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Polymeric Materials for Tissue Engineering of Arterial Substitutes

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Abstract

Cardiovascular disease is the leading cause of mortality in the United States. The limited availability of healthy autologous vessels for bypass grafting procedures has led to the fabrication of prosthetic vascular conduits. Synthetic polymeric materials, while providing the appropriate mechanical strength, lack the compliance and biocompatibility that bioresorbable and naturally occurring protein polymers offer. Vascular tissue engineering approaches have emerged in order to meet the challenges of designing a vascular graft with long-term patency. In vitro culture techniques that have been explored with vascular cell seeding of polymeric scaffolds and the use of bioactive polymers for in situ arterial regeneration have yielded promising results. This review describes the development of polymeric materials in various tissue engineering strategies for the improvement in the mechanical and biological performance of an arterial substitute.

Keywords

biodegradable scaffolds; biopolymers; endothelialization; synthetic polymers; vascular bypass grafting; vascular tissue engineering

Coronary and peripheral vascular bypass graft procedures are performed in approximately 600,000 patients each year in the United States, most commonly with the saphenous vein or the internal mammary artery.¹ Although the use of autogenous vascular substitutes has had a major impact on advancing the field of reconstructive arterial surgery, these tissue sources may be inadequate or unavailable. Moreover, their harvest adds time, cost, and the potential for additional morbidity to the surgical procedure.^{2–4}

In 1954, Blakemore and Voorhess were the first to report the treatment of 10 patients with a synthetic arterial substitute.^{5,6} Textile tubes were fabricated from Vinyon-N fiber with the intent to recapitulate the anatomic structure of the vascular wall through the use of the synthetic fiber as a scaffold for tissue ingrowth. Although early clinical results were promising, Vinyon-N did not display sufficient long-term biostability, nor did it provide an appropriate scaffold for tissue ingrowth. Currently, expanded polytetrafluoroethylene (ePTFE), polyethylene tetraphthalate (Dacron), and polyurethane are used to fabricate synthetic vascular grafts.⁷ However, owing to thrombus formation and compliance mismatch, none of these materials have proved suitable for generating vascular grafts less than 6 mm in diameter that would be

required to replace the saphenous vein, internal mammary, or radial artery as a vascular substitute.^{8–11}

The functional importance of normal physiologic responses of the vascular wall in controlling thrombotic and inflammatory responses has guided attempts to closely mimic the native arterial wall in the design of a new generation of vascular prosthesis. For example, the endothelial lining in the native vasculature not only serves as a protective, thromboresistant barrier between blood and the surrounding tissue but also controls vessel tone, platelet activation, and leukocyte adhesion. Structurally, collagen and elastin are the two main components responsible for the tensile strength and viscoelasticity of the blood vessel, and create a fatigue-resistant structure that displays long-term durability.¹² Other features that define a polymer necessary to the design of an ideal vascular prosthesis are biocompatibility, infection resistance, suturability, and off-the-shelf availability.

The first tissue-engineered blood vessel substitute was created by Weinberg and Bell in 1986.¹³ They generated cultures of bovine endothelial cells, smooth muscle cells, and fibroblasts in layers of collagen gel supported by a Dacron mesh. Although physiologic pressures were sustained for only 3 to 6 weeks, they did demonstrate the feasibility of a tissue-engineered graft with human cells. Since then, strategies to create a suitable polymeric material for a blood vessel substitute have focused on three areas of research: coatings and surface chemical modifications of synthetic materials, biodegradable scaffolds, and biopolymers. Each polymer group can be further organized into tissue engineering strategies for in situ vascular regeneration, in which the body's natural healing response is modulated by polymer design and fabrication, or strategies for ex vivo formation of a blood vessel substitute, whereby the culture of human cells on polymer substrates before implantation defines their mechanical and biological properties.

