Current Status of Prosthetic Bypass Grafts: A Review

Ruben Y. Kannan,[1,2] Henryk J. Salacinski,[1] Peter E. Butler,[2] George Hamilton,[3] Alexander M. Seifalian[1]

[1] Biomaterials & Tissue Engineering Centre, University Department of Surgery, Royal Free and University College Medical School, University College London, London, United Kingdom

[2] Department of Plastic Surgery, Royal Free Hospital Hampstead NHS Trust, London, United Kingdom

[3] Vascular Unit, Department of Surgery, Royal Free Hospital Hampstead NHS Trust, London, United Kingdom

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Abstract: Polymers such as Dacron® and polytetrafluoroethylene (PTFE) have been used in high flow states with relative success but with limited application at lower flow states. Newer polymers with greater compliance, biomimicry, and ability to evolve into hybrid prostheses, suitable as smaller vessels, are now being introduced. In view of the advances in tissue engineering, this makes possible the creation of an ideal off-the-shelf bypass graft. We present a broad overview of the current state of prosthetic bypass grafts. © 2005 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 74B: 570–581, 2005

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INTRODUCTION

Small diameter vascular grafts (< 6 mm) are used predominantly in revascularization and reconstructive procedures. The commonest grafts used are autologous veins or arteries in the 400,000 heart bypass operations done annually in the United States.[1] However, vein grafts in coronary bypass grafts occlude over time due to accelerated atherosclerotic changes with a 10-year patency of 50%, postoperatively.[2] Synthetic prostheses have yet to match natural grafts with patency rates ranging from 40% to 50% for lower limb bypass grafts.[3] As such it is used as an option only when autologous grafts are contraindicated. Among the reasons cited are compliance mismatch, thrombogenicity and poor haemodynamics. The difference in radial compliance between the graft and the native vessels at the site of anastomoses[4] accentuated by the inelasticity of sutures has been shown to cause luminal narrowing due intimal hyperplasia. Thrombogenicity also poses a challenge to biomedical researchers as long-term patency rates are not encouraging. These may be overcome by endothelializing these prostheses or making the surface less thrombogenic with the addition of heparin.[5,6]

The ideal vascular graft should be nonthrombogenic, compatible at high blood flow rates, and have similar viscoelasticity to native vessels. When dealing with small diameter (< 6mm) vessels in low-flow states, the significance of these factors is amplified. While results with polytetrafluoroethylene (PTFE) and Dacron® are satisfactory in larger vessels, patency is far lower in small-diameter grafts.[7–9] *In vivo* studies have shown a 20% to 25% patency rate with 1 mm diameter PTFE microvessels while all vein grafts in similar settings remained patent.[10,11] This is because these biomaterials activate thrombus formation on its lumen while the differential compliance at the anastomotic site contributes to the formation of intimal hyperplasia (IH). As such, autologous vein grafts remain the gold standard for microvascular repairs as they are both compliant and nonthrombogenic. However donor-site morbidity and the need for an additional surgery limit its potential.[12]

From the engineering perspective, the polymers used in prostheses should be available by purchase or synthesis in order to be commercially viable. In addition, polymers like Dacron® with medium-to-high Young's modulus (stiff)[13] can be yarned into fibers to form woven or knitted configurations while PTFE may be expanded into nodules and fibrils. On the other hand, polyurethanes with low modulus (less stiff) need be extruded on a solid mandrel first before setting into tubes with solid or porous walls. In high pressure systems like the aorta, stiffer and stronger polymeric grafts are ideal. However in smaller diameter conducting vessels, radial compliance is more important than strength. An advantage of polyurethanes is that by varying its porosity, the radial compliance of the grafts may be regulated by the manufacturers. This is essential as it has been shown that mechanical properties including compliance mismatch, diameter mismatch, Young's modu-

Correspondence to: A. M. Seifalian (e-mail: a.seifalian@medsch.ucl.ac.uk)
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lus, and impedance phase angle affect graft failure due to intimal hyperplasia.[14] These devices should also be stable both *in vitro* and *in vivo* over protracted periods of time. In this review, an overview of the various types of vascular prostheses in current use has been undertaken.

PROSTHETIC BYPASS GRAFTS

Polymers Used for Graft Fabrications

Biostability of prosthetic bypass grafts is essential as biodegradation of the polymer would result in an irreversible change in graft characteristics. The principal modes of biodegradation include physical and chemical changes. Physical changes include swelling, plasticization, crystallization, fatigue, creep, and kinking. Chemical changes include hydrolysis of susceptible bonds (carbonyl > anhydride > ester > urethane > amide) as compared to hydrocarbons, silicones, and sulfones which are more susceptible, oxidation by inflammatory mediators, and calcification.[15] Apart from mechanical changes to the prostheses, toxic byproducts may also be released postdegradation. This section deals with the state of the art polymeric options for bypass grafts. Other polymers such polyethylene, polydimethylsiloxane (PDMS), and polysulfone have not been discussed here as their use is limited to stents.[16]

