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Tissue engineered vascular grafts: Origins, development, and current strategies for clinical application

Ehsan Benrashid, Christopher C. McCoy, Linda M. Youngwirth, Jina Kim, Roberto J. Manson, James C. Otto, Jeffrey H. Lawson *

Division of Vascular Surgery, Department of Surgery, Duke University Medical Center, Durham, NC, USA

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ABSTRACT

Since the development of a dependable and durable synthetic non-autogenous vascular conduit in the mid-twentieth century, the field of vascular surgery has experienced tremendous growth. Concomitant with this growth, development in the field of bioengineering and the development of different tissue engineering techniques have expanded the armamentarium of the surgeon for treating a variety of complex cardiovascular diseases. The recent development of completely tissue engineered vascular conduits that can be implanted for clinical application is a particularly exciting development in this field. With the rapid advances in the field of tissue engineering, the great hope of the surgeon remains that this conduit will function like a true blood vessel with an intact endothelial layer, with the ability to respond to endogenous vasoactive compounds. Eventually, these engineered tissues may have the potential to supplant older organic but not truly biologic technologies, which are used currently.

1. Introduction

Cardiovascular disease remains the major cause of mortality among adults in the United States [1]. General strategies in the surgical treatment of cardiovascular disease include bypassing of obstructed or aneurysmal vascular segments. Specific examples include coronary artery bypass grafting (CABG), or major arterial reconstruction procedures (i.e. aortic reconstruction or peripheral bypass) with autogenous, synthetic, or cryopreserved materials.

With the preponderance of longstanding diabetes and hypertension, as well as with an ever-increasing aging population, end stage renal disease (ESRD) has also come to the attention of the healthcare community given its associated disability and associated high healthcare expenditures [2]. With the need for renal replacement therapy (RRT) in these patients and the overwhelming demand for a limited number of kidneys available for transplantation, the most frequently employed strategy of choice for RRT in these patients is hemodialysis (HD). In most instances of long-term maintenance HD, either an arteriovenous fistula (AVF) or graft (AVG) is required for adequate access to and filtration of toxins, fluids, and electrolytes, which is normally performed by the kidney in non-diseased individuals.

The commonality between atherosclerotic occlusive disease and HD access procedures, however, remains that a perfect graft material has not yet become available when the preferred autogenous vascular conduit is not permissible or has been expended from prior use. Additionally, complications of the more "preferable" graft materials such as thrombosis or infection can lead to the need for re-intervention or graft explantation, resulting in the clinician having to explore other options for conduit. Traditionally, synthetic compounds have been used, but themselves present the particularly troublesome complication of more frequent infections and thrombosis owing to their imperfect use as a small diameter conduit (<6 mm).

As the capability of modern science and medicine continues to expand and prolong the progression of the disease process, additional complications are encountered with vascular reconstructive and dialysis access procedures over time. There are limitations to the types of materials available given an individual's disease process. Emerging technologies in order to provide individuals who suffer from these afflictions have been in development for the past 20 years thanks to the advent of the field of tissue engineering (TE). Here we review the past, present, and future of bio- and tissue-engineered vascular grafts (TEVGs) from their foundation, construction, and clinical application, with a special focus on those grafts that have reached clinical trials.

* Corresponding author at: DUMC 2622, Durham, NC 27710, USA.
E-mail addresses: ehsan.benrashid@dm.duke.edu (E. Benrashid), christopher.mccoy@dm.duke.edu (C.C. McCoy), linda.youngwirth@dm.duke.edu (L.M. Youngwirth), jina.kim1@dm.duke.edu (J. Kim), roberto.manson@dm.duke.edu (R.J. Manson), jim.otto@dm.duke.edu (J.C. Otto), jeffrey.lawson@dm.duke.edu (J.H. Lawson).

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2. Review

2.1. Past

The field of vascular surgery has experienced several seminal events that have dramatically altered its trajectory (Fig. 1). First was the introduction of the triangulated vascular anastomosis and subsequent development of the field of transplantation by Alexis Carrel [3]. Later, Kunlin first reported the use of autologous saphenous vein for lower extremity bypass procedures in the early 1950s [4]. The field of nephrology and vascular access was established with the advent of the Scribner shunt [5] and subsequent development of the first autogenous vascular access procedure, the Brescia–Cimino AVF [6], in the 1960s. It has now been over half a century since DeBakey and colleagues changed the field of aortic surgery after reporting their use of a purely synthetic material, Dacron, as conduit for aortic replacement and repair [7].

In the interval, additional materials such as polytetrafluoroethylene (PTFE) and expanded PTFE (ePTFE) have been integrated into clinical practice, with their initial experience for lower extremity revascularization reported in the late 1970s [8]. Since these initial reports, the application and use of these materials has expanded to other prevalent conditions under the purview of the general and vascular surgeon, such as conduit for HD access procedures [9–11].

