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MINIREVIEW

Blood Vessel Replacement: 50 years of Development and Tissue Engineering Paradigms in Vascular Surgery

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Summary

The gold standard material in bypass surgery of blood vessels remains the patient's own artery or vein. However, this material may be unavailable, or may suffer vein graft disease. Currently available vascular prostheses, namely polyethylene terephthalate (PET, Dacron) and expanded polytetrafluoroethylene (ePTFE), perform well as large-caliber replacements, but their long-term patency is discouraging in small-caliber applications (<6 mm), such as in coronary, crural or microvessel surgery. This failure is mainly a result of an unfavorable healing process with surface thrombogenicity, due to lack of endothelial cells and anastomotic intimal hyperplasia caused by hemodynamic disturbances. An ideal small-diameter vascular graft has become a major focus of research. Novel biomaterials have been manufactured, and tissue-biomaterial interactions have been optimized. Tissue engineering technology has proven that the concept of partially or totally living blood vessels is feasible. The purpose of this review is to outline the vascular graft materials that are currently being implanted, taking into account cell-biomaterial physiology, tissue engineering approaches and the collective achievements of the authors.

Key words

Small-caliber vascular grafts • Synthetic polymers • Biomaterials • Tissue engineering • Stem cells • Dynamic bioreactor • Shear stress

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Introduction

Atherosclerosis accounts for almost one half of all deaths in Europe (Stehouwer *et al*. 2009). Although advanced pharmacological and minimally-invasive techniques offer a growing therapy option (Met *et al*. 2008), a surgical bypass of blood vessels on the heart or on a lower extremity remains the procedure of choice in a number of patients (Fig. 1) (Guyton 2006, Norgren *et al*. 2007). This approach is also more cost-effective, and in particular preserves the quality of the patient's life better than primary amputation of a limb (Cheshire *et al.* 1992). A synthetic tube or a vascular prosthesis has to be implanted when the patient's own artery or vein is not available. After more than half a century of development work, the results achieved with currently available materials are not optimal in terms of healing and tissue regeneration.

Long-term patency rates of prosthetic grafts are satisfactory in large-caliber arteries (>8 mm), where thrombogenicity (i.e. disposition to blood coagulation) may be overcome by massive blood flow, and the 5-year patency of aorto-iliac substitutes is 90 % (Brewster 1997). There is little difference between the results for prosthetic and autogenous (i.e. patient's own) material in medium-caliber replacements (6-8 mm), e.g. in carotid or common femoral arteries (Ricotta 2005). However, in small-caliber vessels (<6 mm), such as coronary arteries (heart), infrainguinal arteries (below the inguinal ligament), and particularly in low-flow infrageniculate

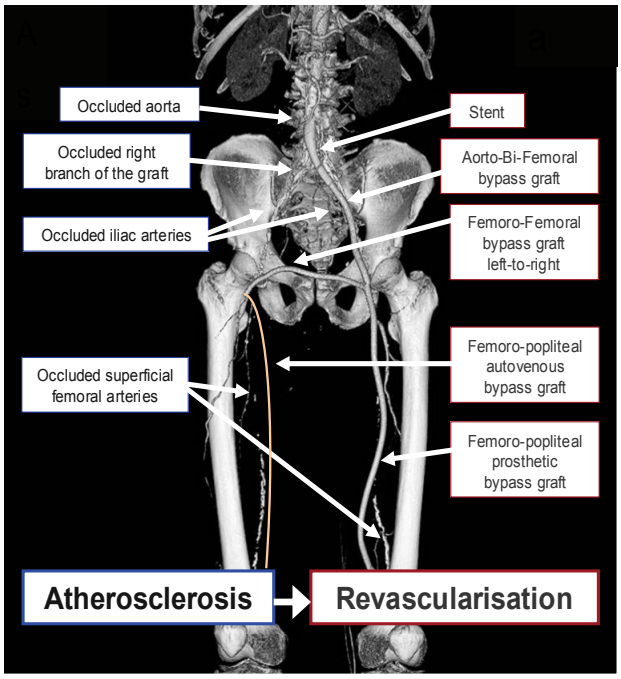

Fig. 1. Surgical repair of multilevel peripheral atherosclerotic disease.

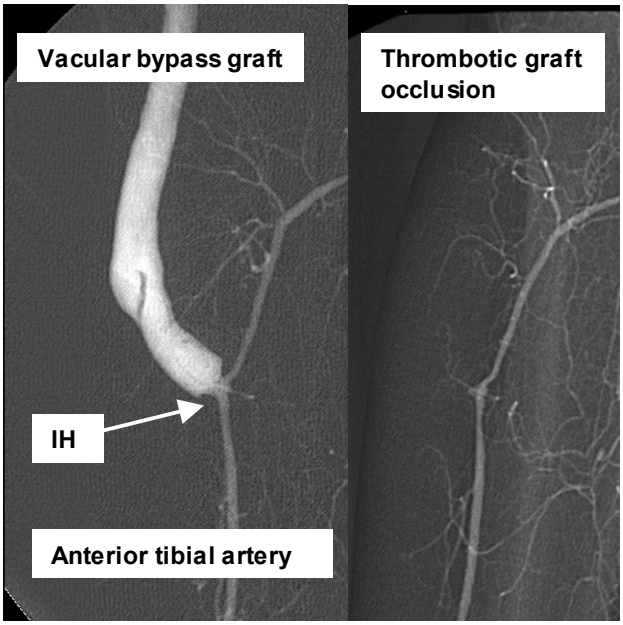

Fig. 2. Intimal hyperplasia (IH) in distal anastomosis of a vascular graft, causing thrombosis and occlusion.

arteries (below the knee joint), the outcomes of vascular prostheses are rather disappointing. Five-year primary patency of prosthetic (ePTFE) above-the-knee femoro-popliteal bypass grafts is as low as 39 %, whereas autovenous bypasses (i.e. performed with own vein) have a rate of 74 % (Klinkert *et al.* 2004). A summary of currently-used vascular replacements is shown in Table 1.