Poly (ethylene terephthalate)/Dacron® [O—C═O—C_6H_6—O—C═O—CH_2CH_2]$_n$. Introduced in 1957 by Ku and colleagues, Dacron® is a type of polyester in the form of multiple filaments either woven or knitted into vascular grafts.[17] While woven grafts have small pores, knitted grafts formed by looping fibers together (velour technique) have larger pores which promote greater tissue ingrowth and are more compliant. Coils or external rings can also be incorporated into the vascular graft to minimize graft kinking. However due to larger pore sizes, knitted Dacron® grafts need to be preclotted prior to use with albumin, gelatin, and even blood to prevent seepage, especially in high pressure vessels like the aorta.[18] While the inner albumin or gelatin coating degrades over 2 to 3 months, Dacron® is strong, with a tensile strength of 170 MPa to 180 MPa, a tensile modulus of 14,000 MPa, and a highly crystalline nature. These properties confer nonbiodegradability (total resorption by 30 years) though Dacron® grafts tend to dilate over time.[19]

Currently, Dacron® is predominantly used as aortic and large diameter peripheral bypass grafts (< 6mm) with relative success. Other polyesters have also been used as grafts in aortic and heart repairs.[20] In a preliminary study, silver-coated polyester prostheses were employed in 27 cases of aortic graft infections. Twenty-four–month actuarial survival stood at 85% with a 15% perioperative mortality rate. Longer term studies would need to be performed prior to extensive clinical application[21] but limited by its inherent thrombogenicity.[22] As such, its use has been for experimental purposes only.

After implantation into the body, proteins adsorb to the lumen of the graft followed by platelets, macrophages, endothelial cells (EC), and smooth muscle cells (SMC). This matrix then organizes itself into an inner fibrin layer, an intermediate layer of foreign body (FB) giant cells, and an outer connective tissue capsule by 18 months. Physical and biological modifications to the internal surface enhance the formation of a neointima but this has not been shown to improve vessel patency rates in PET prostheses.[23]

Polytetrafluoroethylene (PTFE) [—(CF_2—CF_2)—]$_n$. PTFE or Teflon®, an inert fluorocarbon polymer, was first used as an artificial heart valve and subsequently made more microporous by extrusion and sintering to form expanded PTFE (ePTFE). It is highly crystalline (>90%), has a stiffness of 0.5 Gpa, and a tensile strength of 14.0 MPa. In addition, ePTFE has improved cell adhesion characteristics compared to plain PTFE and is now widely used as lower limb bypass grafts (7–9 mm) with excellent results. ePTFE is nonbiodegradable with an electronegative luminal surface that is antithrombotic. While more than 90% of aorto–iliac ePTFE grafts are functional at 5 years,[24] only 45% of them are patent in femoro–popliteal bypass grafts as against the 77% patency of autologous vein grafts at 5 years.[25] In vessels smaller than 7 mm, adherence of materials to its surface limit further application and efforts are under way to modify ePTFE for this purpose.

Carbon-coating can further improve electronegativity. Studies showed an antiplatelet effect but clinical trials have been variable.[26] Following *in vivo* implantation, PTFE elicits an inflammatory response resulting in the formation of a neointima after 18 months or so. The standard pore size of ePTFE is 30 μm and animal experiments suggest that increasing pore sizes up to 90 μm could improve graft endothelialization and neovascularization. These modified grafts have greater patency rates but these results were not reproducible in humans.[27] ePTFE grafts impregnated with heparin have shown improved patency rates in rat vessels. However, concerns have been raised on the rate of heparin release from the graft. A recent study discovered that covalently binding heparin to a bioactive graft could provide controlled release, but long-term results are lacking. Alternatively, heparin could be bound to fibrin glue for controlled release or ECs to fibronectin to improve overall patency rates.[28]

Polypropylene [—(CH3—CH)—CH2)—]$_n$. Polypropylene is relatively inert, biostable with a tensile strength of 400 MPa, tensile modulus of 2.6 GPa, crystalline in nature, and is thermoplastic as well. Its hydrocarbon structure renders it insensitive to hydrolysis but is it still susceptible to oxidation, making the addition of antioxidants to it a necessity.[21] During the early 1990s, 4-mm polypropylene grafts were found to be patent in 81% as compared to 69% for Dacron® and 20% for PTFE at 16 months ($p < 0.05$).[29] This *in vivo* study showed grafts with an inner myofibroblast and macrophage layer with a confluent luminal endothelial cell lining. Early results using composite polymers of polyglactin and polydioxanone (PDS)

with polypropylene showed a tendency for these copolymers to elongate[30] though patency rates were between 86% and 90% at 1 year. Polypropylene was used as the nonresorbable component because it does not inhibit arterial regeneration.[31]

