Keynote Lecture Series

Biomechanics and biocompatibility of the perfect conduit—can we build one?

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No currently available conduit meets the criteria for an ideal coronary artery bypass graft. The perfect conduit would combine the availability and complication-free harvest of a synthetic vessel with the long-term patency performance of the internal mammary artery. However, current polymer conduits suffer from inelastic mechanical properties and especially poor surface biocompatibility, resulting in early loss of patency as a coronary graft. Approaches to manufacture an improved conduit using new polymers or polymer surfaces, acellular matrices, or cellular constructs have to date failed to achieve a commercially successful alternative. Elastin, by mimicking the native extracellular environment as well as providing elasticity, provides the 'missing link' in vascular conduit design and brings new hope for realization of the perfect conduit.

Keywords: Coronary artery bypass; blood vessel prosthesis; biocompatible materials; biomechanics

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Introduction

The perfect conduit for coronary artery bypass surgery would ideally exhibit a low rate of patency failure over the long-term, be readily available without complication arising from its harvest, and be available in sufficient length to revascularize all targets. The best available conduit to date remains the *in situ* internal mammary artery (IMA), with 95.8% patency observed at 5 years compared to free arterial (89.1%) or saphenous vein (82.4%) grafts (1) and 88% 15-year patency seen for the left IMA (2). However harvest of autologous conduits can be time-consuming, the conduit may be poor quality or damaged during harvest, and complications do occur such as an increase in sternal wound reconstruction rate seen after bilateral IMA harvest (1.9% *vs.* 0.6% single IMA) (3). Conduit length is also limited particularly for arterial grafts, with a lack of available conduit given as the reason for 9.1% of patients entering the non-surgery (PCI) registry of the SYNTAX trial (4). An artificial blood vessel able to act as a small arterial substitute has been called the Holy Grail of vascular bypass surgery (5).

Sixty years has passed since the introduction of prosthetic vascular conduits in 1952. Yet despite extensive attempts to develop a truly biocompatible small-diameter vascular conduit there remains no successful alternative to autologous conduits for coronary artery bypass (6). Approaches to conduit development include new or modified prosthetic materials, conduits incorporating biomolecules to mimic biological surfaces or improve mechanical properties, and tissue engineered conduits either partly or wholly comprising cellular tissue. However, a number of important limitations inhibit vascular biomaterial design, affecting such areas as *in vitro* assessment of endothelialization, thrombogenicity, and biomechanical properties, and the selection and utilization of animal models for the assessment of novel conduits *in vivo* (6-8). The development of a successful small arterial substitute will require not only continued innovation but also

solutions to these limiting factors. The recent availability of recombinant human tropoelastin, a promising vascular biomaterial, has given us new insights and the possibility of new solutions in our quest for the perfect conduit.

Polymer vascular prosthetics

Early research into prosthetic vascular grafts aimed to produce conduits from inert polymers that passively transport blood while minimizing interaction with blood and tissue. The first human implant of a prosthetic vascular graft named Vinyon N was produced in 1952; however expanded polytetrafluoroethylene (ePTFE) and polyethylene terephthalate ('Dacron') remain the most common polymers in current use (8). Dacron grafts are used for larger vessel applications such as the aorta, iliac, and proximal femoral arteries where blood flow is relatively high and as a result synthetic conduits maintain patency for prolonged periods. For example, aorto-femoral bypass grafts have 5- to 10-year patency rates of 90% (9). However cardiac bypass surgery is rarely attempted with prosthetic materials due to the high failure rates (10). Dacron has shown patency out to 16 months as a short aorto-proximal coronary interposition graft (3.5 mm × 4 cm) (11); while ePTFE grafts as aorto-coronary conduits show 14% anastomotic patency at 45 months (12). Early patency failure reflects poor luminal surface biocompatibility. Synthetic conduits fail to endothelialize beyond the anastomoses, instead becoming coated with a film of plasma proteins (primarily fibrinogen) and platelets euphemistically termed a 'pseudointima' up to 1 mm in thickness (9,13), resulting in sustained surface thrombogenicity as well as susceptibility to infection from bacteremia. Beyond the early period, failure results from intimal hyperplasia affecting especially the distal anastomosis due in part to mechanical mismatch between the inelastic prosthesis and the elastic vessel wall (9). However, flow disturbance at the anastomosis generating areas of low wall shear stress is also important and it is clear that arterial wall elasticity, intimal hyperplasia, and wall shear stress are related (8,14).