Currently available vascular grafts fail due to the thrombogenicity of the artificial surface and intimal hyperplasia (IH), which is located at distal anastomosis (Fig. 2) of prosthetic grafts (i.e. the site of the junction to the artery). Unlike animal models, most of the prosthetic blood-contacting surfaces remain uncovered by tissue in humans (Berger *et al.* 1972). The etiology of IH, developing usually 2-24 months post implantation, is multifactorial and includes a compliance mismatch between a relatively rigid prosthesis and the more elastic native artery (Sarkar *et al.* 2006), graft/artery diameter mismatch, lack of endothelial cells (EC), surgical trauma and flow disturbances resulting in adaptive changes in the sub-endothelial tissue, characterized by proliferation and migration of vascular smooth muscle cells (VSMC) from media to intima, and synthesis of extracellular matrix (ECM) proteins (Haruguchi and Teraoka 2003).

To overcome these fundamental inconveniencies, novel biomaterials research (Shin and Mikos 2003) and particularly tissue engineering modalities are increasingly being adopted (Isenberg *et al.* 2006). Promising and clinically proven outcomes have been achieved with biohybrid and tissue-engineered vascular grafts.

An ideal vascular graft would possess the following characteristics: mechanical strength and compliance to withstand long-term hemodynamic stresses; non-toxicity; non-immunogenicity; biocompatibility; "off-the-shelf" availability in various sizes for emergency care; operative suturability and simplicity of surgical handling; resistance to *in vivo* thrombosis; ability to withstand infection; complete incorporation into the host tissue with satisfactory graft healing and ability to grow when placed in children (Kakisis *et al.* 2005), and, last but not least, reasonable manufacturing costs. The task is so demanding and the potential rewards are so great that research in the field of small-caliber vascular substitutes has been compared with the search for the Holy Grail (Conte 1998).

The aim of this review is to outline the characteristics and drawbacks of currently-used vascular substitutes, with special emphasis on the physiological cellular response to materials and on vascular tissue engineering approaches, based on the collective experience of the authors.

Historical background

The history of vascular surgery tracks progress made in suturing and replacing damaged vessels. In

Table 1. Vascular substitutes in clinical use according to body region.

Vascular substitute choice	**Vascular regions**				
	Large-caliber arteries (≥ 8 mm)	**Medium-caliber arteries (6-8 mm)**	**Small-caliber arteries (≤ 6 mm)**	**Venous reconstructions**	**Hemodialysis arterio-venous access**
	Aorta, arch vessels, iliac and common femoral arteries	Carotid, subclavian, common femoral, visceral and above-the-knee arteries	Coronary, below-the-knee, tibial and peroneal arteries	Superior and inferior vena cava, ilico-femoral veins, portal vein, visceral veins	Upper > lower extremity
1st choice	Prosthesis (Dacron, ePTFE)	Prosthesis or autograft (equal)	Arterial or venous autograft	Saphenous spiral vein graft, deep venous autograft	Native material
2nd choice	Allograft, deep venous autograft	Prosthesis or autograft	Composite graft, vein interposition, prosthesis (ePTFE, Dacron), allograft, biosynthetic	Allografts, ePTFE, Dacron, biografts	ePTFE, PU, xenografts, biografts, TEBV (clinical trial)

ePTFE (expanded polytetrafluoroethylene), PU (polyurethane), TEBV (totally-engineered blood vessels).

ancient times, vascular interventions were limited to compressing and cauterizing injured vessels to control bleeding. Ambrose Paré developed a vessel ligature in the 15th century, but surgical repair of vessels did not begin until 1759, when Hallowell and Lambert repaired a brachial artery injury with a suture. The first vascular anastomosis (connection of blood vessels) was performed by Nicholas Eck as a porto-caval shunt in dogs in 1877 (Starzl 2003). Carrel and Guthrie optimized the vascular anastomosis transplantation technique and even tissue culture for organ replacement in the early 1900s, and Alexis Carrel received the Nobel Prize for Physiology or Medicine in 1912.

Goyannes first used an autogenous popliteal vein graft for popliteal aneurysm repair in 1906. A femoro-popliteal bypass with a reversed saphenous vein graft was first performed by Kunlin in 1948, initiating a very successful era for this type of graft that has lasted until the present day (Lopez and Ginzberg 2008). At the same time, the first fresh arterial allografts (foreign tissue of the same species) began to be used in human vascular reconstructive surgery (Gross *et al.* 1948). An artificial vascular prosthesis was first implemented as an aortic replacement with a Vinyon "N" tube in a dog experiment (Voorhees *et al*. 1952). The same material was implanted in humans to replace an aneurysm (dilation) of the abdominal aorta (Blakemore and Voorhees 1954), leading to rapid progress in vascular surgery and prostheses research and use (Sauvage 1986).

Arterial replacements

Biological vascular grafts

The gold standard for vascular replacement remains the autologous native vessel, which possesses the most physiological properties. In coronary artery bypass grafting (CABG), the internal mammary artery and the radial artery are superior to a greater saphenous vein graft (SVG), which is also often used (Beghi *et al.* 2002). In the case of lower limb or peripheral bypass surgery, the material of choice is also greater saphenous vein (*vena saphena magna*). It can be cleansed of valves and anastomosed *in situ*, so that the *vasa vasorum* remain intact (Kachlík *et al.* 2007) and the blood flow direction is reversed. In this type of graft, preservation of desired endothelial properties can be expected; however, several studies have failed to confirm superiority to the more widespread *ex vivo* reversed setting of the SVG (Lawson *et al.* 1999). It should be noted that, despite good clinical performance, SVG is also liable to atherosclerosis and intimal hyperplasia occurring throughout the length (Sarjeant and Rabinovitch 2002). In addition, almost 30-40 % of patients lack an appropriate saphenous vein (Faries *et al.* 2000) due to previous phlebitis, vessel removal, varicosities, hypoplasia or anatomical unsuitability. Additionally, any surgical vessel harvest is associated with indispensable donor site morbidity (Swenne *et al*. 2006).

Alternatives include the use of other native vascular materials only in carefully selected indications,

and sometimes with limited clinical performance: arteries, such as the right gastroepiploic artery for coronary application (Sasaki 2008), and veins, such as the lesser saphenous vein (*vena saphena parva*) (Chang *et al*. 1992), arm veins (Calligaro *et al*. 1997) for coronary and peripheral bypasses, or deep leg veins (Ali *et al*. 2009) for infected aortic graft replacement, visceral revascularization or even primary lower limb bypass.