Polyurethanes (PU) [—NH—O═C—O—R—]$_n$. Compliant biomaterials have been recognized as a necessity for biomimetic vascular prostheses. PUs contains urethane —NH(CO)O— groups formed from the reaction of isocyanates with an alcohol group. Depending on the composition of its hard and soft segments, tensile strength ranges between 20 MPa and 90 MPa with a tensile modulus of 5 MPa to 1150 MPa. PU spawns a new generation of radially compliant polymers which should reduce the incidence of intimal hyperplasia (IH) at the anastomotic sites.[32] The hard segments account for stiffness and rigidity while flexibility is provided by the soft segments which can be varied. These characteristics, in addition to its biocompatibility, have seen it being used as a biomaterial. A disadvantage of first generation polyester PU is *in vivo* degradation. In fact, a clinical trial with PU was aborted midway due to graft occlusion.[33] A chemical analysis of these grafts revealed the spontaneous degradation of the polyol soft segment. Ester modifications of PU on the other hand, degrade with oxidative stresses. Polyetherurethaneurea (Vectra®) with pore sizes of 15 μm have been developed and clinical trials have shown them to be patent at 12 months postimplantation. However, it tends to elongate with increased intimal hyperplasia compared to ePTFE.

The next generations of PU are carbonate-based with no ester linkages and should theoretically be stabler. Preliminary *in vivo* results indicate that endothelialization occurred faster and the neointima formation was lesser compared to ePTFE at 6 months.[34] The Corvita® graft (an inner porous polycarbonate PU layer and gelatin–heparin outer surface) showed no changes in diameter at 1 year postimplantation.[35] We have tested poly(carbonate-urea)urethane (Cardiotech®) and found that it is resistant to hydrolytic and oxidative stresses.[15] When implanted into the aorto–iliac segments of four dogs, these prostheses remained patent even after 36 months.[36] This promising biomaterial is now under a clinical trial. Other researchers have shown that polyetherurethane grafts of 28 μm pore sizes (Pulse-Tec®) have excellent radial compliance with concordant increase in hydrogen bonding and homogeneity. However, it is structurally weaker than similar PU grafts.[37] Alternatively, PU could be hydroxylated and bound to hirudin to enhance antithrombogenicity. Our group is currently experimenting on further modifications of PU. Overall, the compliance of PU would depend not only on the initial compliance of the graft but the extent to which tissue incorporates in and around it.

However, PUs composed of diisocyanates like toluene diisocyanate (TDI) degrade into toxic substances. This has been avoided by substituting them with aliphatic diisocyanates like lysine diisocyanate (LDI).[38] PUs have also been known to have a carcinogenic effect on laboratory animals as its degradation products like 2,4-toluene diamine causes hepatocellular carcinoma. Modified PUs like poly(esterurethane)ureas though more flexible and stronger still have drawbacks such as poor cell adhesion and oxidative biodegradation.[39] Long-term results with PEUUs indicate that it degrades with oxidative stress, making it noncompliant. Subsequent modifications like carbonate-based PU may overcome this issue.[40]

Biodegradable Polymers. Polymers that degrade in the human body may be classed into biodegradable and bioabsorbable. Biodegradation refers to the enzymatic degradation of polymers *in vivo* while bioabsorbability means that these polymers degrade with other chemicals in the human body. These biomaterials are collectively defined as polymers which degrade into smaller fragments due chemicals in the human body.

The rate of degradation of these biodegradable polymers depends on pore sizes. Matsuda and colleagues reported that pores between 18 μ and 50 μm in diameter are optimal for endothelialization.[41] Smaller pores would elicit an inflammatory reaction[42] while those too large may allow excessive seepage of blood.[43] Increasing pore sizes and porosities also improves radial compliance of vessels.[131] Hence, accurate titration of these parameters is vital for long-term vascular grafts. Studies have shown that in vascular implants with smooth muscle cells arranged in a circular manner, no graft dilatation occurred. This suggests that organization of cells within the construct is important for long-term function of biohybrid prostheses.[44]

Single component: This group of polymers would serve as temporary scaffolds for vessels before being replaced by ingrowing tissue. This would be balanced by the rate of degradation of the polymer. The current generations of polymers used are polylactic acid (PLA), polyglycolic acid (PGA), polyhydroxyalkanoate (PHA), and polydioxanone (PDS). PGA is a crystalline, hydrophilic polymer that degrades in 2 weeks. PLA is a methylated version of PGA which is less hydrophilic and hence lasts longer within the body. It exists as stereoisomers of which the L-form is commonly used.

Multiple components: Synthetic graft function can be improved by synergizing these homogenous polymers into a single graft. Polyglactin or Vicryl (PG910) is a copolymer of polyglycolic and polylactic acid. As Vicryl degrades within 2 months, it has been fused with slower degrading polymers to slow down absorption and allow sufficient time for arterial regeneration. Researchers have developed composite polymeric grafts of Vicryl (PG910) and PDS (74%:26%) capable of 100% patency rates at 1 year in the rabbit aorta model.[45] Similarly, PDS–polypropylene grafts had an 86% 1-year patency rate in canine aorto–iliac vessels.[31] This strategy prevented aneurysmal dilatation commonly associated with biodegradable polymers.