Surface incompatibility has been the focus of extensive investigation and innovation. Expelling air from the conduit wall results in decreased thrombogenicity (15), meaning that methods of coating ePTFE which entail displacement of mural air (16-18) confound thrombogenicity assessment. Modification of surface texture has been attempted, physiochemical methods (such as oxidation, reduction, and acetylation) have been used to alter surface chemistry, and radiation (including gamma, ultraviolet, gas plasma, and ion beam) employed to attain covalent attachment of numerous compounds including amino acids, peptides, and anticoagulant or antiplatelet agents (8). Heparin coatings by non-covalent physical adsorption showed rapid loss of drug activity (19); however covalent attachment by 'endpoint linkage' to preserve biological activity has shown promising results in a recent randomized trial (20). Simply altering the polymer surface to enhance cellular interactions, such as endothelialization, is inadequate as it has long been recognized that such modifications are associated with increased thrombogenicity (21).

The notion that a lack of compliance in synthetic vascular grafts contributes to poor patency was first proposed in 1976 (22) and since then an association between compliance and patency has been shown in many studies (23-25). However there is little reliable evidence that elastic mismatch per se is the cause of failure, as the resultant intimal hyperplasia occurs predominantly at the downstream (but not upstream) anastomosis and at end-to-side rather than end-to-end anastomoses (26), and other factors such as disturbed flow leading to low shear stress at the endothelial surface are important (27). Creating a synthetic conduit with matched compliance is also problematic as native vessel compliance varies within the vasculature and with patient age and comorbidities (28,29). Permanent suture material is required to prevent anastomotic aneurysms (30) and this, usually inserted as a continuous suture, further reduces anastomotic compliance (31). Attempts to reduce compliance mismatch include interrupted suture technique and anastomotic vein cuffs which do reduce mismatch but are time-consuming and not commonly used (32). An external metal mesh support placed around the graft reduces intimal hyperplasia but only when the graft diameter is constricted (33) and is at the risk of luminal impingement by vein folding (34). An alternative approach is the development of polymer conduits exhibiting elastic mechanical properties, focusing on polyurethanes due to their desirable physical properties and relative blood compatibility (35). Polyester polyurethanes were found to be susceptible to hydrolysis through the ester linkage, while polyether polyurethanes were shown to be vulnerable to oxidative cleavage *in vivo* (36). The incorporation of polydimethylsiloxane and polycarbonate into the polymer backbone instead of polyester or polyether has been shown to improve the resistance of the material to both hydrolytic and oxidative degradation (37). However published reports

usually describe polyurethane conduits incorporating other materials to improve surface biocompatibility, host tissue response, or mechanical properties. Polycarbonate-siloxane polyurethane conduits incorporating collagen and hyaluronan, with heparin and/or sirolimus, have shown good results after six-months implantation in a rabbit model (38). The 'Myolink' polycarbonate-urea-urethane transmits pulsatile flow via compression of a spongy mid-wall without external dilation (39). It has been combined with numerous agents including arginine-glycine-aspartate (RGD) peptides, heparin, collagen, dermatan sulfate, and seeded with endothelial and smooth muscle cells, and reached clinical use as an arterio-venous fistula (40-42). A poly-ether-urethane conduit developed by Thoratec was used in 27 patients for coronary artery bypass surgery and a clinical trial begun, but no further results are available 13 years later (43).

