Mechanisms of Vascular Disease:

A Reference Book for Vascular Specialists

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Edited by Robert Fitridge and Matthew Thompson

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Abbreviation List

a1-PI	a1-protease inhibitor
5-HT	5-Hydroxytryptamine/Serotonin
AAA	Abdominal aortic aneurysm
AAS	Acute aortic syndrome
AAV	Adeno-associated viruses
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ACS	Abdominal compartment syndrome
ACTH	Adrenocorticotropic hormone
ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
ADP	Adenosine diphosphate
AIDS	Acquired immune deficiency syndrome
ALI	Acute lung injury
AMP	Adenosine monophosphate
AMPA	α-amino-3 hydroxy-5-methylisoxazole
ANA	Anti-nuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibody
AOD	Aortic occlusive disease
AP1	Activated protein 1
APC	Activated protein C
APC	Antigen presenting cell
APLAS	Antiphospholipid antibody syndrome
ApoAI	Apolipoprotein AI
ApoE	Apolipoprotein E
APS	Antiphospholipid antibody syndrome
APTT	Activated partial thromboplastin time

ARDS	Acute respiratory distress syndrome
AT	Antithrombin
ATP	Adenosine triphosphate
AVP	Ambulatory venous thrombosis
β2-GPI	β2-glycoprotein Ib
bFGF	Basic fibroblast growth factor
BKCa	Large conductance calcium activated potassium channel
BMPs	Bone morphogenetic proteins
BMS	Bare metal stent
CAD	Coronary artery disease
CaM	Calmodulin
CAM	Cell adhesion molecule
cAMP	Cyclic adenosine monophosphate
CCK	Cholecystokinin
cGMP	Cyclic guanine monophosphate
CD	Cluster of differentiation
CD40L	Cluster of differentiation 40 ligand
CEA	Carotid endarterectomy
CETP	Cholesteryl ester transfer protein
CFD	Computational fluid dynamics
CG	Cationized gelatin
CGRP	Calcitonic gene regulated peptide
CHD	Coronary heart disease
CI	Confidence interval
CIMT	Carotid intimal-media thickness
c-JNK	c-Jun N-terminal kinase
CK-MB	Creatinine kinase (Myocardial specific)
CNCP	Chronic noncancer pain
cNOS	Constitutive nitric oxygen synthase enzyme
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CROW	Charcot restraint orthotic walker
CRRT	Continuous renal replacement therapy

CRP	C-reactive protein
CRPS	Complex regional pain syndromes
CT	Computational tomography
CTA	Computed tomographic angiography
CTD	Connective tissue disorders
CTGF	Connective tissue growth factor
CYP	Cytochrome P450
CVD	Cardiovascular disease
CVI	Chronic venous insufficiency
DAG	Diacylglycerol
DES	Drug-eluting stent
DRG	Dorsal root ganglion
DNA	Deoxyribonucleic acid
DSA	Digital subtraction arteriography
DTS	Dense tubular system
DVT	Deep vein thrombosis
EC	Endothelial cell
ECM	Extracellular matrix
EDCF	Endothelium-derived contracting factor
EDH	Endothelium-dependent hyperpolarisation
EDS	Ehlers-Danlos syndrome
EET	Epoxyeicosatrienoic acids
ELAM-1	Endothelial-leukocyte adhesion molecule-1
ELG	Endoluminal grafts
ELISA	Enzyme linked immunosorbent assay
E_K	Equilibrium potential
E_M	Membrane potential
eNOS	Endothelial nitric oxide synthase enzyme
EPC	Endothelial progenitor cells
EPCR	Endothelial protein C receptor
ePTFE	Expanded polytetrafluoroethylene
ERK	Extracellular signal-regulated kinase
ESR	Erythrocyte sedimentation rate