Poly (ethylene glycol)/poly (lactic acid) (PELA) is another type of biodegradable copolymer. In a study comparing

6-mm PELA-coated polyurethane (PU) and ePTFE grafts in a carotid artery model it was found that the PELA–PU grafts were patent and pulsatile at 3 months with a uniform intimal lining by this time.[46] Because PELA is a low modulus polymer, it could be extruded into porous grafts with sufficient hydrophilicity to enhance neoarterial regeneration within the scaffold. The radial compliance of PELA grafts decreased by from 2.5%/100 mmHg to 2.0%/100 mmHg over 3 months. While the increased compliance may be attributed to PU, this drop was attributed to tissue ingrowth but may also be possible to degradation of PELA. Compliance values were still greater than the ePTFE group (1.6%/100 mmHg) and closer to native vessel compliance than ePTFE.

Polyhydroxy–butyrate (PHB) is a polyester derived from bacterial cytoplasm. It is crystalline, hydrophobic, brittle, and resistant to aneurysmal dilatation. PDS is more commonly used as osseous scaffolds. This strong polymer has been shown to resist high pressures without bursting. Researchers found that grafts composed entirely of PLA tended to dilate early in ovine pulmonary arteries.[47] This behavior was prevented by coating the PLA graft with a nonporous PHB sheath that is more resistant to degradation and hence, aneurysm formation.[48] This finding was seconded in another study which showed that PLA grafts lost 80% of its original radial compliance after 3 months. Alternatively, hybrid polymers also exhibited higher bursting strengths and patency rates as well.[45,49]

Acellular Vascular Grafts. The use of acellular, xenogeneic vascular grafts is an emerging concept in the construction of vascular prostheses. The critical component is the cell extraction stage when all cells need to be removed whilst the biological scaffold should be kept intact.[50] Bursting strength of these vessels improved following treatment and by 18 weeks postimplantation, the graft was endothelialized sufficiently with good mechanical properties as well.[51] Collagen from porcine intestinal submucosa and bovine type I collagen have already been used in canine models. Eighty-eight percent of these grafts remained patent at 9 weeks postimplantation with no evidence of aneurysmal dilatation, cellular inflammation, or clot formation with maximal cellular infiltration at the midportion of the graft.[52]

Prosthetic Graft Seeding. The biocompatibility and patency rates of prostheses may be further improved by the construction of biohybrid constructs; for instance, coating vascular prostheses with endothelial or smooth muscle cells. One of the technological limitations of this is the low seeding density of these cells to current biomaterials, particularly when exposed to arterial flow. Numerous studies have now shown that cell adherence may be improved further using endothelial specific adhesion proteins such as fibrin–gelatin[53] and granulocyte-stimulating factor (G-CSF).[54] Of these, fibronectin coating is the most successful but has been hampered by the loss of its coating at high flow rates. More recently, covalently binding short peptide sequences representing the functional ligand for fibronectin; Arg-Gly-Asp (RGD) sequence[55] onto the prosthetic lumen has been shown to improve cell adhesion properties.[56] This is the functional ligand for fibronectin and has been shown to promote cell adhesion and attachment. Newer studies have shown the existence of similar fibronectin ligands like the C5 domain.[57]

Nonligand based techniques such as carbon deposition, photo discharge, chemical vapor deposition,[58] and plasma discharge technology have been used to deposit reactive groups onto prostheses or to modulate surface protein adsorption but this has so far proved to be nonspecific. Recently, lumina modified with polyelectrolyte multilayers have been shown to improve cell-interface adhesion, particularly on hydrophobic surfaces.[59] Alternatively, physical methods have also been used to develop surface pseudointima by engineering both surface porosity and nanotexture[60] in order to promote tissue ingrowths into the graft or by electrostatically seeding ECs onto the lumen. A limitation of this is that the neointima formed does not physiologically mimic natural endothelium. This limits the integration of the implanted device with the host by this method.

In Vivo and Clinical Applications

Peripheral Bypass Graft. Dacron® has been used as a large-diameter graft (7–9 mm) since 1957 and studies have shown 5-year patency rates of 93% in aortic bypass grafts but this decreases significantly with smaller vessel diameters (<7 mm). Patency can be improved by coating its lumen with heparin and its outer surface with collagen. Patency rates of femoro–popliteal bypass grafts at 3 years with heparin-bonded Dacron® is 55% as compared to 43% in the untreated version.[61] Therefore, ePTFE has been used as an alternative for smaller-diameter grafts (<7 mm). A 10-year retrospective study in Japan on 564 Dacron® grafts showed no statistically significant difference between Dacron® and ePTFE in infrainguinal bypass grafts. Other studies have showed similar results and suggests that the current preference for ePTFE grafts in femoro–popliteal bypass grafts is not evidence based.[3]

ePTFE bypass grafts are more commonly used than Dacron® in femoro–popliteal bypass procedures. In one study involving 75 infrainguinal bypasses, postoperative results were compared between autologous vein and ePTFE grafts. There was no statistical difference between these groups with 4-year primary patency rates being 82% for veins and 80% for ePTFE grafts.[62] This was verified by another study which showed similar patency rates but no statistical difference ($p = 0.36$) between ePTFE grafts with Miller cuffs and Distiflo® grafts.[63] Stretch ePTFE grafts have been found to be significantly superior ($p < 0.05$) to standard PTFE (83% vs 60%) for femoro–popliteal bypasses but not so for infrapopliteal bypass grafts (59% vs 53%).[64] Most clinical trials indicate that both Dacron® and ePTFE are acceptable as femoro–popliteal bypass grafts and some suggest that graft biomaterial in high flow sates as in above-knee vessels reconstructions.[65] However, in lower pressure, smaller diameter infrapopliteal vessels prostheses have not been as success-

ful[66] and it has been hypothesized that in this environment, material characteristics are important.