Approaches and problems with conduits incorporating acellular organic material

The incorporation of proteins and other biomolecules results in a conduit designed to positively interact with the blood and tissue environment rather than just passively transport blood. The simplest of these approaches involves applying a luminal coating to available polymer conduits to reduce negative blood-materials interactions. One problem is achieving strong protein binding whilst preserving function of the bound molecule (44), while non-covalent binding results in weak attachment and early loss of attached compounds (8). A large number of biomolecules such as enzymes, antibodies, proteins, and cell receptor ligands have been chemically or physically immobilized onto biomaterials and detailed reviews are available (45,46). Extracellular matrix (ECM) compounds are a particular area of interest as they provide an ideal cellular environment; ECM laid down by cells seeded onto prosthetic conduits *in vitro* results in enhanced host cellular incorporation *in vivo* (47). Subendothelial ECM components are especially attractive as a surface coating to facilitate endothelialization from circulating endothelial cells, which must otherwise migrate through the usually impermeable conduit wall or very slowly along the length of the graft (9,48,49). Fibronectin coatings on ePTFE are effective at enhancing endothelialization, but endothelial cell (EC) seeding is generally performed *in vitro* before conduit implantation due to concerns regarding increased thrombogenicity (50,51). Collagen coatings also enhance EC attachment to ePTFE or Dacron (52) but native collagen is intrinsically thrombogenic and type I collagen has been shown to increase platelet attachment compared to uncoated ePTFE (53). Cross-linking and gas plasma immersion have been used to modify collagen by destroying platelet binding sites to reduce thrombogenicity (54,55). An alternative to whole ECM proteins is to select desired amino acid sequences. The binding site arginine-glycine-aspartic acid (RGD) present in the adhesive proteins fibronectin and vitronectin binds to an integrin receptor on cell surfaces (8) and RGD-coated surfaces have been shown to enhance EC attachment and proliferation as well as alignment under shear stress *in vitro* (56). Non-ECM proteins have also been attempted such as plasma proteins, particularly albumin which induces less platelet adhesion compared to fibrinogen and γ-globulin, however albumin-coated prostheses showed little improvement over uncoated conduits in animal models and clinical studies (46). Recognizing that platelet adhesion to biomaterial surfaces is related to adsorbed fibrinogen, Sivaraman *et al*., showed that it is the conformation rather than the amount of adsorbed fibrinogen that is the critical determinant of platelet adhesion as adsorption-induced unfolding of fibrinogen exposes platelet binding sites (57).

An acellular ECM scaffold would provide an appropriate environment after implantation for host cellular infiltration throughout the conduit wall, while potentially avoiding the need for support by prosthetic material and avoiding the problems associated with protein binding to polymer surfaces. Incorporation of an elastic component would also allow conduit mechanical properties to be tailored to match native vessels. A potential ECM source is decellularized tissue from another species, either vascular or non-vascular, yet the major concerns of all decellularization protocols remain ECM disruption, immunogenicity, and thrombogenicity (58). Decellularized intestinal submucosa provides a sheet of type I collagen that can be wrapped into a small-diameter conduit, and has shown successful incorporation as a neovessel in a rabbit model (59). Decellularized porcine ureters show similar mechanics to fresh specimens but with reduced immunogenicity as a xenograft (60). Removal of cells from canine arteries and veins leaves a tubular collagen/elastin matrix (61) with preserved mechanics, and no aneurysm formation after 4.5 years (62). Cross-linking may be used to reduce immunogenicity and strengthen the scaffold, but this alters mechanical properties and toxic residues inhibit cellular ingrowth (63). Yet without manipulation to reduce immunogenicity the ECM xenograft may be seen as a

