

Technology Insight: the evolution of tissue-engineered vascular grafts—from research to clinical practice

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SUMMARY

There is a considerable clinical need for alternatives to the autologous vein and artery tissues used for vascular reconstructive surgeries such as CABG, lower limb bypass, arteriovenous shunts and repair of congenital defects to the pulmonary outflow tract. So far, synthetic materials have not matched the efficacy of native tissues, particularly in small diameter applications. The development of cardiovascular tissue engineering introduced the possibility of a living, biological graft that might mimic the functional properties of native vessels. While academic research in the field of tissue engineering in general has been active, as yet there has been no clear example of clinical and commercial success. The recent transition of cell-based therapies from experimental to clinical use has, however, reinvigorated the field of cardiovascular tissue engineering. Here, we discuss the most promising approaches specific to tissue-engineered blood vessels and briefly introduce our recent clinical results. The unique regulatory, reimbursement and production challenges facing personalized medicine are also discussed.

KEYWORDS cardiovascular tissue engineering, CABG surgery, tissue-engineered blood vessel, tissue-engineered vascular graft, tissue engineering

REVIEW CRITERIA

Papers cited were selected from the bibliographies of leading research groups in the fields; we did not perform an exhaustive database search. All cited papers are English-language, full-text papers.

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Received 4 October 2006 Accepted 23 March 2007

www.nature.com/clinicalpractice
doi:10.1038/npcardio0930

INTRODUCTION

Despite over 50 years of research examining synthetic materials, native vein and artery segments remain the gold standard of grafts for revascularization procedures. Unfortunately, suitable vein or artery tissue is not always available for peripheral or coronary revascularization, because of previous vessel harvesting or disease progression. A small diameter conduit with patency equivalent to that of native tissue has been hailed as the holy grail of vascular surgery since the advent of widespread bypass surgery in the 1960s.^{1,2} While synthetic materials such as expanded polytetrafluoroethylene (ePTFE) and Dacron® (Invista, Wilmington, DE) have been used with great success for bypass conduits greater than 6 mm in diameter, synthetics have performed poorly in smaller diameter indications.^{3–5} For vascular access in hemodialysis patients, ePTFE arteriovenous grafts are associated with complication rates that are close to three times higher than rates with vein fistulae.⁶ Even worse performance in coronary or below-knee bypasses than in hemodialysis access precludes synthetics from widespread clinical use.

Historically, synthetic grafts have been associated with three primary failure modes: acute thrombosis caused by the lack of a functional endothelium; restenosis caused by chronic inflammatory responses and compliance mismatch; and susceptibility to infection.^{3,7–11} Work by Zilla and associates overcame the problems associated with acute thrombosis by lining ePTFE grafts with a functional autologous endothelium,¹² however, this approach still requires the presence of a permanent synthetic scaffold. Over the past 20 years, advances in cell biology and tissue engineering have introduced the concept of a cell-based graft that addresses these failure modes. Conceptually, tissue-engineered blood vessels (TEBVs) would contain a viable endothelium and have mechanical properties that mimic those of native tissues, but lack synthetic or foreign

materials that initiate chronic inflammatory responses. In contrast to native vessels, TEVVs would provide diameter-matched conduits free from bifurcations, existing disease and harvest-related damage.¹³ This approach would also eliminate the considerable morbidity associated with vein harvest.^{14,15} In this Technology Insight we briefly review the evolution of tissue-engineered vascular grafts from the research environment toward clinical practice. Now that two approaches have been used clinically, we also address the key challenges we face in the transition from innovation to widespread clinical use.

HISTORY OF TISSUE-ENGINEERED VESSELS

Weinberg and Bell sparked the idea of living blood vessels produced *in vitro* with their seminal 1986 manuscript describing cell-seeded collagen gel tubes.¹⁶ Since then, the field of cardiovascular tissue engineering has blossomed; reviewed in excellent detail by Tranquillo's and Niklason's study groups.^{17,18} While Bell can be credited with developing the first tissue-engineered graft constructed *in vitro*, the approach could not realize his vision of a completely biological autologous approach. Ultimately, he was forced to use a variety of synthetic sleeves to support his cell-seeded collagen gel constructs. This concession, of course, reintroduced the problems associated with foreign materials and compliance mismatch.