Synthetic Nondegradable Polymers

ePTFE and Dacron

ePTFE is a porous polymer that is nonbiodegradable, with an electronegative luminal surface. Only 45% of standard ePTFE grafts are patent as femoropopliteal bypass grafts at 5 years, whereas autologous vein grafts have 60 to 80% patency.^{14,15} In standard ePTFE grafts, the fibril length or intermodal distance measures about 30 μm , and neither transanastomotic nor transmural endothelialization occurs to any significant extent. Experimental ePTFE variants with a larger fibril length of 60 μm have been produced, which in animal models has facilitated luminal endothelialization.¹⁶ Nonetheless, these observations have not been replicated in clinical studies. Currently, Dacron is most commonly used for aortic replacement and to a lesser extent as a conduit for femoropopliteal bypass surgery. Characteristically, knitted grafts incorporate a velour finish, which orients the loops of yarn upward, perpendicular to the fabric surface, thereby increasing available surface area and enhancing the anchorage of fibrin and cells to promote tissue integration. The preference for a velour finish has been primarily motivated by improved handling characteristics, with few data demonstrating that internal, external, or double velour grafts exhibit greater patency rates.¹⁷ Dacron grafts are often crimped longitudinally to increase flexibility, elasticity, and kink resistance. However, these properties are lost soon after implantation as a consequence of tissue ingrowth. Despite some evidence that suggests that platelet deposition^{18–20} and complement activation²¹ are lower on ePTFE than Dacron prostheses, the patency rates of Dacron and ePTFE grafts are similar.²²

The poor patency rates of these materials have motivated research that has focused on coatings, chemical and protein modifications, and endothelial cell seeding on existing polymeric materials. For example, carbon deposition, photodischarge, and plasma discharge technologies have been used to deposit reactive groups onto the polymer surfaces to interact with cell-

specific peptides and influence protein adsorption to the surface.²³ Nishibe and colleagues found that in a dog carotid implant model, fibronectin bonding improved graft healing in high-porosity ePTFE grafts.²⁴ Cell adhesion peptide sequences, such as the P15 peptide found in type I collagen, increased endothelial cell adhesion to ePTFE in vivo via integrin-specific binding.²⁵ Endothelial attachment was significantly improved on surfaces coupled with another potent adhesion peptide, RGD, when compared with fibronectin-coated grafts.^{26,27} Zilla and colleagues further improved cell retention on shear stressed grafts with precoated RGD-cross-linked fibrin.²⁸ ePTFE grafts were also impregnated with fibrin glue containing fibroblast growth factor (FGF)-1 and heparin, which in a dog model promoted transmural endothelialization, as well as the proliferation of smooth muscle cells.^{29–31} The delivery of endothelial cell growth factor and vascular endothelial growth factor from coatings on synthetic grafts has also facilitated the rate of in situ endothelialization.^{32,33}

In situ tissue engineering strategies also include partially resorbable Dacron grafts for enhanced infiltration and proliferation of vascular cells and promotion of capillary growth. Greisler and colleagues developed hybrid grafts made of polyglycolide fibers reinforced with a Dacron outer sleeve, which remained patent for 9 months after implanting into a rabbit aorta model.³⁴ Endothelial cell and smooth muscle-like cell infiltration and proliferation demonstrated the regenerative potential of biodegradable polymers supported by a mechanically stable synthetic polymer such as Dacron. Yu and colleagues further investigated the polyglycolic acid (PGA) and Dacron fiber blends to optimize compositional ratios for in vivo healing responses and luminal surface cell lining while maintaining graft strength.^{35,36}

Polyurethanes

Polyurethane is a copolymer that consists of three different monomer types: a diisocyanate hard domain, a chain extender, and a diol soft domain. At physiologic temperatures, the soft domains provide flexibility, whereas the hard domains impart strength. The most common medical grade polyurethanes are based on soft domains made from polyester, polyether, or polycarbonate. Further development has yielded a poly(carbonate-urea)urethane vascular graft that exhibits a compliance profile similar to that of human arteries.³⁷ Various components have been added to the graft design to improve synthetic graft function and yield biohybrid conduits. Nakagawa and colleagues developed a poly(ether-urethane) graft (PEUG) reinforced with knitted polyester fibers for hemodialysis, which was found to be more durable than ePTFE.³⁸ Furthermore, gelatin-coated PEUG improved graft patency when implanted in dogs.³⁸ However, clinical trials with human patients on maintenance hemodialysis resulted in limited success owing to low patency rates compared with ePTFE controls.^{39,40} Polyurethane-based grafts coated with heparin and FGF-2 have accelerated transmural endothelialization.⁴¹ In addition, poly(ethylene glycol)/poly(lactic acid) coated polyurethane grafts, when implanted in a carotid artery model, were found to be patent at 3 months and enabled a uniform intimal lining, with radial compliance values closer to native vessel compliance than ePTFE grafts.⁴²