Although the use of fresh (cold-stored) or cryopreserved homografts (i.e. human allografts from cadaver donors) was abandoned in the early 1960s because of difficulties in preserving them, late graft deterioration, aneurysm formation and the anticipated availability of synthetic prostheses, they have been reintroduced for managing aortic prosthetic graft infection (Kieffer *et al.* 2004), lower extremity primary revascularization (Dardik *et al*. 2002, Fahner *et al.* 2006, Matia *et al*. 2007) and simultaneous or sequential revascularization surgery in solid organ transplant-recipients (Matia *et al*. 2008). Although allografts are not routinely used (usually in limb-threatening situations, in redo surgery or in an infected field), some studies suggest improved patency of these grafts, e.g. in the case of preserved externally-supported human umbilical vein (harvested from newborns) when compared to ePTFE (Johnson and Lee 2000).

The application of heterografts (xenografts, i.e. tissue from different species) (Schmidt and Baier 2000) involves mainly studies on alternative hemodialysis vascular access. Although bovine carotid artery heterografts did not show superiority to PTFE (Hurt *et al*. 1983), and decellularized bovine ureteric grafts have been implanted with ambiguous results (Chemla and Morsy 2009), glutaraldehyde-crosslinked bovine mesenteric vein provided a considerable reduction in infection, thrombosis and reintervention rate (Katzman *et al.* 2005). Importantly, decellularized natural tissue of allogenic (human) or xenogenic (animal) origin serves as a scaffold for cell seeding within the scope of tissue engineering of vascular grafts (Dahl *et al.* 2003). A summary of biological vascular conduit materials is presented in Table 2.

Synthetic vascular grafts

For more than 50 years, two polymers have been used for synthetic vascular prostheses: 1) polyethylene terephthalate (PET), Terylene or Dacron, and 2) polytetrafluoroethylene (PTFE), Teflon or Gore-Tex. Both of these molecules are highly crystalline and hydrophobic. Prosthetic rings or coils can be applied to the external surface of both materials to resist kinking and compression in anatomically required positions (long bypasses, grafts crossing the joint or body midline).

PET/Dacron (polyethylene terephthalate, [-O-C=O-C_6H_4-O-C=O-CH_2-CH_2-]) was introduced in England in 1939, and was further developed and patented as Dacron by DuPont in 1950. It is a thermoplastic polymer resin of the polyester family and is used in synthetic fibers of round cross-section. These fibers are bundled into multifilament yarns, which can be woven (over-and-under pattern) or knitted (looped fashion) into textile vascular graft fabrics and tubes. A crimping technique (an undulating surface) is sometimes used to increase distensibility and kink-resistance. The porosity of a textile Dacron graft is defined by water permeability, which is greater for knitted Dacron. Knitted Dacron is impregnated with albumin, collagen or gelatin to make it more impervious, to decrease the porosity/permeability, and to avoid the need for blood preclotting prior to implantation. Depending on the cross-linking agent (formaldehyde or glutaraldehyde), the albumin impregnation is degraded 2 to 8 weeks after implantation (Marois *et al*. 1996). Although collagen impregnation increased platelet deposition and delayed the healing process in a dog experiment (Guidoin *et al*. 1996), a prospective randomized trial with aorto-iliac prostheses indicated that collagen impregnation does not stimulate the coagulation cascade more than conventional Dacron (De Mol Van Otterloo *et al.* 1991). There are no differences in clinical graft patency between woven and knitted Dacron, when used as an aorto-iliac bypass graft (Quarmby *et al.* 1998). Dacron is reported to dilate over time, but direct association with graft complications and failure has been rare (Blumenberg *et al.* 1991).

Host reactions to the vascular prosthesis start immediately after restoration of blood circulation. The tissue-prosthesis and blood-prosthesis interfaces are complex microenvironments, and the physico-chemical properties of the surface of the prosthesis, such as charge, energy, wettability and roughness, may be responsible for the graft patency. The first step is the plasma protein adsorption/desorption process typical for any blood/material interface (Vroman and Adams 1969), followed by platelet deposition, white blood cell and erythrocyte adhesion, and eventually endothelial and smooth muscle cell migration. Fibrin deposits, which contain platelets and blood cells, build up during the first few hours to days after implantation. They are stabilized

Table 2. Biological vascular grafts in clinical use.

	Biological vascular grafts				
	Autografts		**Allografts (homografts)**		**Xenografts (heterografts)**
	Arterial	**Venous**	**Arterial**	**Venous**	
Advantages	Closest approximation, less diameter mismatch, internal mammary artery anatomically nearby, excellent function	Durable and versatile, good results, infection resistance, relative availability	Off the shelf availability, better resistance to infection, transplant-recipient patients		
Disadvantages	Availability, vasospasm (radial artery), donor site morbidity	Availability, harvest injury, vein graft disease	Antigenicity, graft deterioration, early occlusions, chronic rejection, intake of drugs, infection risk		
Healing	Intimal thickening, myointimal hyperplasia (radial artery)	Endothelial desquamation, vein dilation, wall thickening, arterialization, re-endothelialization	Endothelial denudation, immune response, fibrotization		
First use	Jaboulay and Briau 1896	Goyannes 1906	Gross *et al*. 1948	Linton 1955	
Review e.g.	Nezic *et al.* 2006	Cooper *et al*. 1996	Fahner *et al*. 2006	Dardik *et al*. 2002	Schmidt and Baier 2000

over a period of up to 18 months and form an inner compacted fibrin layer. Fibrin also fills the interstices within the graft wall. Generally, this fibrin/platelet pseudointima remains acellular; however, after 5 months, capillaries and fibroblasts can grow into the tight intersticial spaces even in humans (Stewart *et al*. 1975) and reach the inner fibrin layer. Only a few sparse small islands of endothelialization appeared in areas remote from the anastomosis region on woven excised Dacron grafts (Wu *et al.* 1995). External fibrin matrix surrounding the graft is gradually invaded by macrophages, and granulation tissue and foreign-body giant cells (FBGC) are usually seen under the external surrounding connective tissue capsule (Rahlf *et al.* 1986). In the case of knitted Dacron, endothelial islands can occasionally be observed on human explants during redo surgery or autopsy 1-11 years after implantation (Shi *et al*. 1997). Mature endothelium and a well-developed smooth muscle layer, described only in animal studies, is attributable to extended transanastomotic ingrowth rather than a midgraft healing process (Clowes *et al*. 1987, Zacharias *et al.* 1987).