ET	Essential thrombocytosis
ET-1	Endothelin 1
EVAR	Endovascular aortic aneurysm repair
EVLA	Endovenous LASER ablation
FDA	Food and drug administration
FDPs	Fibrin degradation products (soluble)
FGF	Fibroblast growth factor
FGF-2	Fibroblast growth factor 2
FMN	Flavin mononucleotide
FVL	Factor V Leiden
GABA	Gamma-aminobutyric acid
GABA B	Gamma-aminobutyric acid subtype B
G-CSF	Granulocyte colony stimulating factor
GMCSF	Granulocyte-macrophage colony stimulating factor
GP	Glycoprotein
GPCR	G-protein coupled receptor
GSV	Great saphenous vein
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
HIF	Hypoxia inducible factor
HIT	Heparin induced thrombocytopenia
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMG Co-A	Hydroxymethylglutaryl coenzyme-A
HMW	High molecular weight
HPETE	Hydroperoxyeicosatetraenoic acid
HETE	Hydroxyeicosatetraenoic acids
HR	Hazard ratio
hsCRP	High-sensitive C-reactive protein
HSP	Heat shock protein
HUV	Human umbilical vein
IAH	Intra-abdominal hypertension

IAP	Intra-abdominal pressure
IAPP	Intra-abdominal perfusion pressure
ICAM-1	Inter-cellular adhesion molecule-1
ICAM-2	Inter-cellular adhesion molecule-2
ICP	Intra-compartmental pressure
ICU	Intensive care unit
IFN	Interferon
IGF-1	Insulin-like growth factor-1
IHD	Ischemic heart disease
IL	Interleukin
IL-1	Interleukin-1
IL-1α	Interleukin-1 alpha
IL1-β	Interleukin-1 beta
IL-6	Interleukin-6
IL-8	Interleukin-8
ILT	Intraluminal thrombus
IKCa	Intermediate conductance calcium-activated potassium channels
IMH	Intramural haematoma
IMP	Inosine monophosphate
iNOS	Inducible nitric oxide synthase enzyme
IP(3)	1,4,5-inositol triphosphate
IRI	Ischemia reperfusion injury
IVIG	Intravenous pooled immunoglobulin
IVUS	Intravascular ultrasound
KGF	Keratinocyte growth factor
KGF-2	Keratinocyte growth factor-2
LAP	Latency associated peptide
LCS	Limb compartment syndrome
LDL	Low density lipoprotein
LDS	Loeys-Dietz syndrome
LLC	Large latent complex
LEC	Lymphatic endothelial cells

LFA-1	Lymphocyte function-associated antigen-1
LO	Lipoxygenase
LOX	Lysyl oxidase
LOPS	Loss of protective sensation
LPA	Lysophosphatidic acid
LPS	Lipopolysaccharide
LTA	Lipoteichoic acid
LTGFBP	Latent TGF binding protein
MAC-1	Macrophage-1 antigen
MAPK	Mitogen activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
M-CSF	Macrophage-colony stimulating factor
MFS	Marfan syndrome
MHC	Major histocompatibility
MI	Myocardial infarction
MIP-1	Macrophage inflammatory protein-1
MLC_{20}	Myosin light $chain_{20}$
MLCK	Myosin light chain kinase
MLCP	Myosin light chain phosphatase
MMP	Matrix metalloproteinase
MODS	Multiple organ dysfunction syndrome
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MRSA	Methicillin resistant *Staphylococcus aureus*
MRSE	Methicillin resistant *Staphylococcus epidermidis*
MRTA	Magnetic resonance tomographic angiography
MTHFR	Methylenetetrahydrofolate reductase
MT-MMP	Membrane-type MMP
MVPS	Mitral valve prolapse syndrome
NADPH	Nicotinamide adenine dinucleotide phosphate
NGF	Nerve growth factor