Ex Vivo Endothelial Cell Seeding

In 1978, Herring and colleagues introduced a single-stage technique whereby venous endothelial cells were seeded onto grafts with enhanced patency in a canine model.⁴³ Although a promising concept, translating these results to the clinic has been challenging. Zilla and colleagues noted in an early clinical report the absence of a confluent endothelial cell lining 14 weeks after bypass grafting.⁴⁴ A subsequent clinical study revealed that at 30 months, the patency of single-stage endothelial cell-seeded ePTFE grafts in the femoropopliteal position was significantly worse when compared with that of vein bypass (38% vs 92%).⁴⁵ Similarly, endothelial cell-seeded Dacron aortobifurcated grafts did not demonstrate improved late outcome.⁴⁶ These disappointing outcomes were attributed to insufficient initial cell density, poor adhesion under flow, and failure to achieve confluence.

Cell density was increased using a two-stage technique and a 3- to 4-week culture period.^{47, 48} The two-stage technique has yielded encouraging clinical results, with a randomized study reporting that seeded grafts had greater patency than nonseeded grafts at 32 months (85% vs 55%).⁴⁹ In a follow-up report, the 9-year patency was 65% for cell-seeded grafts compared with 16% for nonseeded grafts.⁵⁰ In a subsequent report, similar primary patency rates were observed for 153 seeded ePTFE grafts.⁵¹ Fourteen patients have received cell-seeded 4 mm ePTFE grafts for coronary bypass, with 91% patency rates noted at 28 months.⁵²

Adhesive proteins, such as fibronectin, collagen, and fibrin, and adhesive peptide sequences have been investigated as coatings to increase cell anchorage, but the most appropriate coating for clinical studies is unclear.⁵³ Other techniques, such as electrostatic seeding and shear conditioning, may also increase cell adhesion.^{54–57} Endothelial progenitor cells from either the bone marrow or peripheral blood, as well as the microvasculature in the omentum or subcutaneous fat, have been highlighted as potential sources for endothelial cells.^{58–64}

Several investigators have endeavored to endothelialize the luminal surfaces of synthetic vascular grafts to mimic the biologic responsiveness of the native vasculature.^{30,51,65–69} The success of cell transplantation is limited because of difficulties in cell sourcing and cell attachment and retention during pulsatile flow conditions.⁷⁰ Strategies that promote in situ regeneration of a functional endothelial lining have also met with difficulties owing to chronic inflammatory and prothrombotic responses to the synthetic polymeric materials.⁷¹ Endothelial cells growing onto prosthetic graft surfaces that display a procoagulant phenotype can, in principle, promote rather than retard thrombosis.⁷² Furthermore, activated endothelial cells may increase growth factor production and secretion that encourages smooth muscle cell (SMC) proliferation. Indeed, subintimal SMC proliferation occurs predominantly in areas that have an overlying endothelium.⁷³ As an additional example, ePTFE grafts coated with anti-CD34 antibodies and implanted in pigs captured endothelial progenitor cells and increased endothelial cell coverage. However, intimal hyperplasia at the distal anastomosis was significantly increased at 4 weeks.⁷⁴

Degradable Polymers as Scaffolds

The use of biodegradable polymers as scaffolds on which layers of cells are grown is an alternate tissue engineering approach for the development of a functional vascular graft. The scaffold degrades and is replaced and remodeled by the extracellular matrix (ECM) secreted by the cells. PGA is commonly used in tissue engineering applications as it degrades through hydrolysis of its ester bonds, and glycolic acid, in turn, is metabolized and eliminated as water and carbon dioxide. PGA loses its strength in vivo within 4 weeks and is completely absorbed by 6 months. Biodegradation rates can be controlled by copolymerization with other polymers, such as poly-L-lactic acid (PLLA), polyhydroxyalkanoate (PHA), polycaprolactone-copoly-lactic acid, and polyethylene glycol.^{75–77}