The structure of knitted and, to a lesser extent, also woven Dacron allows a certain degree of transmural tissue ingrowth. However, the compacted inner fibrin layer forms a barrier and, even if the barrier is overcome by undifferentiated connective tissue, the capillaries remain unconnected to the poorly endothelialized blood surface (Herring *et al.* 1979, Xue and Greisler 2003).

PTFE (polytetrafluoroethylene, $[-CF_2-CF_2-]$) was patented by DuPont as Teflon in 1937, and ePTFE was patented by Gore as Gore-Tex in 1969. ePTFE is an expanded polymer which is manufactured by a heating, stretching, and extruding process resulting in a non-textile porous tube composed of irregular-shaped solid membranes ("nodes"). The molecule is relatively biostable, i.e. less prone to deterioration in biological environments than PET (Guidoin *et al.* 1993a,b), and the graft surface is electronegative, which minimizes its reaction with blood components. It is characterized by a node-fibril structure, and its average porosity is described by the internodal distance (IND), which is usually 30 to 90 μm. However, the actual available ingrowth spaces between fibrils are much smaller than IND.

Optimal IND of 60 μm (high porosity) was experimentally proposed for tissue ingrowth and endothelialization of 4mm ePTFE grafts in a baboon model (Golden *et al.* 1990). Though a human trial with high-porosity ePTFE showed capillary ingrowth, it did not extend more than half the distance from the outside, and did not produce an endothelial lining (Kohler *et al.* 1992). Human host responses to standard low-porosity

ePTFE (IND ≤ 30 μm) material are similar to the responses to Dacron grafts: a thin fibrin coagulum or amorphous platelet-rich material develops over time, and a lack of luminal surface endothelial cellular coverage is found after human implants. Collagenous external encapsulation develops within 1 to 6 months, penetrating the material structure with minimal cellular infiltration (Guidoin *et al.* 1993a). Systematic evaluation and meta-analysis of randomized controlled trials comparing Dacron and ePTFE showed no evidence of an advantage of one material over the other (Roll *et al.* 2008).

Polyurethanes (PU) comprise a large family of elastic polymers containing a urethane [-NH-(CO)-O-] group. Polyurethanes were originally developed in Germany in the 1930s. They were commercialized by DuPont in 1962, and have been available for biomedical applications since the 1960s (Boretos and Pierce 1967). Generally, they are copolymers consisting of three different monomers: crystalline (hard) and amorphous (soft) segments, the former accounting for rigidity and the latter for flexibility, which can be varied by the manufacturer. The third monomer serves as a chain extender (Zdrahala 1996). The disadvantage of the first generation polyester-based PU was hydrolytic biodegradation, which resulted in abortion of one of the clinical trials (Zhang *et al.* 1997). The next generation of polyether-based PU, which is hydrolysis-resistant but more susceptible to oxidation, underwent succesful clinical assessment as hemodialysis access graft (Glickman *et al.* 2001), and received Food and Drug Administration (FDA) approval in 2000.

The latest generation of polycarbonate-based PU is hydrolytically and oxidatively stable, and promoted faster luminal endothelialization and less neointimal formation as small-calibre vascular prostheses in a rat experiment compared to ePTFE (Jeschke *et al.* 1999). After 36-month implantation in aorto-iliac position in dogs, a histological analysis of poly(carbonate-urea) PU grafts showed well-developed neointima only in distal anastomosis, only minor hydrolysis of the amorphous segments and, in addition, the grafts retained their compliance with time – a feature not observed in Dacron or ePTFE. These promising results led to a phase I clinical trial (Seifalian *et al.* 2003).

According to their microstructure, polyurethanes can be divided into fibrillar or foamy. Both structures tend to lack communicating spaces for potential capillary ingrowth. Upon implantation, the blood surface of the fibrillar PU is covered by a fibrin layer that is thinner than on knitted Dacron, and the outer surface is encapsulated by scar formation containing FBGC. In microporous foamy PU with 15 μm pore size, relatively little capillary ingrowth can be accomplished, whereas with increasing pore size up to 157 μm, the undesired inflammatory FBGC reaction could be diminished and capillary sprouting was allowed from the outside in a Chacma baboon model. However, before its completion, transmural ingrowth slowed down when reaching the dense inner fibrin layer that was "squeezed" into the pores from the inside (Zilla *et al.* 2007).

Although PU grafts possess many interesting features, e.g. the presence of EC under poor hemodynamic conditions, excellent healing, good surgical handling and low suture bleeding (Tiwari *et al.* 2002), further investigations are required before more recommendations can be made, because there is a lack of evidence for their use in human peripheral bypass surgery (Dereume *et al*. 1993). An outline of synthetic vascular prostheses is summarized in Table 3.

Vascular grafts with modified lumen

Several attempts have been adopted to suppress the thrombogenicity of synthetic material by affixing chemicals or anticoagulants to the graft lumen: early studies showed decreased platelet deposition on carbon-coated ePTFE grafts, but the overall patency rates were not improved (Kapfer *et al.* 2006). A heparin-bonded Dacron graft exhibited slightly better patency than an untreated ePTFE graft (Devine *et al.* 2004), and heparin-immobilized ePTFE provided better thromboresistance in humans (Bosiers *et al.* 2006). Applying a polyethylene glycol (PEG)-hirudin/iloprost coating to 4 mm ePTFE prostheses reduced IH and led to superior patency in a pig experiment (Heise *et al.* 2006). Heparin coating significantly reduced aortic graft thrombosis in rats both for ePTFE and for PU (Walpoth *et al*. 1998). A dipyridamole (anti-platelet drug) coating positively influenced the patency rate of a 5 mm PU vascular prosthesis in animal experiments (Aldenhoff *et al*. 2001). Fibroblast growth factor-1 and heparin affixation enhanced ePTFE graft capillarization and surface endothelialization without significant IH in a canine aorta model (Gray *et al.* 1994). Antithrombotic agents are of course routinely administered to patients with vascular disease, with an obvious influence on graft patency and overall cardiovascular mortality (Watson *et al*. 1999).

Interestingly, an effort has been made to increase the resistance of synthetic vascular grafts to infectious

Table 3. Synthetic vascular grafts in clinical use.