NFκB	Nuclear factor kappa B
NiTi	Nitinol
NJP	Non-junctional perforators
NMDA	N-methyl-D-aspartate
NNH	Number needed to harm
NNT	Number needed to treat
NO	Nitric oxide
NOS	Nitric oxide synthase enzyme
NSAID	Non-steroidal anti-inflammatory drug
NV	Neovascularisation
OCP	Oestrogen/progesterone contraceptive pill
OPN	Osteopontin
OPG	Osteoprotegerin
OR	Odds ratio
OxLDL	Oxidised low density lipoprotein
PAD	Peripheral arterial disease
PAF	Platelet activating factor
PAI	Plasminogen activator inhibitor
PAI-1	Plasminogen activator inhibitor-1
PAR	Protease activated receptor
PAR-1	Protease activated receptor-1
PAR-4	Protease activated receptor-4
PAU	Penetrating aortic ulcer
PC	Protein C
PCA	Poly (carbonate-urea) urethane
PCI	Percutaneous coronary intervention (angioplasty)
PCWP	Pulmonary capillary wedge pressure
PDGF	Platelet-derived growth factor
PDGFβ	Platelet-derived growth factor-β
PDS	Polydioxanone
PECAM-1	Platelet-endothelial cell adhesion molecule-1
PEDF	Pigment epithelium-derived factor
PES	Paclitaxel-eluting stent

PET	Positron emission tomography
PF4	Platelet factor 4
PGI_2	Prostacyclin
PGG_2	Prostaglandin G_2
PGH_2	Prostaglandin H_2
$PGEI_2/PGI_2$	Prostaglandin I_2
PGN	Peptidoglycan
PHN	Postherpetic neuropathy
PHZ	Para-anastomotic hyper-compliant zone
PI3K	Phosphatidylinositol 3-kinase
PIP2	Phosphatidylinositol 4,5-bisphosphate
PLC	Phospholipase C
PLOD	Procollagen lysyl hydroxylase
PMCA	Plasma membrane Ca^{2+} APTases
PMN	Polymorphonuclear leukocyte
POSS	Polyhedral oligomeric silsesquioxanes
PPAR	Peroxisomal proliferation activating receptor
PPI	Proton pump inhibitor
PRV	Polycythaemia rubra vera
PS	Protein S
PSGL-1	P-selectin glycoprotein ligand-1
PT	Prothombin time
PTCA	Percutaneous coronary angioplasty
PTFE	Polytetrafluoroethylene
PTS	Post-thrombotic syndrome
PUFA	Polyunsaturated fatty acid
PVI	Primary valvular incompetence
rAAA	Ruptured AAA
Rac	Ras activated cell adhesion molecule
RANTES	Regulated upon activation, normal T cell expressed and secreted
RAS	Renin angiotensin system
RCT	Randomised controlled trial

RF	Rheumatoid factor
RFA	Radiofrequency ablation
rhAPC	Recombinant human activated protein C
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RR	Relative risk
RSD	Reflex sympathetic dystrophy
S1P	Sphingosine-1-phosphate
SAPK	Stress-activated protein kinase
SCF	Stem cell factor
SCS	Spinal cord stimulation
ScvO2	Superior vena cava venous oxygen saturation
SDF-1	Stromal-cell-derived factor-1
SERCA	Sarco/endoplasmic reticulum CaATPases
SEP	Serum elastin peptides
SES	Sirolimus-eluting stent
SEPS	Subfascial endoscopic perforator surgery
SFA	Superficial femoral artery
SFJ	Sapheno-femoral junction
SIRS	Systemic inflammatory response syndrome
SKCa	Small conductance calcium-activated potassium channels
SLE	Systemic lupus erythematosus
SMA	Smooth muscle alpha actin
SMC	Smooth muscle cell
SMP	Sympathetically maintained pain
SNARE	Soluble N-ethylmaleimide-sensitive factor activating protein receptors
SNP	Single nucleotide polymorphisms
SNRI	Serotonin/Noradrenaline reuptake inhibitors
SPJ	Sapheno-popliteal junction
SPP	Skin perfusion pressure
SR	Sarcoplasmic reticulum
SSRIs	Selective serotonin re-uptake inhibitors
SSV	Small saphenous vein

