Are there Technical/Clinical Tools to Improve the Present Vascular Access Outcome in Haemodialysis Patients?

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When native vein and artery are not available due to previous harvest, anatomical limitations, or disease progression, synthetic materials such as Dacron or ePTFE have been used with varying degrees of success. Synthetic graft materials are used with great success in larger diameter applications such as aortic or iliac reconstruction, but they have demonstrated unacceptably poor performance in most small diameter applications (below 6 mm inside diameter). The poor efficacy of small diameter synthetics is linked to short-term thrombosis, increased rate of infection, chronic inflammatory responses to the foreign materials, and compliance mismatch between the native tissue and the prosthetic material. These problems are well illustrated in A-V access grafts, where the intervention rates for synthetic grafts are three-fold higher than for native vein fistulas [1]. Attempts to improve the durability of prosthetic grafts began in the 1970s with the concept of seeding the luminal surface of the graft, considered to be thrombogenic, with endothelial cells [2]. The major technical feat overcome by extensive work in the 1980s and 1990s centered on preventing the cells from being dislodged by luminal blood flow on implantation of the graft. Strategies to overcome this problem include precoating the graft with various adhesives, pressure sodding, modification of the graft surface with RGD moieties, prolonged culture of the graft, and flow conditioning. The field of Cardiovascular Tissue Engineering has attempted to produce a clinically viable synthetic conduit by using a variety of in vitro approaches that typically combine living cells seeded into reconstituted scaffolds to create living tissue engineered blood vessels (TEBVs) [3].

Scaffold Choice

As noted, prosthetic material has served as the traditional scaffold for vascular graft creation. Its availability and biocompatibility make it attractive for use; however, in spite of seeding, it remains prone to infection and anastomotic intimal hyperplasia owing to compliance mismatch [4]. Biodegradable scaffolds, such as poly glycolic acid, may yield a more compliant construct. In theory, the extracellular matrix is linked to short-term thrombosis, increased rate of infection, chronic inflammatory responses to the foreign materials, and compliance mismatch between the native tissue and the prosthetic material. These problems are well illustrated in A-V access grafts, where the intervention rates for synthetic grafts are three-fold higher than for native vein fistulas [1]. Attempts to improve the durability of prosthetic grafts began in the 1970s with the concept of seeding the luminal surface of the graft, considered to be thrombogenic, with endothelial cells [2]. The major technical feat overcome by extensive work in the 1980s and 1990s centered on preventing the cells from being dislodged by luminal blood flow on implantation of the graft. Strategies to overcome this problem include precoating the graft with various adhesives, pressure sodding, modification of the graft surface with RGD moieties, prolonged culture of the graft, and flow conditioning. The field of Cardiovascular Tissue Engineering has attempted to produce a clinically viable synthetic conduit by using a variety of in vitro approaches that typically combine living cells seeded into reconstituted scaffolds to create living tissue engineered blood vessels (TEBVs) [3].

Cell Choice

The traditional cell used for luminal seeding is the differentiated endothelial cell obtained from jugular or saphenous vein segments. This strategy is disadvantaged by the need for ex vivo cell culture to obtain the number of cells necessary to seed the graft lumen. Harvest of micro vessel endothelial cells from liposuctioned adipose tissue appeared promising in terms of immediate cell number [10]; however, subsequent evaluation has suggested that contaminating cells in the isolates leads to the development of hyperplasia within the seeded grafts [7]. Endothelial progenitor cells isolated from peripheral blood hold promise for vascular tissue engineering. These cells originate from bone marrow and are a source of autologous cells for vascular repair. Their presence in peripheral blood varies with patient characteristics and may diminish with aging; therefore, use of this cell for vascular tissue engineering would also likely require ex vivo expansion [11]. Many researchers are currently investigating adipose tissue as a source of stem cells for use in graft creation. Adipose derived stem cells (ASCs) can be isolated in abundance from liposuctioned abdominal wall fat, making them attractive for seeding. In a study of patients undergoing peripheral vascular surgical procedures, an average of 210,000 ASCs/g of adipose tissue was obtained [12]. The ASC is multi potent, having been shown to differentiate into bone, cartilage, adipose, and neuron cell lines. Studies from Di Muzio, et al. [13] have begun to define its ability to differentiate into cells with an endothelial phenotype. Endothelial characteristics in these experiments were defined as realignment in the direction of luminal flow, cord formation in response to extracellular matrix (Matrigel), and the expression of endothelial cell message and protein (endothelial nitric oxide synthase, von Willebrand factor, CD31). ASCs have been seeded onto the luminal surface of decellularized vein within a bioreactor that maintains the necessary culture conditions for cell survival. Under gravitational force, cell attachment

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and spreading typically occur within 2 hours. Seeding with a minimum of 2 x 10^5 cells/cm², ASCs form a confluent monolayer on the luminal surface. Preliminary study revealed a thin layer of fibrin on the graft surface, suggesting that undifferentiated ASCs may not immediately form a non-thrombogenic layer. These early results indicate that differentiation of these cells prior to implantation may be necessary for ultimate clinical success.

**Clinical applications**

McAllister, et al. [14] have recently reported the successful implantation of a completely biologic tissue engineered graft for vascular access in 10 patients with end stage renal disease receiving haemodialysis. Patency rates at 1 and 6 months were 78 and 60% respectively. This study is the first encouraging result of the use of a tissue engineered vascular graft in a clinical setting. McAllister and colleagues used the cell self assembly technique, as opposed to the cell-seeded gels or cell scaffold technology, for the construction of their tissue engineered vessel. As previously described, these vessels are constructed by taking advantage of the natural ability of cells to produce their own extracellular matrix (ECM). Briefly, human fibroblasts, extracted from patient's skin biopsies, were cultured to form 15 sheets of living fibroblasts with associated ECM. These sheets were then rolled over a stainless steel mandrel to allow them to fuse. After 10 weeks of culture the vessels were dried and the lumen seeded with autologous endothelial cells. Total time production for the Graft ranged from 6 and 9 months. 7 days prior to implantation the lumen of the vessel was seeded with autologous endothelial cells and pre conditioned to flow and pressure. Grafts with an average length of 23.2 cm (range 14-30 cm) were implanted into 9 patients (one was excluded prior to surgery due to gastrointestinal haemorrhage) and were assessed for both mechanical stability and effectiveness during a safety phase (0-3 months long) and after haemodialysis was started. While the patency rates were good, it was possible to use the graft for haemodialysis for longer than 12 months in only 3 patients.

The advantages of this approach are that the tissues are completely autologous so that the grafts are non immunogenic and non thrombotic. Moreover, since the graft develops in its own matrix and does not need an external scaffold, there are not concerns about the use of xenogenic scaffolds, especially cross infection. The major limitation of this approach is the long time of culture required to develop the graft and this will limit its clinical applicability especially in emergency. Other concerns arise from the very high costs of production, the requirement for patient specificity and the lack of off-the-shelf availability.

**Conclusions**

Vascular tissue engineering is a rapidly developing discipline and it likely will become a major modality for the treatment of advanced cardiovascular disease. Encouraging in vitro and in vivo results show that vascular engineering is now well established. Probably we are no very far from the time when the use of engineered vascular tissues will become an integral part of vascular surgical practice; we still need for regulatory approval (CE marking, FDA approval) for adoption of these very promising approaches.

**References**