	Synthetic vascular grafts					
	PET (Dacron, Terylen)		**ePTFE (Teflon, Gore-Tex)**		**Polyurethane**	
	Woven	**Knitted**	**Low-porosity (<30 µm IND)**	**High-porosity (>45 µm IND)**	**Fibrillar**	**Foamy**
Advantages	Better stability, lower permeability and less bleeding	Greater porosity, tissue ingrowth and radial distensibility	Biostability, no dilation over time	Biostability, better cell ingrowth	Compliance, good hemo- and biocompatibility, less thrombogenicity	
Disadvantages	Reduced compliance and tissue incorporation, low porosity, fraying at edges, infection risk	Dilation over time, infection risk	Stitch bleeding, limited incorporation, infection risk, perigraft seroma formation	Late neointimal desquamation in 90 µm IND, infection risk	Biodegradation in first generation, infection risk, carcinogenic?	
Healing	Inner fibrinous capsule, outer collagenous capsule, scarce endothelial islands	Fibrin luminal coverage, very sporadic endothelium, transanastomotic endothelialization in animals	Luminal fibrin and platelet carpet, connective tissue capsule with foreign body giant cells, no transmural tissue ingrowth	Macrophages and polymorphonuclear invasion, capillary sprouting, fibroblast migration, certain angiogenesis, thicker neointima, endothelialization in animals	Thin inner fibrin layer, outside foreign body cells, limited ingrowth	Better ingrowth with bigger pores
First use	Ku *et al.* 1957		Norton and Eiseman 1975		Boretos and Pierce 1967	
Review e.g.	Xue and Greisler 2003		Nishibe *et al.* 2004		Tiwari *et al.* 2002	

IND (internodal distance).

agents. Antibiotics such as rifampicin bonded to Dacron did not reduce the incidence of vascular graft infection (Earnshaw *et al.* 2000); however, a silver-coated collagen-impregnated Dacron prosthesis offers an alternative approach in the treatment of vascular graft infection (Mirzaie *et al.* 2007).

Composite and vein-interposition vascular grafts

Attempts at improving disadvantageous anastomotic hemodynamics include alternative surgical techniques and interposition of an autologous vein segment.

Despite the theoretical and experimental advantage of end-to-end (straight) rather than end-to-side (Y-shaped) anastomosis between the graft and the artery (O'Brien *et al*. 2007), clinical trials did not prove superiority, and moreover an increased limb amputation rate was revealed in the end-to-end setting, probably due to exclusion of collateral vessels (Schouten *et al*. 2005). Suturing materials and techniques may also decrease the anastomotic compliance difference, e.g. in the case of interrupted sutures (more than one single suture). However, running sutures are most widely used, because they are quicker and achieve better hemostasis (Tiwari *et al*. 2003).

Own venous tissue is placed in the form of a vein patch or cuff between an ePTFE graft and the artery to reduce the anastomotic compliance mismatch and to improve the prosthesis patency. Procedures implemented during the 1980s and 1990s include the Miller cuff, the Linton patch, the Taylor patch and the St. Mary boot (Moawad and Gagne 2003). When the patient's own vein graft is of insufficient length, feasible options that increase the patency rates may be: a *composite bypass* - prosthesis and vein are spliced together with an additional anastomosis (Bastounis *et al*. 1999), a *sequential bypass*, which is formed as a distal venous extension graft to the preceding proximal prosthetic bypass (Mahmood *et al.* 2002), and a *bridge graft*, which connects two patent distal arteries with a short vein segment (Deutsch *et al.* 2001). Although adjunctive arterio-venous fistula placement increases the blood flow through femoro-distal (i.e. below knee) bypasses, thus theoretically preventing thrombosis, several trials failed to show evidence of

benefit (Laurila *et al.* 2006).

Vein interposition techniques are generally useful in the case of distal anastomosis located below the knee, but are unimportant in the above-the-knee position (Mamode and Scott 2000). The underlying mechanism consists in reducing the compliance mismatch and suppressing IH (Cabrera Fischer *et al.* 2005). Research derived from this evidence led to the evolution of specially formed ePTFE grafts, capable of better harnessing the hemodynamic forces by an enlarged anastomotic hood. Interestingly, clinical studies have shown patency rates of this pre-cuffed ePTFE (Panneton *et al.* 2004) and carbon-lined ePTFE Distaflo graft (Fisher *et al.* 2003) that are comparable to interposition vein cuffs.

Biosynthetic/biohybrid vascular grafts (biografts)

The idea of introducing viable biological components into an artificial material-based vascular graft was established to produce more biocompatible vascular substitutes. A viable endothelial layer is the best antithrombogenic surface. There are three possible sources of graft lumen endothelialization *in vivo* post implantation: trans-anastomotic ingrowth from the native artery, transmural tissue and capillary ingrowth through the prosthesis wall, and a "fall-out" or blood-borne source from circulating progenitor cells. Unlike animals, humans seldom achieve spontaneous endothelialization more than 1-2 cm from an anastomosis, and transmural ingrowth is hampered by the structure of currently-used prostheses (Zilla *et al*. 2007).

The concept of seeding endothelial cells onto the graft lumen before implantation was experimentally implemented (Herring *et al.* 1978), and consequently this autologous EC "transplantation" managed to improve the patency of human Dacron prostheses (Herring *et al.* 1984) in a non-smoker population. Endothelial cells from a subcutaneous vein segment (*e.g.* saphenous, cephalic or jugular vein) are harvested and immediately seeded onto the graft lumen within the timeframe of one operation. The results of the first clinical trials performed during the 1980s were controversial and disappointing, mainly due to insufficient cell density (Bordenave *et al.* 1999). However, sophisticated EC extraction and retention techniques (Tiwari *et al.* 2001) and the search for more abundant cell sources, such as microvascular endothelium from fat tissue or an omentum biopsy, improved the outcome of this single-stage cell seeding method (Alobaid *et al.* 2005).