SVT	Superficial thrombophlebitis
STIM1	Stromal interacting molecule 1
TαCE	TNFα converting enzyme
TAAD	Thoracic aortic aneurysm disease
TAD	Thoracic aortic dissection
TAFI	Thrombin-activatable fibrinolysis inhibitor
Tc-99 MDP	Technetium-99 methylene diphosphonate
TCA	Tricyclic antidepressant
TCC	Total contact cast
TCR	T-cell receptor
TENS	Transcutaneous electrical nerve stimulation
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TGF	Transforming growth factor
TGF-α	Transforming growth factor-alpha
TGF-β	Transforming growth factor-beta
TGL	Triglycerides
Th	T helper
TIA	Transient ischemic attack
TIMP	Tissue inhibitors of metalloproteinase
TLR	Toll-like receptors
TNF	Tumour necrosis factor
TNF-α	Tumour necrosis factor-alpha
tPA	Tissue-type plasminogen activator
TRP	Transient receptor potential
TRPC	Transmembrane receptor potential canonical
TRPV1	Transmembrane receptor potential Vanilloid-type
TXA2	Thromboxane A2
uPA	Urokinase
UT	University of Texas
VCAM	Vascular cell adhesion molecule
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor

VEGF-R	Vascular endothelial growth factor receptor
VIP	Vasoactive intestinal peptide
VLA-1	Very late activating antigen-1
VOCC	Voltage operated calcium channels
VPT	Vibratory perception threshold
VSMC	Vascular smooth muscle cells
VTE	Venous thromboembolism
VV	Varicose veins
vWF	von Willebrand factor
XO	Xanthine oxidase

28 • Graft Materials Past and Future

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THE PATHOPHYSIOLOGY OF GRAFT HEALING

The mechanisms of graft healing are of central importance in understanding the successes and failures of current bypass grafts. The tissue response to implantation of a prosthetic graft is complex with many variable factors involved such as the material used, its construction, its porosity, and its length. Further important factors relate to the interaction between the graft and the host artery at the anastomotic areas. Until recently graft design focused on simple conduits for blood flow which were strong (resistant to pressure), biologically inert (resistant to biodegradation) and non-leaking. Each of the major causes of graft failure, luminal thrombogenicity, compliance mismatch and anastomotic intimal hyperplasia, have the potential to be modulated if their aetiology could be better understood. A further stimulus to study of this area is the still unresolved puzzle of man's inability to endothelialise a prosthetic graft beyond the immediate 2 cm or so from the anastomosis.

The peri-anastomotic area

Intimal or neointimal hyperplasia is a characteristic healing reaction to vascular injury.[1] In prosthetic grafting the injury typically involves the direct trauma of implantation, and subsequent exposure of the anastomotic areas to haemodynamic stress (compliance mismatch, turbulent flow and altered shear stress). This results in injury which is transmural with endothelial removal, variable disruption of the internal elastic lamina and medial smooth muscle cells (SMC).

The three phases of intimal hyperplasia will develop quite rapidly with the first being proliferation of medial smooth muscle cells as soon as 24 hours after injury and lasting up to 4 weeks. The second phase of SMC migration into the intima starts as early as 4 days after injury and continues for about a month. The final phase is of intimal expansion by the dual action of SMC migration and intimal proliferation by deposition of matrix proteins such as collagen, elastin and proteoglycan. This phase is complex and is mostly self-limiting but may continue unabated if certain factors are present, (refer to Chapter 7 for a more detailed discussion of intimal hyperplasia).

The endothelial cell plays a pivotal role via its mechanoreceptors which will be sensitive to changes in flow and shear stress. High shear stress, as found in laminar flow, promotes endothelial cell survival and quiescence,

and secretion of nitric oxide (NO). Low or changing shear stress direction (turbulent flow), promotes endothelial proliferation and apoptosis, shape change, and reduced secretion of NO. If by a process of flow change towards high shear stress and endothelialisation by regrowth in the injured area, a balance between stimulatory and inhibitory factors is achieved, the drive towards intimal hyperplasia will cease. If this balance is not achieved because of ongoing factors such as lack of endothelial cover, major haemodynamic disturbance such as severe compliance mismatch or turbulent flow with areas of stagnation and low shear stress, then the drive towards intimal hyperplasia will continue unabated leading to severe narrowing at the anastomosis and graft failure. In prosthetic grafting therefore several factors will persist which have the potential to promote intimal hyperplasia.