foreign body and encapsulated by inflammatory cells and organized scar tissue rather than being integrated into the surrounding tissue (64). Some species such as pigs have been thought to be less immunogenic, yet the cellular environment remains inferior, for example improved human fibroblast proliferation and migration on human decellularized dermal matrix compared to pig matrix scaffold (65). Complete destruction of a decellularized porcine pulmonary valve xenograft has been seen in humans due to foreign body reaction (66). An alternative to decellularization for the generation of ECM scaffolds is the manufacture of tubular constructs using ECM proteins especially collagen and elastin. While simple molds may be fragile (67), electrospinning uses fibers with diameters in the range of 0.1-10 μm collected onto a target to achieve desired mechanical properties according to choice of polymer, fiber thickness and orientation, and construct thickness and shape. One or more polymers may be used, either synthetic (permanent or degradable) or naturally occurring biopolymers able to match the intended cellular environment. However xenogeneic biopolymers have the same disadvantages of the ECM scaffolds mentioned above, including immunogenicity, susceptibility to degradation, and the need to obtain them from animal sources using extraction processes which may alter the native structure (8).

Approaches and problems with conduits incorporating cellular tissue

A conduit that acquired luminal endothelialization would achieve ideal blood-surface interactions, while one that also incorporated living host tissue throughout the wall would potentially be able to grow and demonstrate vasoreactivity. EC seeding of prosthetic polymer conduits before implantation is an attractive solution to the failure of endothelialization *in vivo*, however ePTFE is non-adhesive to ECs (68) and methods to promote EC adhesion may lead to a more non-thrombogenic surface upon implantation (64) especially as many ECs are lost upon exposure to *in vivo* shear stress unless preconditioned against graded shear stress *in vitro*. 'Two-stage seeding' involving autologous EC harvest then proliferates *in vitro* before conduit seeding and subsequent implantation necessitates waiting several weeks for expansion of the EC population as well as two operative procedures. Furthermore, EC function such as ability to proliferate and migrate declines with age (69) and may be altered in response to injury by manipulation and/or exposure to a non-physiologic environment (54) and the biomaterial substrate may further influence EC phenotype through influences such as mechanical cues and availability of ECM contacts in the pericellular environment (70). Attempted solutions include genetically modified ECs (71) and the use of stem cells as an alternative EC source particularly for single-stage seeding without an *in vitro* proliferation step (72). Despite these limitations, Zilla's group successfully applied EC-seeded ePTFE as infrainguinal bypass grafts in 153 patients with peripheral vascular disease (73) and EC-seeded ePTFE has been used for coronary artery bypass surgery in a small number of patients (74) with a case report demonstrating patency after 9 years (75). However the time and expense needed to create EC-seeded prostheses remain important limiting factors.

Tissue-engineered conduits have mainly been constructed by coculture of cells (endothelial cells, smooth muscle cells, and/or fibroblasts) with ECM proteins before implantation, although Campbell *et al*., inserted a mandrel in an extra-vascular location to allow host tissue incorporation before transfer of the inverted conduit to its intended site (76). The conduit must be compatible with host tissue, possess a nonthrombogenic surface if designed for endothelialization *in vivo*, and demonstrate appropriate mechanical properties to avoid hyperplasia and aneurysm formation (64). Weinberg in 1986 developed a smooth muscle cell (SMC) and collagen media, coated with fibroblasts on the outside and ECs at the luminal surface, and noted longitudinal SMC orientation, a lack of elastin, poor SMC and collagen density, and poor radial strength requiring Dacron mesh support (77). Niklason introduced the bioreactor, using simulation of pulsatile pressure to improve mechanical properties, allowing implantation of autologous tissue-engineered blood vessels in the arterial system of miniature swine (78). However, they again noted a lack of elastin as well as poor contractility (79) and described problems with terminally differentiated SMCs from older donors (80), leading the group to investigate bone marrow-derived stem cells (81). L'Heureux dispensed with SMCs by employing 'sheet-based tissue engineering' to develop wrapped human fibroblast and collagen sheets into a tubular conduit, preconditioned under pulsatile flow before implantation into immunosuppressed animal models where they demonstrated infiltration by SMCs and deposition of elastin (82). These conduits have since been used in humans for hemodialysis access (83) and designs targeting the mechanical properties of autologous

saphenous vein and internal mammary artery for coronary artery bypass have been reported (84), but again a separate tissue harvest procedure and the time and expense of *in vitro* culture and manufacture are necessary. To be commercially successful, a vascular graft that is cellularized *in vivo* would be beneficial (64).