On the other hand, the double-stage approach involves a prolonged incubation and cell multiplication period (2-4 weeks) between cell harvesting and implantation (Bordenave *et al*. 2005). Nevertheless, *in vitro* flow pretreatment or shear stress preconditioning of the cell-material constructs before exposing them to arterial conditions enhances cell retention by inducing structural changes and adaptation (Rademacher *et al.* 2001). This means that an endothelial cell monolayer is physiologically exposed to certain mechanical forces, namely hydrostatic pressure resulting from blood pressure, shear stress resulting from tangential friction of blood flow against the vessel wall, and finally longitudinal and circumferential cyclic stretch resulting from repeated blood vessel distension due to the cardiac cycle (Lehoux *et al.* 2006). Chronic laminar versus turbulent shear stress seems to be of utmost importance for endothelial and vascular smooth muscle cell function (Chien 2007), regulating signal transduction in these cells (Daculsi *et al.* 2007), their alignment, molecule secretion, cytoskeleton reorganization, gene expression, cell migration, proliferation and survival. These processes ultimately influence thrombogenesis and atherogenesis (Yoshizumi *et al*. 2003), and similar cellular events and phenotypes (Rémy-Zolghadri *et al*. 2004, Fernandez *et al.* 2006) can be observed when cells are seeded on biomaterials (Fernandez *et al*. 2007).

Early results of clinical *in vitro* double-stage endothelialization were promising (Magometschnigg *et al.* 1992, Meinhart *et al.* 1997), and recently published overall 5-year and 10-year patency of endothelialized fibrin glue-precoated ePTFE femoro-popliteal bypass grafts of 69 % and 61 %, respectively (Deutsch *et al*. 2009) has already been correctly reported to close the gap between prosthetic and vein grafts (Meinhart *et al.* 1997). Interestingly, the feasibility of endothelium-seeded vascular prostheses was also confirmed in coronary bypass grafting, though it is not widely used (Laube *et al*. 2000).

To improve the above-mentioned clinical success, additional cell sources and cell retention technologies are being investigated. Vascular cells are anchorage-dependent, and integrin receptor-mediated adhesion occurs via ECM proteins that are adsorbed from the cell culture media *in vitro* or from blood *in vivo* (Bačáková *et al.* 2004). Thus, to regulate cell attachment, biomaterials are coated with ECM proteins such as collagen, laminin and fibronectin (Vara *et al.* 2005) or are modified by covalent bonding of short adhesive peptides

which may be cell specific, such as the Arg-Gly-Asp (RGD) sequence (Bačáková *et al*. 2007). Fibrin, as a natural scaffold for cell migration and healing, plays a pivotal role in tissue engineering of vascular grafts (Filová *et al.* 2009). In addition, less specific physical surface modifications, non-ligand based techniques (Salacinski *et al.* 2001) and surface nanoarchitecturing (de Mel *et al.* 2008) are being explored.

An alternative approach aimed at improving seeding efficiency is to use progenitor cells. Bone marrow cells infiltrated into the ePTFE vascular grafts and implanted in the aortic position of dogs retained complete endothelialization and patency after six months (Noishiki *et al*. 1996). Similarly, human endothelial progenitor cells (EPC) were isolated from peripheral blood (Asahara *et al*. 1997), and it has been shown in a canine model that a subset of CD34+ bone marrow cells can be mobilized to the circulation and can colonize the flow surfaces of Dacron vascular prostheses (Shi *et al*. 1998). Moreover, seeding of bone marrow-derived cells (BMC) accelerated early Dacron graft endothelialization without increasing thrombogenicity in a dog model (Bhattacharya *et al.* 2000). Taken together, due to their high proliferative capacity and differentiation potential, stem cells may represent the next era of cell-sourcing technology (Riha *et al.* 2005).

Genetically-modified cells have also been considered for the construction of vascular replacements. For example, genetically-modified endothelial cells over-expressing tissue plasminogen activator (t-PA) and urokinase-type PA, or bone marrow mesenchymal stem cells transduced to express endothelial nitric oxide synthase (eNOS), would promote cell repopulation of the graft and help to eliminate thrombotic events (Zarbiv *et al.* 2007). However, the use of genetically-modified cells inherently raises ethical questions. A conventional approach is directly to load the materials with anti-coagulant, anti-inflammatory and cell growth-regulating substances, such as heparin and heparin-like molecules, as mentioned above (Walpoth *et al*. 1998, Lee *et al.* 2002), hirudin (Heise *et al.* 2006), dipyridamole (Aldenhoff *et al.* 2001), growth factors, such as vascular endothelial growth factor (Ehrbar *et al.* 2005) or fibroblast growth factor (Gray *et al.* 1994, Sato *et al*. 2008), or antimigratory and antiproliferative drugs paclitaxel (Lim *et al.* 2007), sirolimus (Ishii *et al.* 2008) and inhibitors of CDK2 kinase (Brooks *et al.* 1997). These drugs can be incorporated directly into the prosthesis wall or delivered through drug-eluting stents (Lee *et al.* 2008), catheters and perivascular collars (for review see Sriram and Patterson 2001). Artificial materials releasing NO are also being developed, consisting of synthetic polymers (e.g. polyurethane, PTFE) incorporated with NO donors, such as diazeniumdiolates and S-nitrosothiols (Varu *et al.* 2009).

Living vascular grafts, totally-engineered blood vessels (TEBV)

The concept of completely biological living grafts implies the ability to remodel, grow, self-repair and respond to the immediate environment. Similarly to the native artery, the graft would consist of a functional endothelial cell layer resting on metabolically active smooth muscle cells which are in a contractile (i.e. non-synthetic and anti-atherogenic) phenotype (Muto *et al.* 2007). The graft would also contain enough collagen and elastin proteins to display desirable viscoelastic properties, and would lack any synthetic foreign material that would initiate chronic inflammatory responses or be susceptible to infection. If a synthetic material is used, it should be non-immunogenic, non-thrombogenic and of appropriate compliance. In the ideal case, it should be degradable, providing a temporary scaffold for vascular tissue regeneration, gradually removed and replaced by the newly-forming tissue.

In the construction of tissue-engineered vascular grafts, three major components must be addressed: a scaffold to provide the initial graft shape and strength, adhesive matrix and living vascular cells (Baguneid *et al*. 2006). For the scaffold, four major approaches can be identified: permanent synthetic support, natural acellular tissues, a biodegradable scaffold, and non-scaffold technology (Campbell and Campbell 2007).