In the ensuing 20 years, other groups have used similar approaches of cell-seeded collagen or fibrin gels, but no group has been able to produce an autologous arterial graft with clinically useful burst pressures.^{19–24} Man-made reconstituted protein-based scaffolds lack tensile strength, and are susceptible to rapid degradation by the immune system. More recently, realizing the need for synthetic supports but recognizing the deleterious effects of permanent synthetic scaffolds, cells have been seeded into partially resorbable polymers.^{25–27} This approach demonstrated impressive mechanical properties when animal cells were used in the construct, but lacked appropriate mechanical strength in human models.²⁸ Nonetheless, in the first clinical use of a vascular construct produced *in vitro*, Shin'oka *et al.* were able to reconstruct the low-pressure pulmonary outflow tract in pediatric patients with cyanotic congenital defects.^{29,30} In this approach,

autologous bone marrow cells were seeded into tubes of a copolymer of L-lactide and ε-caprolactone reinforced with a polyglycolic acid sleeve. Twenty-three tubes, ranging from 12 to 24 mm in diameter and approximately 6 cm in length, were grafted as modified Blalock–Tausig shunts or other pulmonary arterial repairs. While the grafts were not suitable for high-pressure arterial implantation (i.e. the nonpulmonary circulation), this landmark paper was an important demonstration of the feasibility of the tissue-engineered model of autologous personalized medicine.

Other investigators have completely eliminated the presence of exogenous materials in their grafts. Campbell and co-workers use a method reminiscent of the Sparks mandril approach,^{31,32} whereby a mandril of foreign material is surgically implanted in the peritoneal cavity of the recipient to induce the growth of tubular tissues.^{33,34} This technique has demonstrated high mechanical strength and good mid-term patency in animal models, but it remains to be seen whether this approach can be repeated in humans. This method also presents unique challenges in terms of manufacturing reproducibility and safety.

TRANSITION TO CLINICAL PRACTICE

During the evolution of the various tissue-engineered approaches, there has been a tendency to report imminent clinical applicability before essential milestones have been reached. At a minimum, we believe there are four key criteria that need to be met in order to justify transition to clinical use: firstly, demonstration of burst strength similar to that of saphenous veins (i.e. >1,700 mmHg), using human cells; secondly, demonstration of adequate fatigue strength using human cells (i.e. stable diameter after 30 days of pulsatile loading *in vitro* or as a xenogeneic implant); thirdly, demonstration of a stable, nonthrombogenic human endothelium; and finally, in the case of autologous approaches, demonstration of manufacturing feasibility and consistency, using cells isolated from an age-matched and risk-matched human population.

We have developed a completely autologous approach called sheet-based tissue engineering.³⁵ In this technique, dermal fibroblasts are obtained from a small skin biopsy and grown in conditions that promote the production of extracellular matrix proteins.

After approximately 6 weeks in culture, sheets of dermal fibroblasts are detached from the culture substrate and rolled around a temporary support mandril. After a maturation period of approximately 10 weeks, the individual plies fuse into a homogenous tissue. This process can be repeated to produce multi-layer vessels with burst pressures in excess of 3,000 mmHg. A few days before implantation, the vessel is seeded with autologous endothelial cells harvested from either a peripheral vein or endothelial precursors taken from circulating blood. While this approach is time consuming—total production time is approximately 24 weeks—it is the only approach to meet all four criteria. Clinical trials have been initiated to examine the use of these grafts as arteriovenous shunts, as well as coronary and lower limb bypass grafts.

Our initial clinical trial is focused on the safety of the arteriovenous shunt model (Figure 1). Given the large number of patients that lack suitable vein for hemodialysis and the deplorable efficacy of synthetic vascular grafts, from a clinical perspective the arteriovenous shunt seemed an appropriate first model in which to trial grafts created using sheet-based tissue engineering. Moreover, graft failure in this model is unlikely to be life or limb-threatening. Hemodialysis access is, however, the most challenging model with respect to the mechanical environment. In addition to the obvious challenges associated with repeated puncture, the high flow rates encountered (typically greater than 800 ml/min) generate considerable hemodynamic loads.