Results are not as promising for infrapopliteal vessels. A prospective randomized clinical trial using ePTFE showed a 12% primary patency at 4 years for infrapopliteal prosthetic bypasses. This has been verified by similar studies showing patency rates of 23% to 25% at 5 years.[62,67] In 211 tibial artery ePTFE bypass grafts, patency rates were 37% and 23% at 2 and 5 years postsurgery. It was found that distally occluded vessels and poor run-off decreased chances of success. Secondary patency rates were lower in these grafts.[67] A recent trial in 80 tibial bypass ePTFE grafts with the addition of venous cuffs revealed a 4-year primary patency rate of 63%.[68] It has been postulated that venous cuffs[69,70] can decrease intimal hyperplasia at sites of anastomoses[71] but more randomized, controlled trials comparing this with standard PTFE need to be performed.[72] In a prospective study involving 704 revascularization procedures where autologous vein grafts were compared against ePTFE grafts, there was a statistically significant difference ($p < 0.05$) between 3-year patency rates: 73% for vein grafts versus 55% for vascular prostheses.[73]

In a randomized clinical trial conducted over 9 years using endothelialized 6-mm ePTFE grafts, 5-year patency rates in infrapopliteal grafts was 76%.[74] This provides strong evidence for coating grafts with autologous endothelial cells. Other surgeons have utilized autologous vein grafts which were prosthetically reinforced.[75] Matsuda and colleagues coated ECs and smooth muscle cell (SMC) collagen matrices with elastomeric polyurethane films to confer increased radial compliance.[76] They found good patency rates which were also dependent on its porosity. These results still need to be confirmed as the numbers were small. Alternatively, impregnating ePTFE grafts with carbon has been hypothesized to decrease thrombogenicity. In a study comparing 81 carbonized ePTFE grafts to standard ones, primary patencies were 45% in the former compared to 35% in the latter.[77]

Polyurethane bypass grafts for lower limb revascularization procedures are currently under clinical trial.[78] Preliminary *in vivo* work suggests that they are resistant to degradation and have similar compliance to native arteries as shown in Figure 1. Manufacturing them by using coaxial technology to vary the porosities throughout the graft could potentially provide surgeons with designer vessels for particular flow and pressure conditions.[79] PU grafts are less thrombogenic than either ePTFE or Dacron® but efforts are still on to improve on this. In the canine femoral artery model, endothelialized polyurethane grafts remained patent 4 weeks after implantation with little or no thrombus formation.[80] Immobilizing dipyradimole onto 5-mm porous polyurethane grafts was found to inhibit platelet adhesion/aggregation and minimize smooth muscle cell (SMC) proliferation with *in vivo* experiments showing a 38% patency rate.[81] RGD peptide sequences have been shown to inhibit fibrinogen binding to activated platelets and promote EC and smooth muscle cell attachment. This confers antithrombogenicity to the graft.[82]

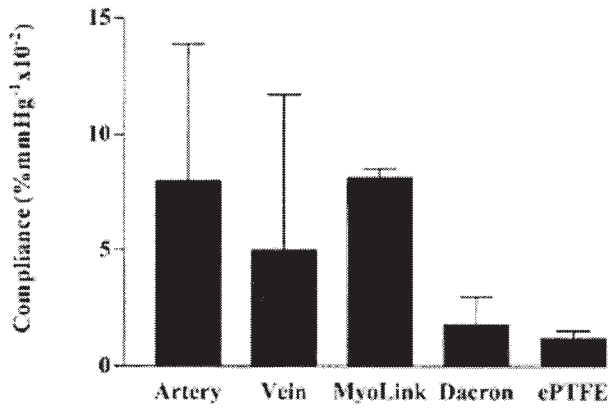

Figure 1. Radial compliance values of arteries, veins, and artificial vascular prostheses.[130] (Reprinted from Cardiovascular Surgery, Volume 10, No. 1, Tiwari, Salacinski, Seifalian, and Hamilton, New prostheses for use in bypass grafts with special emphasis on polyurethanes, pp 191–197, Copyright 2002, with permission from Elsevier.)