The first seminal attempt involved seeding bovine EC, VSMC and fibroblasts onto collagen gel tubes (Weinberg and Bell 1986). An external Dacron mesh reinforcement had to be added because of poor mechanical strength. An example of the use of a natural scaffold involves seeding human cells on decellularized porcine aorta (Bader *et al*. 2000) or small intestinal submucosa implanted as vascular grafts (Lantz *et al.* 1993). The most commonly used biodegradable polymer is polyglycolic acid (PGA). Under shear stress preconditioning, VSMC followed by EC were seeded onto this scaffold, and the resulting vascular grafts were implanted in pigs, with excellent results (Niklason *et al.* 1999). Seeding bone-marrow cells (BMC) onto a biodegradable scaffold enabled the establishment of a

Table 4. Composite, biosynthetic and totally engineered vascular grafts in experimental and clinical use.

	Composite grafts	**Biosynthetic grafts**		**Totally engineered blood vessels**	
	Clinical	**Experimental**	**Clinical**	**Experimental**	**Clinical**
Advantages	Reduced compliance mismatch and intimal hyperplasia, improved patency in femoro-distal bypasses, easier redo surgery	Antithrombogenic, better patency		Responsiveness, non-thrombogenicity, self-repair, growth, metabolically active, potentially cost-effective	
Disadvantages	Technically demanding, prolonged surgery time	No emergency use, cell amplification problems, cell culture contamination risk		Demanding fabrication, time- and cost-consuming, bioreactor cell laboratory, specialized centers only	
Healing	Less intimal hyperplasia	Self-renewing functional endothelium		Complete integration	
First use	Siegman 1979	Herring *et al.* 1978	Herring *et al.* 1984	Weinberg and Bell 1986	Shin´oka *et al.* 2001
Review e.g.	Moawad and Gagne 2003	Seifalian *et al.* 2002	Bordenave *et al.* 2008	Isenberg *et al.* 2006	L'Heureux *et al.* 2007a

totally-engineered autograft implanted into the inferior vena cava of a dog, and explant analysis showed that BMC were able to differentiate both in endothelial and smooth muscle cells (Matsumura *et al*. 2003).

The non-scaffold or "self-assembly" approach produced a graft composed exclusively of human cells by wrapping and culturing fibroblast and VSMC cellular sheets on a PTFE mandril, which was then removed and EC were seeded in the lumen. This was the first completely biological TEBV to display mechanical resistance comparable to that of human vessels (experimental burst strength up to 2000 mm Hg). A short-term experiment in a canine model demonstrated good surgical handling (L´Hereux *et al*. 1998). Another vascular graft was developed without a scaffold by inducing an inflammatory reaction. A silastic tube was placed into the peritoneal cavity of rats and rabbits and was in 2 weeks spontaneously covered by layers of myofibroblasts, collagen matrix, and a single layer of mesothelium. It was everted to resemble the blood vessel and grafted in carotid or aortic position, and remained patent after 4 months (Campbell *et al* 1999).

A TEBV construct consisting of autologous bone marrow cells seeded onto a biodegradable scaffold was first clinically implanted to replace the pulmonary artery in a pediatric patient with a cyanotic defect (Shin´oka *et al.* 2001), and there was no graft-related complication in a group of 42 patients (Shin´oka *et al.* 2005). Another clinical success was achieved by TEBV produced by the cell-sheet multilayer method (L'Heureux *et al.* 2006) and implanted as a hemodialysis access graft in 10 patients (L'Heureux *et al.* 2007b). A recent paper reports primary 1-month and 6-month patency of 78 % and 60 %, respectively, meeting the approved criteria for a high-risk patient cohort (McAlister *et al*. 2009).

A summary of composite, biohybrid and totally-engineered vascular grafts is outlined in Table 4.

Venous replacements

Unlike arterial reconstructions, venous reconstructions are limited to large-diameter central veins, such as the inferior (Schwarzbach *et al.* 2006) or superior vena cava and the ilico-femoral veins (Kalra *et al.* 2003). Autologous size- and length-matched veins such as superficial femoral vein, internal jugural vein, left renal vein and mainly the gold-standard composite saphenous spiral vein graft (Doty *et al.* 1999) produce the best results, *e.g.* for a bypass for an occlusion of the superior vena cava of iatrogenic origin (catheter-related thrombosis). Venous allogenous homografts, either fresh or cryopreserved, have been used in experimental and clinical venous reconstruction (Sitzmann *et al.* 1984). The patency of externally supported ePTFE is better than the patency of grafts fashioned from ePTFE alone. However, the use of synthetic prostheses may be limited by low-flow thrombogenicity, contaminated tissue beds, as in venous vascular trauma or tumor resection cases, *e.g.* in portal vein resection for pancreatic carcinoma (Leon *et al*. 2007). Venous reconstructions may be combined with an