In the initial safety study, we implanted the grafts in three patients. In some patients, follow-up is currently reaching 12 months. All grafts demonstrated excellent surgical handling characteristics. In terms of tissue handling, the grafts were similar to native vein segments, allowing anastomoses to be made using standard techniques with 7–0 prolene. The kink radius allowed the use of looping grafts up to 30 cm long between the humeral artery and the axillary vein. Hemostasis times after cross clamp removal were favorable relative to ePTFE grafts. The grafts have met all continuation criteria for the initial safety phase and have functioned well for hemodialysis access. Furthermore, hemostasis times after dialysis access were, as expected, lower for the TEBV than for ePTFE grafts. The vessels were easy

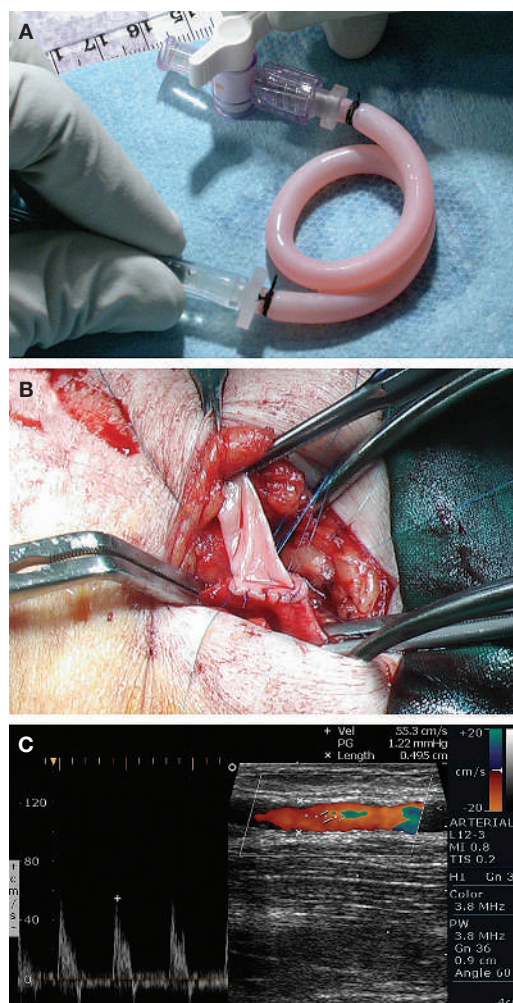


Figure 1 The first clinical use of a tissue-engineered blood vessel for high pressure arterial revascularization. **(A)** A completely autologous graft was implanted as an arteriovenous shunt between the humeral artery and the axillary vein. **(B)** The tissue-engineered blood vessel resembled native tissue and had normal surgical handling and suturing properties. The vessel synthesized met safety criteria and showed excellent flow under routine Doppler surveillance. **(C)** At 6 months, the shunt maintains high flow without signs of restenosis or aneurysm.

to puncture, without the resistance encountered with ePTFE that can result in back-wall damage. While the results from this initial safety study are clearly preliminary, the comparisons with ePTFE are encouraging. Efforts by both Medicare (the ‘Fistula First’ initiative) and the National Kidney Foundation (the Dialysis Outcomes Quality Initiative) to reduce the use of ePTFE grafts for arteriovenous

fistula might finally be realized with the development of this tool.