Carotid Artery Bypass Grafts. In situations with excessive atherosclerotic changes within these vessels, recurrent carotid stenosis particularly following irradiation, prosthetic bypass grafts are indicated. Currently, it accounts for less than 10% of carotid revascularization surgeries. Carotid artery bypass grafting with autologous vein grafts has been shown to have patency rates greater than 80% at 3 years postimplantation. However, up to 26% of these vein grafts stenose within a year of surgery.[83] In a study involving 110 of these procedures, 96.7% of these grafts were patent at 3 years and only 0.9% of them had stenosed.[84] Roddy and colleagues compared 6-mm ePTFE and autologous vein grafts at one year post–carotid bypass grafting. They found that 20% of autologous vein grafts underwent stenosis compared to 5% among the ePTFE grafts.[85] In an earlier study involving carotid–subclavian bypasses, 94% of ePTFE grafts were patent at 5 years compared to 58% for autologous veins ($p < 0.01$).[86] All these results suggest that ePTFE grafts are comparable if not better than autologous vein grafting. As such, prospective controlled trials with larger numbers and longer follow-up still need to be performed.

Experiments have been performed on sheep carotid arteries using porous 5-mm polyurethane vascular grafts with a 38% patency rate. This was due to the biodegradation of ester-based polyurethanes[81] due to hydrolysis. Polyurethane grafts made with tetrahydrofuran (THF) and dimethylformamide followed by coagulating it with hydrochloric acid formed microporous grafts with antithrombotic effects in canine carotid vessels.[87] Patency rates of these grafts may also be increased by binding heparin and hirudin onto their luminal surfaces.[88,89]

Coronary Artery Bypass Grafts. With the rise in the number of bypass surgeries, more patients are undergoing repeat coronary revascularization. Fifteen percent of these patients need alternative grafts like polymeric grafts.[90] Table I summarizes the current status of prosthetic bypass grafts.

TABLE I. Current Status of Prosthetic Bypass and Microvascular Graft

Authors	Vessels	Graft Type	Subjects	ID (mm)	Patency Rates	Outcome
Harris et al., 2002[9]	Superficial epigastric	PTFE	Rats	< 1	20% at 4 weeks	Vein grafts had 100% patency
Demiri et al., 1999[8]	Femoral	PTFE	Rats	1	25% at 4 weeks	Vein grafts had 100% patency
Hehrlein et al., 1984[91]	Coronary	ePTFE	Humans	3 to 4	59% at 1 year	Vein grafts had an 86% patency rate
Chard et al., 1987[92]	Coronary	PTFE	Humans	3 to 4	14% at 45 months	Sharp fall in patency rates after a year
Okoshi et al., 1993[93]	Aorta	Polyurethanes	Rats	1.5	76% at 3 months	Suitable substitutes for coronary bypass grafts
Seifalian et al., 2003[36]	Aorto–iliac	CPU	Dogs	5	100% at 3.5 yrs	Human trials under way
Shum-Tim et al., 1999[48]	Aorta	PHA–PGA	Sheep	7	100% at 21 weeks	Outer PHA ring prevented ↑ in diameter due to its slower degradation
Greisler et al., 1988[45]	Aorta	PG910–PDS	Rabbit	3 to 4	100% at 1 year	PDS resorbs after 6 months allowing time for arterial regeneration
Greisler et al., 1991[31]	Aorto–iliac	PDS–Polypropylene	Dogs	5	86% at 1 year	Partially resorbable graft with polypropylene being permanent
Meinhart et al., 2001[6]	Infrapopliteal	EC-seeded ePTFE	Humans	6 to 7	73.8% at 7 years	Comparable to vein grafts
Lambert et al., 1999[94]	Infrapopliteal	Heparin-coated Dacron®	Humans	6 to 7	58% at 2.5 years	Better results than plain Dacron®
Sala et al., 2003[62]	Infrapopliteal	PTFE	Humans	6 to 7	80% at 1 year	Need longer follow-up analysis
Lu et al., 2002[64]	Infrapopliteal	Stretch PTFE	Humans	6 to 7	59% at 2 years	No improvement over standard PTFE
Schweiger et al., 1993[67]	Infrapopliteal	PTFE	Humans	6 to 7	23% at 5 years	Dismal longer term results compared to vein grafts.
Neville et al., 2001[68]	Infrapopliteal	PTFE with venous cuffs	Humans	6 to 7	63% at 4 years	A vein cuff decreases compliance mismatch at anastomoses site
Bacourt et al., 1997[77]	Infrapopliteal	Carbonized PTFE	Humans	6 to 7	45% at 2 years	35% of noncarbonized PTFE were patent
Deutsch et al., 1999[74]	Infrapopliteal	EC-coated PTFE	Humans	6 to 7	76% at 5 years	ECs prevent long-term thrombogenicity
Devine et al., 2001[95]	Femoro–popliteal	Heparin-bonded Dacron	Humans	7 to 9	55% at 3.5 years	This trial shows better results than PTFE
Dereume et al., 1993[96]	Femoro–popliteal	Polyurethanes + polyesters	Humans	7 to 9	59% at 6 months	Longer follow up required.
Ziomek et al., 1986[86]	Carotid	PTFE	Humans	7 to 9	94% at 5 years	Statistically superior to vein grafts ($p < 0.01$)
Izhar et al., 2001[46]	Carotid	PELA	Dogs	6	100% at 6 weeks	Limited interpretation due to short-term study
Camiade et al., 2003[84]	Carotid	PTFE	Humans	7 to 9	96.7% at 3 years	Far superior to vein graft and with less stenoses
Garcia-Pajares et al., 2003[97]	Arterio–venous fistulas	Tapered PTFE	Humans	6	39% at 5 years	Superior to standard PTFE, caused a steal phenomenon in diabetics.
Allen et al., 1996[98]	Arterio–venous fistulas	Polyurethanes	Humans	—	45% at 1 years	Triple-layered graft ensures quick resealing after cannulation
Glickman et al., 2002[99]	Arterio–venous fistulas	Polyurethanes	Humans	—	72% at 3 years	Promising alternative to venous grafts