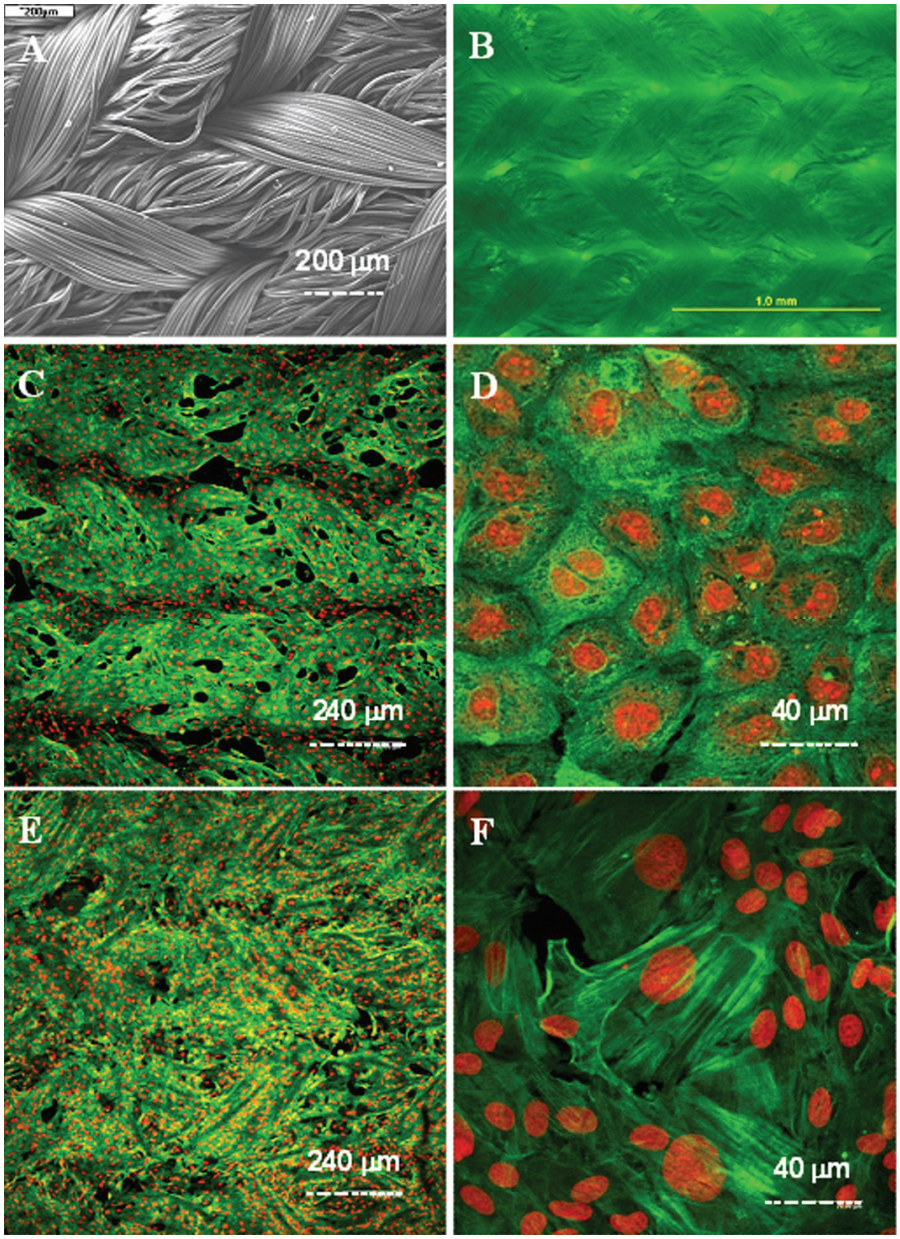

Fig. 3. Innovation of knitted PET vascular prostheses produced by VUP a.s., Brno, Czech Republic. **A**: the rough and highly hydrophobic inner surface of the prosthesis not suitable for cell adhesion; **B**: coating of this surface with defined molecular assemblies such as collagen I (Co), laminin (LM), fibronectin (FN) or fibrin (Fb) makes it more adhesive; **C, D, E, F**: confluent layer of bovine vascular endothelial cells (line CPAE) on CoFb (C, D) and multilayer of rat aortic smooth muscle cells on CoFN (E), CoLM (F) on the inner surface of a knitted wrapped prosthesis. Immunofluorescence of beta-actin (C, D) or alpha-actin (E, F), nuclei counterstained with propidium iodide. NOVA nanoSEM 200 FEI electron microscope (A), Olympus IX 51 fluorescence t microscope, obj. 4x (B) or Leica TCS SP2 AOBS confocal microscope, obj. 10x, 29x5 µm (C), 40x, zoom 2x, 4x1 µm (D), obj. 10x, 9x15 µm (E), 40x, zoom 2x, 55x1 µm (F).

adjuvant arterio-venous fistula to improve graft patency. Interestingly, the success rates of repeated percutaneous angioplasty approached those of operative reconstruction (Wisselink *et al.* 1993).

Hemodialysis vascular access

Creating a native arterio-venous fistula for chronic hemodialysis access is obviously superior to creating a prosthetic fistula. However, patients with depleted veins receive a prosthetic access graft, which has to provide sufficient blood flow and sustain repeated puncturing. It is difficult to identify the ideal access graft from a large number of biologic and prosthetic conduits. Randomized trials suggest that cuffed ePTFE grafts offer reasonable patency and that "early access" PU grafts can provide a safe conduit. Biologic/semibiologic grafts give better results than synthetic grafts, in some respects (Scott and Glickman 2007).

Collective experience of the authors

Static experiments performed in our laboratory enabled us to assess the cell colonization of various biomaterials without flow of culture medium. Clinically-used PET vascular prostheses (produced by VÚP, Brno, Czech Republic) were impregnated with biodegradable polyester-based copolymers (Pamula *et al*. 2008) as a background for further modification with multilayers of adhesive matrix proteins, such as collagen, fibronectin,

laminin and particularly fibrin, which can be derived in autologous form from the patient's blood (Brynda *et al.* 2005, Filová *et al.* 2009). For the purposes of vascular tissue engineering, we explored the adhesion and growth of animal-derived endothelial and vascular smooth muscle cells (Chlupáč *et al.* 2008a) (Fig. 3). Research work carried out on some fibrin-based surfaces (Riedel *et al*. 2009) has led to a common patent (Brynda *et al.* 2008).

Dynamic experiments were conducted under defined medium flow to better mimic *in vivo* conditions. Dacron vascular prostheses were modified on the luminal surface with ECM protein assemblies (Chlupáč *et al*. 2006a), and an investigation was made of the adhesion and growth of human patient-derived EC (Chlupáč *et al.* 2006b). Their resistance to shear stress was also investigated (Chlupáč *et al.* 2006c). The gene expression profile of endothelium seeded on similar planar ECM analogues was also determined (Chlupáč *et al*. 2008b). Hybrid vascular graft constructs *in vitro* seeded with autologous EC and preconditioned under shear stress in a bioreactor (Provitro Co., Berlin Germany) are currently being investigated in a porcine model.

Conclusions

Open arterial surgery in the form of a lower limb bypass remains the standard treatment for extensive and multilevel atherosclerotic disease. Over the past 50 years, no synthetic alternative has been found to compare with the patency rates of gold-standard autologous conduits. However, appropriate native material is often unavailable and alternative vascular prostheses show poor clinical performance. To address this issue, luminal modifications of grafts, interposition of vein segments and particularly tissue engineering of small-sized blood vessels have been introduced. Biohybrid and tissue-engineered vascular grafts have been manufactured with the help of materials research, complex tissue culture and cell seeding technologies. The outcomes of experimental and clinical implants seem to be favorable. It is likely that cell therapy will become a frequent option in vascular and endovascular surgery in the coming decades.

Conflict of Interest

There is no conflict of interest.

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