Although it is commonly accepted that, if available, the conduit of choice for infrainguinal arterial reconstruction should be autologous vein [12], due to varying patient factors (i.e. prior use of saphenous vein for coronary bypass procedures) and the intermittent need for reoperation due to occlusion of the newly implanted graft, the decision to utilize non-autogenous compounds is sometimes imposed on the surgeon. In particular, issues remain utilizing small diameter synthetic materials as conduit in the aforementioned procedures, with a particular propensity for in-graft thrombosis in lower extremity bypass.

Given the limitations in available and suitable autologous vascular graft and the higher complication rate with synthetic material, the search for a truly ideal conduit continues. This has led to the use and development of many other forms of bio- and tissue-engineered vascular grafts, including the Artegraft (North Brunswick, NJ), Procol (Hancock Jaffe Laboratories Inc., Irvine, CA), and Cryovein (CryoLife, Kennesaw, GA) [13–15]. These are constructed from bovine carotid artery, bovine mesenteric, and cryopreserved human saphenous vein, respectively. Each has demonstrated varying rates of patency and associated complications over time, and has contributed to the field of vascular engineering in its present state. However, as we aim to limit our discussion of TEVG to current principles, techniques, and limitations of their use in regenerative medicine, further discussion of the aforementioned commercially available conduits is beyond the scope of this review.

2.2. TEVG introduction

Utilizing the principles and methods gained from techniques to create synthetic graft materials, over the past 30 years, teams of bioengineers, basic scientists, and clinicians have forged tremendous inroads toward a completely bioengineered vascular conduit. The characteristics that make the bioengineered approach to vascular conduits ideal include the following potential attributes [16–18]:

- low incidence of infectious complications
- lack of generation of the immune response
- long term patency that rivals autogenous tissue as conduit
- withstands degradation
- maintains adequate suture strength and is suturable
- retains ability to remodel as a functional tissue
- maintenance of the response to physiologic stimuli
- antithrombotic blood-contacting surface
- porosity that precludes leakage of contents but allows for cellular migration/seeding
- durability and mechanical strength
- cost effectiveness
- ready availability for use

The essential principle driving much of the field of tissue engineering and creation of TEVGs is that of biomimicry. Biomimicry is a broad scientific strategy, and in the context of TEVG design and clinical implementation, relates to not only creation of a vascular tube with properties inherent to blood vessels themselves, but one that also replicates the process of endogenous ECM assembly after implantation while avoiding the body's innate response to foreign material, hence allowing incorporation of the graft into the vascular system [19]. One area of particular advantage is in the ability of the TEVG to function as an "implantable device" in which the prosthetic portion – oftentimes the scaffold upon which the graft is created – is degraded over time and progressively replaced with autogenous tissue, forming a functional vessel [20]. The early challenge in the production of TEVG was determining how to best take advantage of the body's endogenous response to the synthetic scaffold utilized for TEVG creation. Eventually, the science behind TEVG took advantage of both the inherent remodeling and response to foreign body processes to create scaffolds that were biodegradable over varying timeframes.

2.3. TEVG methods

With these concepts and challenges in mind, the first group to create a TEVG was that of Weinberg and Bell in 1986, who reported creating an *in vitro* multilayered collagen tube from animal collagen and bovine endothelial and smooth muscle cells (SMC) that demonstrated both structural and functional characteristics of an artery, with a robust endothelial layer lining the inner lumen of the vessel [21]. A similar approach to creation of vascular tubes utilizing SMCs, fibroblasts, and endothelial cells was reported by L'Heureux and colleagues in 1993 [22]. A chief difference between the two was that the latter group's technique involved complete omission of any synthetic material from creation of the conduit, and was constructed exclusively from human and human-derived constituents cultured around a glass mandrel, and hence served as the first of its type. In contrast, the collagen gel tube formed by Weinberg and Bell utilized Dacron to structurally support the graft, and thus incorporated synthetic material

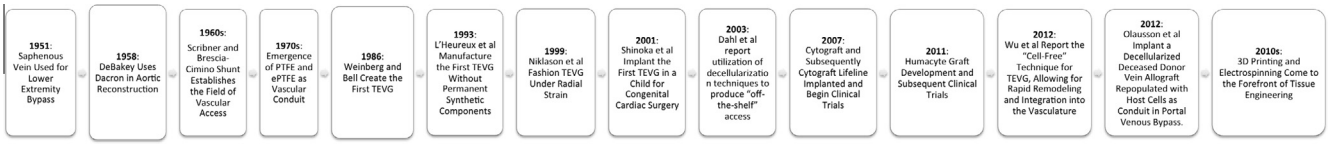

Fig. 1. Timeframe of tissue engineered vascular graft (TEVG) creation. PTFE = polytetrafluoroethylene; ePTFE = expanded polytetrafluoroethylene; 3D = three-dimensional.