Abbreviations: PTFE, polytetrafluoroethylene; ePTFE, expanded polytetrafluoroethylene; CPU, compliant polyurethane; ID, internal diameter; PHA, polyhydroxyalkanoates; PGA, polyglycolic acid; PG910, polyglactin; PDS, polydioxanone; PELA, polyethylene glycol-polylactic acid; ↑, increased.

However, artificial coronary bypass grafts are rarely in use because they have far lower patency rates compared to autologous vein or artery grafts. These grafts are only used if vein grafts are not available or contraindicated.[100] This practice is supported by a study which compared ePTFE and saphenous vein grafts. At 1 year follow up, 86% of the vein grafts were patent while only 59% of ePTFE grafts were patent.[91] Other evidence for artificial coronary artery bypass grafts (CABG) is anecdotal. Dacron®, for instance, has been utilized as a polymeric graft (3–4 mm) in a few case reports with patent vessels at 17 months.[101,102] However, no longer term results are available. Chard and colleagues found that ePTFE coronary bypass grafts were 86% patent at 1 week, 64% at 12 months, 32% at 24 months, 21% at 36 months, and 14% at 45 months.[92] This has been confirmed by a separate group who found that only 59% of these grafts were patent at 1 year.[103] Patency in synthetic coronary vessels is maintained by high blood flow rate because of a venturi resistorlike system.[104] Further clinical applications have been limited by the small number of cases using synthetic coronary bypass grafts.

As such, researchers have constructed more compliant polymers like PU. A heterogenous polymeric graft composed of polyetherurethaneurea with a silicone-modified lumen underwent *in vivo* tests in sheep but their patency rates were not reported. A prospective, randomized, controlled clinical trial is now under way.[90] In a rat aorta model, 1.5 mm diameter electrosprayed polyurethane–polydimethylsiloxane grafts (Cardiothane 51) were implanted. At 3 months postimplantation, 8% of the low porosity grafts (hydraulic permeability 2.7 mL/min/cm^2) were occluded while those with medium porosity (hydraulic permeability 39 $\pm$ 8 mL/min/cm^2) had a 76% patency rate with no intimal hyperplasia and complete endothelialization, which emphasizes the importance of pore sizes and porosity for long-term graft patency.[93] These results will have to be repeated in humans prior to clinical use.[78]

Compliance mismatch aside, thrombogenicity is the major cause of artificial coronary graft failure. This can be reduced by either coating these grafts with endothelial cells (ECs) and RGD–peptide sequences[105] or ensuring high blood flow rates within the graft. In one trial, autologous ECs sodded onto Permaflow grafts were implanted into nine canine left circumflex coronary arteries. At 3 weeks postimplantation, these grafts were patent with no thrombus formation.[106] No statistical comparison was made with nonendothelialized Permaflow grafts. This stresses the importance of endothelialization in lower flow conditions. Laube and coworkers found that 4-mm internal diameter, two-stage EC-seeded ePTFE coronary bypass grafts had a 90% patency rate at 28 months.[107] The same group have developed a twin-axes rotating bioreactor with a seeding efficiency of 80% to 85% in 3 to 4 h.[108] This would improve seeding technology and enable surgeons to seed grafts at short notice as in emergency procedures.[78]

Hemodialysis Access Devices. With rapid advances in hemodialysis technology, increasing numbers of patients are in need of long-term access devices. Apart from maintaining flow, they would also need to seal themselves after cannulation and minimize thrombus propagation following access. Currently, arterio–venous fistulas remain the cornerstone for this modality while prosthetic substitutes are not used commonly.[109] Of the artificial grafts used, ePTFE is the most commonly used. Even so, a recent multicentered, randomized controlled clinical trial on standard 6-mm access grafts showed a 43% 1-year patency rate with a 27% rate of stenosis.[110] The U.S. renal data system dialysis morbidity and mortality study among 2247 patients comparing prosthetic grafts against arterio–venous fistulas found that artificial substitutes had a 41% increased risk of primary failure ($p < 0.01$).[111] In a similar study with 84 patients, the primary patency rate of PTFE grafts was 37% as compared to 68% in bovine vein grafts. These results indicate that biological grafts are superior to ePTFE ones.[112]

ePTFE grafts have been modified in order to improve its patency. A newer design involved tapering 6-mm grafts. A study of 507 patients revealed a primary patency rate of 77% at 1 year compared to 72% for standard 6-mm grafts and 39% versus 19% at 5 years. This was statistically significant ($p < 0.001$) except in the diabetic subpopulation where a steal phenomenon was observed.[97] Problems with ePTFE include thromboses following use and poor resealing qualities after puncture. Endothelializing ePTFE grafts may improve long-term patency rates.[113] The addition of cuffs to the ePTFE–vein anastomoses also improves inflow into the graft patency but results so far have been mixed.[114,115]