Mooney and colleagues seeded cells onto a PLLA/poly(lactide-co-glycolide) (PLGA) copolymer-coated PGA mesh.^{76,78} Similarly, Vacanti and colleagues used PLGA to fabricate capillary networks for artificial microvasculature applications.⁷⁹ Niklason and colleagues developed a pulsatile bioreactor to remodel PGA scaffolds seeded with bovine smooth muscle and endothelial cells.⁸⁰ After a 10-week culture period, the resulting tissue-engineered vessel achieved a burst pressure of up to 2,300 mm Hg. Mechanical strength was dependent on the smooth muscle cell production of collagen and the culture medium supplements that promoted collagen cross-linking. After 5 weeks, the PGA scaffold had degraded to 15% of its initial mass. Although the endothelial lining was not confluent, vessels did display contractile responses to serotonin, endothelin-1, and prostaglandin, and implants remained patent for 1 month in a swine model. Attempts to translate this approach to human cells have led to poor

mechanical properties owing to the limited proliferative and synthetic capacity of human smooth muscle cells, especially when harvested from elderly patients. Further, the notable absence of elastic fibers could limit fatigue resistance and predispose the construct to subsequent aneurysmal degeneration.

PHAs, linear polyesters that are produced by bacterial fermentation of sugar or lipids, have also been employed in graft design as they can be modified to display a wide range of degradation rates and mechanical properties. Shum-Tim and colleagues engineered an aortic graft consisting of a polymer scaffold of PGA and polyhydroxyoctanoate (PHO) seeded with ovine carotid artery cells.⁸¹ The inner layer of the construct was made of a nonwoven mesh of PGA fibers, whereas the outer layers were composed of nonporous PHO. The PGA scaffold promoted cellular growth and ECM production, whereas the slower degradation rate of PHO provided mechanical support as this remodeling occurred. Significantly, the graft did not require extensive in vitro conditioning. The construct was implanted directly in the abdominal aorta of lambs, with 100% patency noted at 5 months. Histologic analysis revealed that the remodeled graft contained uniform collagen and elastin fibers that had aligned in the direction of blood flow. The mechanical stress-strain curve of the engineered construct approached that of the native vessel, although some permanent deformation was observed 6 months after implantation, indicating either insufficient or non-cross-linked elastin. Fu and colleagues investigated the effects of ascorbic acid and basic FGF, which stimulated cells on a PGA-poly-4-hydroxybutyrate construct to proliferate and generate large quantities of collagen, thereby accelerating the improvement in mechanical properties.⁸²

Polycaprolactones (PCLs) slowly degrade by hydrolysis of ester linkages with elimination of the resultant fragments by macrophages and giant cells. Shin'oka and colleagues reported the use of PCL-based scaffolds to engineer venous blood vessels.^{83,84} The PCL-PLA copolymer was reinforced with woven PGA and seeded with autologous smooth muscle and endothelial cells harvested from a peripheral vein. After 10 days, the construct was implanted as a pulmonary bypass graft into a 4-year old child.⁸⁵ Subsequent studies that used autologous bone marrow cells on the constructs have reported > 95% patency at a mean follow-up of 16 months.⁸⁶ Further evaluation of endothelial cell function and mechanical properties of vascular grafts constructed with autologous bone marrow cells was conducted with a canine inferior vena cava model.⁸⁷ The biochemical properties and wall thickness of cell-seeded scaffolds were similar to those of the vena cava 6 months after implantation.

