18	Dead	Patent	Stenosis
4	22	PLA	24	Alive	Patent	None
5	13	PLA	22	Dead	Patent	None
6	4	PLA	20	Alive	Patent	Stenosis
7	14	PLA	24	Dead	Patent	None
8	17	PLA	24	Alive	Patent	None
9	22	PLA	22	Dead	Patent	None
10	4	PLA	12	Dead	Patent	Stenosis
11	2	PLA	16	Dead	Patent	None
12	2	PGA	16	Alive	Patent	Stenosis
13	2	PGA	16	Alive	Patent	Thrombosis, stenosis
14	2	PGA	18	Alive	Patent	None
15	2	PGA	12	Alive	Patent	Stenosis
16	2	PGA	16	Dead	Patent	None
17	24	PGA	18	Alive	Patent	None
18	1	PGA	16	Alive	Patent	Stenosis
19	11	PGA	18	Alive	Patent	None
20	2	PGA	14	Alive	Patent	None
21	3	PGA	16	Alive	Patent	None
22	5	PGA	18	Alive	Patent	None
23	4	PGA	18	Alive	Patent	None
24	13	PGA	16	Alive	Patent	None
25	2	PGA	18	Dead	Patent	None

TEVG, tissue engineered vascular graft; PLA, polylactic acid; PGA, polyglycolic acid.

that are presented in small diameter and high-pressure systems, we implanted TEVGs in a modified Fontan procedure that provided an optimal balance of utility and safety by focusing on a high-flow, low-pressure vascular environment.

Follow-up data currently extends out to 9 years (*Table 1*). At 1-year follow-up, the cohort revealed no major graft-related complications or mortality (39). Long-term follow-up, 4 years post implantation, revealed no significant evidence of graft-related mortality, rupture, aneurysm, or ectopic calcification (40). Additionally, serial imaging demonstrated long-term growth capacity of the grafts (*Figure 2*). However, 6 patients developed an asymptomatic graft narrowing. Of these patients, 1 had a stent inserted at the site of stenosis and four underwent successful balloon angioplasty.

Upon autopsy of a patient who died due to non-graft related issues, gross and histologic examination of the TEVG revealed an appearance similar to that of native vasculature (*Figure 3*). The current iteration of our work



		4/24/2006	10/7/2015
PA side	Diameter	15.36	15.62
	Area	219.35	207.45
Mid	Diameter	18.80	16.41
	Area	312.63	223.59
IVC side	Diameter	17.38	20.77
	Area	239.72	320.16
Graft Length		43.36	60.43

Figure 2 Postoperative growth of a TEVG. A TEVG was implanted in a 5-year-old patient undergoing a Fontan procedure. Angiography 2 years (A) and 11 years (B) after implantation demonstrate growth, with length of the graft increasing from 43.4 to 60.4 cm. Reused with permission from Shinoka T. What is the best materials for extracardiac Fontan operation? *J Thorac Cardiovasc Surg* 2017. TEVG, tissue engineered vascular graft.

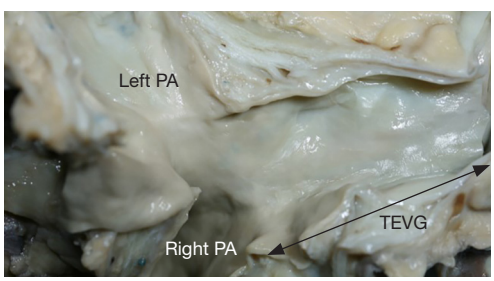


Figure 3 Gross image of a TEVG 13 years after implantation. The appearance is similar to native vein. Reused with permission from Shinoka T. What is the best materials for extracardiac Fontan operation? *J Thorac Cardiovasc Surg* 2017. PA, pulmonary artery; TEVG, tissue engineered vascular graft.

continues in Columbus, Ohio as a phase I clinical trial investigating the use of TEVGs in congenital heart surgery. Stenosis of the TEVG remains a valid concern and continues to be a focus of investigation. However, our current and past pediatric patients continue to do well and display signs of robust TEVG growth and remodeling.

Conclusions

TEVGs have been successfully implanted in arteriovenous and large, low-pressure vascular systems. In the classic tissue engineering model, it is vital that a scaffold be biocompatible and present adequate mechanical properties to maintain a vessel's structural integrity as host cells

adhere to it and remodel. The ideal TEVG is resistant to thrombosis, stenosis, ectopic calcification, and infection, while also being easily handled, cost effective, and readily available "off the shelf". Keeping that in mind, current TEVG studies have focused on synthetic biodegradable and biological material approaches. Both approaches are apparent in the two TEVG clinical trials that are currently ongoing. Although the methodologies utilized in both clinical trials appear promising, the exact mechanisms of tissue formation and TEVG pathologies must be further elucidated. While there are challenges ahead, further investigations to optimize scaffold neotissue formation will broaden the clinical utility of TEVGs. Even though they are relatively new areas of study, the prospects of tissue engineering and TEVGs is exciting and hold immense promise for the future of pediatric surgery.

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Footnote

Conflicts of Interest: Dr. Shinoka has received grant support from Gunze Ltd. Toshihiro Shoji has no conflicts of interest to declare.

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