Polyurethanes[116] have recently been used as an alternative due to its ability to self-seal at the puncture site. A 4-year follow-up study revealed a primary patency rate of 73% at 1 year and a secondary patency rate of 72% at 3 years. These grafts were accessed for hemodialysis within a median time of 19 days after surgery due to the puncture-site self-sealing property of the polymer unlike ePTFE.[99] This characteristic has prompted manufacturers to seal Dacron® grafts with ionic polyurethanes.[117] Most graft losses (61.5%) were due to infection.[118] Another prospective medium-term study involving 58 cases of polyurethane grafts found a slightly lower primary patency rate (60.7%).[119] Kiyama and co-workers conducted a randomized controlled clinical trial on ePTFE and polyurethanes. They found no statistical difference between the two after 4-year follow up.[119] Higher infection rates remain the principal problem with the use of prosthetic grafts.[120]

Microvessels. This is a term reserved for vessels with internal diameters of 1 mm or less. As described, current grafts like ePTFE and Dacron® function well in high pressure, high flow conditions as in the aorta but their patency has been shown to bear an inverse relationship to the internal diameter of the grafts.[7,10,11] *In vivo* studies have shown a 20% to 25% patency rate with ePTFE microvessels while all vein grafts in similar settings remained patent.[8,9] In this field, autologous vein grafts still remain the gold standard for microvascular repairs as they are both compliant and biocom-

patible. However, donor-site morbidity and the need for an unnecessary procedure limit its potential.

Microvascular grafts can be constructed by using (a) biopolymers, (b) luminal coating with antithrombogens or endothelial cells, and (c) constructing completely biological grafts *in vitro* prior to re-implantation.[121] In microvascular grafts, the first two options seem more probable in the near future. By modifying its physical or chemical characteristics using irradiation and antiplatelet/anticoagulant/growth factor incorporation,[122,123] one can emulate some functions of Ecs.[124] The ideal situation would preferably be EC-lining of these microvessels.[125,126]

An *in vivo* experiment using a 1-mm interpositional ePTFE vascular graft in rat aortas coated with extracellular matrix (ECM) and incorporated with keratinocyte cell lines formed an endothelialized vascularized graft 5 weeks after implantation into the body.[127] These results need to be replicated in humans particularly in those with peripheral vascular disease.[78]

Synthetic materials currently being experimented upon in the construction of microvessels are polyglycolic acid (PGA), polylactic acid (PLA), polyhydroxyalkenoate (PHA), and elastic polymers like poly-(GVGVP). Van der Lei and colleagues synthesized a PU:poly-L-lactide (PLLA) graft in the ratio of 95:5 to function as a temporary arterial scaffold. In rat aortic models, these 1.5-mm PU–PLLA grafts were patent at 1 year but 63% of these implants showed signs of dilatation.[44]

CONCLUSION

Prosthetic materials have been used for many years. They are most commonly used in high pressure, high flow conditions like the aorta and femoral arteries. However, they have not been as successful in other regions like carotid and heart bypass surgeries. This has prompted a new generation of polymers like polyurethanes to be used. These polymers are more compliant and reseal after use. Though some are now under trial, no long-term results are available as yet. Based on records so far, it is postulated that the type of polymer does not matter in high flow conditions so long as they can withstand the pressures. The principle that the choice of vascular prostheses varies with lower diameters is inaccurate. Clinical studies so far have suggested that ePTFE and polyurethane grafts in high flow vessels like carotid arteries and arterio–venous fistulas are not more suitable than autologous vein grafts which have the propensity to undergo accelerated atherosclerosis in this environment. Therefore, flow rate and shear stress rather than internal diameter of the vessel should be the determining factor in the choice of current prostheses. As for now, ePTFE and Dacron® are more suited to high flow conditions while materials such as polyurethanes look promising in lower flow conditions and as hemodialysis access devices. As far as microvessels and the construction of an artificial capillary bed are concerned, it would be premature to embark on them without first solving the problem of thrombogenicity and graft occlusion in lower flow states.

Future Perspectives

Poly(GVGVP) is a prototype protein-based polymer crosslinked by γ-irradiation. Preliminary reports suggest that it has similar elasticity to arteries with a controllable rate of degradation.[128] Manufactured using DNA recombinant technology, it contains core repeating sequences of elastin. The rate of degradation can be regulated by the addition of asparagine and glutamine into the polymer chain. The breakdown products are nontoxic carboxylates. The next generation of protein polymers will see the emergence of bioelastic materials such as poly (N-isopropylacrylamide) which convert one form of energy like heat or hydration into mechanical energy.[129] Apart from regulating the diameters and hence pressure heads within vessels, these biomaterials may also modulate cell patterning of biohybrid prostheses.[128] This process is called *mechanotransduction*.

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