Biodegradable polymer systems may also provide an option for the spatial and temporal release of various growth factors to promote vascular wall regeneration. For example, vascular endothelial growth factor release from PLGA scaffolds has been shown to promote angiogenesis in vivo.⁸⁸ Likewise, FGF-2 release from biodegradable poly(ester urethane)urea (PEUU) scaffolds combines the favorable mechanical properties of polyurethane with the bioactivity of an angiogenic protein.⁸⁹ Although tissue-engineered vascular grafts based on biodegradable scaffolds have yielded promising results, limitations remain. Challenges of cell sourcing are compounded by long culture periods that range between 2 and 6 months, and the proliferative capacity of cells isolated from elderly patients is limited. Further, although mechanical strength is comparable to that of native vessels, compliance mismatch limits long-term patency.

Biopolymers

An alternative strategy to synthetic and degradable scaffold-based vascular grafts is the manipulation of protein materials that constitute the architecture of native ECM. One such protein is type I collagen, a major ECM component in the blood vessel.⁹⁰ Collagen fibers function to limit high-strain deformation, thereby preventing critical rupture of the vascular

wall.^{91,92} Collagen gels and fibers reconstituted from purified collagen are ideal in artificial blood vessel development because of their low inflammatory and antigenic responses.⁹³ Integrin binding sequences in collagen allow for cell adhesion during fibrillogenesis. As mentioned previously, collagen gels as substrates for cells were first reported by Weinberg and Bell.¹³ Since then, Habermehl and colleagues have developed a process to obtain large quantities of collagen from rat tail tendons to scale up production.⁹⁴

Variables such as fiber orientation, cross-linking conditions, and cell seeding techniques have also been explored to improve the mechanical integrity of collagen-based constructs. A wide range of cross-linking agents can enhance covalent links between the collagen fibers, the most efficient of which is glutaraldehyde.⁹⁵ The cytotoxicity of this chemical, however, has led investigators to explore other options, such as the enzymatic reactions of lysyl oxidase and transglutaminase, as well as photocross-linking.^{96–98} Various groups have investigated fiber orientation and smooth muscle cell alignment as a means to increase mechanical properties in the circumferential direction of a tubular construct.^{99–101} Preconditioning treatments involve applying a mechanical strain or shear stress to the construct and compaction of SMC-containing collagen gels around a mandrel to increase mechanical strength.^{102–104}

The shortcomings of a stiff collagen-based scaffold have motivated researchers to explore the potential of more elastic fibrin gels in vascular tissue engineering.¹⁰⁵ Fibrin is formed when fibrinogen polymerizes with the addition of thrombin to form a fibrillar mesh. An advantage of this biopolymer is the ability to produce it with the patient's own blood, thereby preventing an inflammatory response on implantation.¹⁰⁶ Fibrin also binds to critical proteins that direct cell fate, such as fibronectin and vascular endothelial growth factor.¹⁰⁷ In vivo degradation can be controlled with the proteinase inhibitor aprotonin¹⁰⁸ and cross-linking agents, although there are concerns that the concentrated presence of these natural proteins may interfere with local coagulation cascades.

Interestingly, smooth muscle cells embedded in fibrin gels produce more collagen and ECM than those that are entrapped in collagen gels.¹⁰⁹ Furthermore, Tranquillo and colleagues demonstrated that the enmeshed SMCs directed compaction and alignment of both the fibrin fibers and the cell-synthesized collagen fibers in a circumferential orientation around a nonadhesive mandrel.¹¹⁰ A fibrin-based vascular graft developed by Swartz and colleagues incorporated ovine SMCs and endothelial cells and was implanted in the jugular vein of lambs.¹¹¹ These grafts remained patent for 15 weeks and on histologic examination were found to contain both collagen and elastin. The mechanical integrity of the construct was comparable to that of native coronary arteries.

Elastin is the other major constituent in the vasculature, with cross-linked elastic fibers forming concentric rings around the medial layer of arteries.¹¹² This structural protein provides elasticity to the vascular graft by stretching under a stress and recoiling back to the original dimensions as the load is released.^{113–115} Elastin regulates vascular smooth muscle cell activity by inhibiting SMC proliferation.