Recombinant human tropoelastin—a promising biomaterial

Elastin is a key ECM protein of elastic tissues such as arteries, where it imparts the mechanical properties of durability and recoil essential for their normal function (85) with age-related degenerative arterial changes seen to result from elastin loss (86). Elastin deficiency is also associated with atherosclerotic plaques (87), especially disruption of the subendothelial internal elastic lamina (88) and the rarity of IMA atherosclerosis may partly result from its high elastin component (89,90). Other key biological properties of elastin include low thrombogenicity (91) and enhancement for endothelial cells (92), but inhibition for smooth muscle cells (93,94) of proliferation and migration. Therefore elastin is ideally suited for vascular biomaterial applications and it has been described as an essential 'missing link' in vascular substitutes (95). Despite its remarkable properties, elastin has found little use as a biomaterial due to substantial challenges in the isolation of native elastin so that elastin degradation products or recombinant polypeptides (sometimes called 'elastin mimetics') were used until Weiss and colleagues constructed a synthetic gene enabling expression by Escherichia coli of recombinant human tropoelastin (rhTE) (96), the monomeric form of the elastin polymer secreted by many cell types including ECs, SMCs, and fibroblasts (85). Combined with a modification of gas plasma surface treatment to allow covalent binding of protein with retained function (44), our group has shown rhTE-coated coronary stent surfaces demonstrate low thrombogenicity and enhanced endothelialization *in vitro* (97) and rhTE-coated ePTFE vascular grafts demonstrate a striking reduction in anastomotic intimal hyperplasia in an ovine carotid artery interposition model (98). That such suppression occurs due to surface coating alone without a change in conduit compliance suggests that environmental cues from cellular contacts are more important than mechanical mismatch in the genesis of this hyperplasia. Nevertheless the realization of a conduit devoid of compliance mismatch remains the ultimate goal in the design of a small arterial substitute and elastin is an essential component (95), not only for its mechanical properties but also to provide the correct ECM context. As the microfibrillar component of elastin fibers is not required for their mechanical properties (99) rhTE is an ideal solution to this problem. Electrospinning allows rhTE to be combined with a strength component (collagen substitute) such as polycaprolactone (PCL), a non-toxic biodegradable polymer (100), weaving the nanofibres into a vascular graft while retaining circumferential alignment of the fibres to approximate native vessel composition and mechanical properties (101). PCL fibres alone lack the requisite mechanical properties (100) and the addition of a biopolymer (previously fibrin or collagen) has been shown to enhance SMC interactions (102,103). Our group developed a multilayered rhTE/PCL small-diameter conduit with burst pressure, hydraulic permeability, and compliance matching that of the IMA and showed endothelialization and low platelet attachment *in vitro* as well as retention of mechanical properties after a one month implantation as a carotid interposition graft in a pilot rabbit study (92).

Summary

The perfect conduit would show the durable patency of the IMA yet be readily available 'off the shelf'. Current polymer conduits suffer from inelastic mechanical properties and especially poor surface biocompatibility. Innumerable approaches to develop a conduit using new polymers, acellular matrices, or cellular constructs, have resulted in only a handful of clinical trials and no commercially successful alternative for coronary artery bypass surgery. Elastin, by mimicking the native extracellular environment as well as providing elasticity, provides the 'missing link' in vascular conduit design and recombinant human tropoelastin has shown great promise as a biocompatible coating and as an elastic conduit component. Realization of the perfect conduit remains an attainable goal through such continued innovation.

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