CHALLENGES TO WIDESPREAD CLINICAL USE

Tissue engineering is a burgeoning academic field, however, the clinical and therapeutic promise of tissue and organ replacement has remained largely unrealized. With the possible exceptions of skin, cornea, and bone marrow amplifications, demonstrating the clinical efficacy of cell-based therapies has been a struggle. There are no examples of commercial successes to offset several high-profile financial failures.³⁶ Now that some cell-based cardiovascular therapies have made the transition to human use (including TEBVs and myocardial regeneration) we face the challenge of developing a successful commercialization strategy to integrate these therapies into routine clinical practice. In comparison with other fields of tissue engineering that have failed commercially, cardiovascular tissue engineering has two key advantages in that it is both a life-saving or limb-saving treatment and targets a very large patient population. These advantages suggest high reimbursement levels and a sufficient market size to drive engineering innovations, which in turn will offset the high production costs. Despite these advantages, cardiovascular tissue engineering faces considerable clinical, regulatory and reimbursement hurdles.

Clinical challenges

Irrespective of the production strategy, few would contest that autologous endothelium will be required for TEBVs to match the efficacy of saphenous veins. This constraint indicates that even the simplest cell-based approaches will require weeks or months of preparation to source and expand autologous cell lines—adding to the challenges that will be faced in terms of patient management and production costs. Indeed, the long lead time associated with the production of an autologous TEBV is commonly invoked as a major limitation to widespread clinical use. While this criticism is quite valid for emergency CABG surgery procedures or critically ischemic limbs, in reality, most coronary and distal vascular bypass procedures can be predicted and delayed over extended periods, allowing TEBV production. In fact, the Trial of Invasive versus Medical therapy in Elderly patients with chronic symptomatic

coronary-artery disease (TIME) and the Medicine, Angioplasty or Surgery Study (MASS) showed no differences in myocardial infarction rates or mortality at 6 months between patients receiving optimum medical treatment and those undergoing surgical intervention.^{37–39} The potential benefits of using a TEBV could outweigh any additional risks associated with delayed surgery, especially for older patients with chronic stable angina. Furthermore, lower limb ischemia and patients in need of a hemodialysis graft often follow a well-established process of disease progression. For these patients, tissue biopsies can be performed and vessels produced in advance of clinical urgency.

Not surprisingly, many groups have attempted to resolve the lead time issue by focusing on acellular approaches that prioritize production simplicity and availability. While these off-the-shelf approaches are enticing at first glance, they have failed to improve on results with ePTFE grafts. By contrast, cell-based therapies are costly and complex but hold the promise of a considerable improvement in efficacy. Indeed, complex or expensive technologies that actually work, such as Holter electrocardiography and MRI, have set a clinical precedent and shown that such technologies can achieve widespread clinical use, as engineering innovations and economies of scale lessen cost and increase availability. Concentrating on production simplicity above clinical efficacy can, therefore, be misguided.

Regulatory challenges

Before 1997, the FDA had no formal guidance for the use of manipulated autologous cells. The European Union is still working on a harmonized code for advanced medicinal therapeutics. As a result, investigators working with cell-based therapies in both the US and Europe are faced with ill-suited regulatory requirements that were initially designed for mass production of pharmaceuticals. These regulations do not account for the fundamentally different lot sizes and subsequent risk management decisions, with respect to quality control and lot release, which are typical of autologous cell-based therapies. In the context of large-scale, cell-based bioprocessing (e.g. recombinant protein production), which arguably has the most relevant regulatory and clinical history to autologous cell use, cells are used as a tool that must be extensively and regularly

validated. As this cellular tool is used repeatedly to produce large quantities of the final product, the costs associated with quality control testing are absorbed.

In the case of autologous cell-based therapies, however, each patient is a separate lot. When the same scheme of validation testing is applied to a series of vessels for each individual, the magnitude of the quality control testing and the subsequent costs become a crippling burden to the production process. Consequently, the countries that have a more realistic regulatory pathway in place, with a risk–benefit analysis tailored to small autologous cell lots, will take the lead in clinical applications of cell-based therapeutics. The quality control strategy applied to organ transplantation could prove to be a more appropriate model to define a balanced risk–benefit analysis for cell-based therapies than the model for mass production of pharmaceuticals, which is currently used. Continued adherence to the mass bioprocessing regulatory pathway could prevent widespread clinical use of all but the simplest of tissue-engineered therapies.