Unlike collagen, the stable, cross-linked fiber network of native elastin makes isolation and purification techniques difficult. Different strategies have emerged to incorporate elastin into tubular constructs. Whereas some investigators have attempted to promote elastogenesis in vascular grafts indirectly with smooth muscle cell culture techniques,^{116–118} others have developed protocols to process insoluble and soluble elastin.¹¹⁹ For example, collagen and elastin have been freeze-dried to produce a porous scaffold.¹²⁰ Elastin protein polymers composed of amino acid repeat sequences from native elastin have been genetically engineered.^{121–124} Specifically, polymers with pentapeptide repeat motifs similar to VPGVG exhibit elastic behavior with features that are consistent with native elastin, including a mobile

backbone and the presence of beta turns.^{125–128} These biopolymers, in turn, can be cast as hydrogels or electrospun into nanofibrous scaffolds.^{129–133}

Decellularized allogenic or xenogenic tubular tissues that contain an intact and structurally organized ECM have been investigated as vascular conduits and include human umbilical vein and bovine and porcine carotid arteries. Although a readily available supply of artificial arteries is attractive, drawbacks include the inability to tailor matrix content and architecture, progressive biodegradation, and the risk of viral transmission from animal tissue. Decellularization removes most cellular antigenic components in allogeneic and xenogeneic tissue. A combination of physical agitation, chemical surfactant removal, and enzymatic digestion disrupts cells and removes protein, lipids, and nucleotide remnants.^{134–137} Following decellularization, chemical cross-linking is used to enhance mechanical strength and reduce immunogenicity.^{138,139} The addition of an external support such as a Dacron mesh is also common to provide mechanical strength and prevent late dilation. Efforts to improve the durability and the healing response of decellularized scaffolds have included coating with heparin and FGF, as well as seeding with endothelial cells, endothelial progenitor cells, smooth muscle cells, bone marrow–derived cells, and adipose-derived stem cells.^{140–148}

Alternative tubular tissue sources have also been explored, including small intestinal submucosa (SIS) and the intraperitoneal graft model. Decellularized SIS is composed of approximately 90% collagen, fibronectin, proteoglycans, growth factors, glycosaminoglycans, and glycoproteins.¹⁴⁹ Implantation of the SIS construct leads to neovascularization, host cell migration and adhesion, and matrix remodeling.^{150–153} The development of a tissue-engineered vascular graft from another avascular tissue source was conducted by Campbell and colleagues beginning in 1983.¹⁵⁴ The intraperitoneal graft model utilizes the peritoneal cavity as an in situ bioreactor for the creation of a tubular construct seeded with layers of host cells. The investigators observed that foreign objects implanted into the peritoneal cavity became encapsulated by a fibrous capsule containing myofibroblasts and a surrounding layer of mesothelial cells.^{154,155} They then inserted Silastic tubing into the peritoneal cavities of dogs, rabbits, and rats. After 2 to 3 weeks, the tubing was removed, and the mesothelium-lined, myofibroblast-rich construct was grafted into the carotid artery (rabbit), abdominal aorta (rat), or femoral artery (dog) of the animal in which it was grown.^{156,157} Remodeling of the autologous grafts included differentiation of myofibroblasts to smooth muscle–like cells, increased wall thickness, elastin and collagen production, and circumferential alignment of cells and matrix proteins.¹⁵⁸ The constructs displayed endothelium-dependent relaxation when stimulated with acetylcholine and were patent in rabbits for at least 16 months and in dogs for 6.5 months.

Conclusions

The development of a synthetic arterial substitute represents a major milestone of twentieth century medicine yielding technology that has saved the lives and limbs of millions of patients. Nonetheless, a durable, small-caliber ($d < 6$ mm), synthetic conduit remains elusive, and patency rates for infrainguinal revascularization through the use of a prosthetic graft have changed little over the past 30 years. The challenges of creating the ideal tissue-engineered vascular substitute are numerous, but significant progress has been made to understand the importance of both the mechanical and the biologic requirements of polymeric materials for this application. In vitro, in vivo, and computational models continue to provide new insights into the complex interplay of cellular, biochemical, and biomechanical processes that lead to graft failure. Through continued collaboration among vascular surgeons, biologists, material scientists, and biomedical engineers, existing barriers in the creation of an arterial substitute, undoubtedly, will be broken.

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