Reimbursement challenges

The high cost associated with advanced therapeutics coupled with the increased sensitivity to spiraling health-care costs makes sound reimbursement models critical. In addition to the safety and efficacy data required by the FDA, Medicare reimbursement demands demonstration of cost-effectiveness. Other tissue-engineered products such as Carticel® (Genzyme Corporation, Cambridge, MA), Apligraf® (Novartis AG, Basle, Switzerland) and Dermagraft® (Advanced BioHealing Inc., New York, NY) have obtained reasonable reimbursement levels (approximately US\$17,600, \$1,200 per 44 cm², and \$535 per 37.5 cm², respectively). Our reimbursement models rely on the assumption that TEBVs will have an efficacy approaching that of native veins. Given the presence of a functional endothelium, the lack of synthetic materials and the appropriate mechanical properties, this assumption seems plausible.

In the arteriovenous-shunt model, the 2-fold to 3-fold increase in intervention rate associated with prosthetic grafts relative to native vein fistula, and the average intervention cost of approximately \$8,000 per procedure, will make TEBVs cost-effective within 2 to 3 years, with

reimbursement levels of \$20,000–30,000 for each device.^{6,40} Similarly, lower limb revascularization studies have shown that intervention rates and direct costs are considerably lower for vein grafts than for ePTFE grafts. When indirect costs associated with the long-term care of immobile amputation patients are factored in, there is a clear economic and social justification for using a TEBV when native vein is not available. For CABG surgery applications, the obvious first use is in ‘no option’ patients, an indication with simplified reimbursement analyses. Even with the increased number of revisions and the shift towards older and sicker patients, this group probably represents less than 5% of the total population undergoing CABG surgery. If the TEBVs perform well in this initial coronary application, the indications will be expanded for TEBVs to compete directly with saphenous vein harvest. Elimination of the complications associated with vein harvest would yield a cost savings of more than \$5,000 per patient;⁴¹ however, this saving alone would not justify the cost of the TEBV. The reimbursement model would depend upon improvements in quality of life and potential increases in efficacy compared with use of native vein. Saphenous vein grafts have a relatively high incidence of early thrombosis (approximately 15% in the first 12 months after implantation), which is probably associated with harvest-related damage to the endothelium.^{42,43} While short-term patency rates might be improved through the use of TEBVs, it is likely that data 4–6 years after initial implantation will be required to prove long-term cost-effectiveness.

CONCLUSIONS

To date, no synthetic-based approach has been able to match the efficacy of native veins for vascular reconstruction. While approaches to creating TEBVs have clearly evolved over the past 20 years, only two techniques have made the transition to clinical use thus far. Early clinical trial results for both techniques are quite encouraging with both types of TEBVs showing clear advantages relative to ePTFE grafts. Whether Shin’oka and colleagues’ clinical work or our own can overcome the unique combination of scientific, clinical, regulatory and reimbursement challenges to provide better clinical solution than native vessels remains to be seen.

KEY POINTS

- Tissue-engineered blood vessel technologies should target four criteria to maximize the likelihood of clinical success: appropriate burst pressure (>1,700 mmHg); appropriate fatigue resistance (30 days of *in vitro* cycling under physiological loading without marked dilation); an autologous endothelium; and reproducible demonstration of these characteristics using human cells
- The recent transition to clinical use by two tissue-engineering groups suggests that cell-based therapeutics are clinically viable approaches for patients lacking suitable autologous vein/artery for vascular reconstruction
- To accommodate the increased time and complexity associated with these cell-based solutions, clinicians will have to shift some clinical management decisions from an ‘off-the-shelf’ reactive strategy toward a more proactive and preventative treatment plan
- Reimbursement models suggest that the efficacy of these costly therapies will have to approach that of native vein to show a cost-benefit relative to other synthetic grafts
- Regulatory challenges could hinder large-scale commercialization of autologous cell-based therapies unless lot release and quality criteria are softened from the current regulations, which are more relevant to the larger batch sizes associated with aseptic drug production or cell-based bioprocessing

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Competing interests

N L'Heureux, N Dusserre and T McAllister have declared associations with Cytograft Tissue Engineering. See the article online for full details of the relationship. The other authors declared they have no competing interests.