Healing of prosthetic grafts

Healing of prosthetic grafts takes place by two main mechanisms, capillary in-growth through the graft wall, and growth of endothelial cells along the luminal surface of the graft from each anastomosis.[2] Studies of prosthetic graft healing in various animal models used short lengths of graft, typically 10cm or less, which readily developed a full lining of endothelial cells. In man however, endothelialization is restricted to the first centimetre or two of the anastomotic regions with no evidence of healing having taken place beyond this area. This observation based on a few individual explants has led to the conviction that man is different from other species in his inability to endothelialise a graft.

The healing process at the anastomosis

Endothelialisation along the graft from the host artery occurs more aggressively in animals compared to man. A review of all animal studies found that the average graft length was 10 cm with 89% being only 5.5 cm. In all of these studies therefore it is very likely that anastomotic ingrowth was the sole avenue for endothelialization.[4]

The speed of trans-anastomotic endothelialization differs between species. Many of the models used young animals with rapid endothelialization but in low porosity grafts, endothelialization stopped 2 cm from the anastomosis. To set this species difference in context, trans-anastomotic endothelialization is 7–8 times more pronounced in any animal compared to man.[4] Two factors are foremost among the possible explanations. The first is the exclusive clinical use of low or zero porosity grafts. The second is the clinical reality of grafting performed in the sick and elderly in whom vascular cells are known from tissue culture studies to be less vigorous.

Graft porosity and permeability

The terms porosity and permeability are used interchangeably but have separate meanings. Permeability is the property of material to allow passage of substances through its interstices and classically is measured by the volume of water traversing a given area and pressure. Porosity refers to the spaces or pores that exist within the graft material, which depending on the material, may not traverse its entire thickness but end blindly. Zilla suggests that to facilitate transmural healing and endothelialization, graft spaces should be wide enough to allow ingrowth of a capillary tuft with accompanying fibroblasts or pericytes requiring minimum pore diameters of 60–80μm.[4,9] Currently available grafts, even those described as having high porosity fail in this regard. (Table 28.1)

Macrophages are the predominant inflammatory cells found in large numbers after implantation and later as part of

TABLE 28.1: The effects of graft porosity

Low porosity ePTFE grafts: **(<45μm of internodal distance)**

- Low porosity ePTFE grafts (<30mm) no difference in healing between animal and human.
- Within two weeks surface is covered with fibrin and platelet thrombus 15μm thick which over following months increases to between 80–300μm.
- Pannus persists for years and is actively thrombogenic.
- Ingrowth of connective tissue is limited to the outer graft wall.

High porosity ePTFE grafts: **(>45μm internodal distance)**

First layering similar to that of low porosity ePTFE grafts.

- In older animals very little ingrowth – luminal thrombus without any cellular component.
- Early and spontaneous endothelialization is found in young animals.
- These changes happen as early as 1–2 weeks.
  - patches of endothelial cells and capillary orifices found approximately 100-500μm apart which proceed to confluence.[3]
  - These endothelial cells lie over a layer of arterial smooth muscle cells probably derived from pericytes.
  - Stable neo-intima evenly distributed along the surface, as compared to the limited peri-anastomotic coverage in low porosity grafts.
  - This extensive endothelialization arises from cells reaching the luminal surface by transmural ingrowth.
  - In older primate models and also in the dog these developments take longer but only with sprouting capillaries reaching the outer third to one half of the graft wall.[4]

Low porosity Dacron grafts (woven)

- Immediately after implantation thin pannus of fibrin and platelets deposited on the surface.
- Thrombus compacts over time and in man stabilises after one year.[5]
- Endothelialization does not happen either in animals or in humans.
  - small islands of endothelial cells found after many years in explants in man.[6,7]
- Narrow graft interstices filled with fibrin.
- Foreign body giant cell reaction present.
- Variable spread of some capillaries and fibroblasts into interstitial spaces never breaks through the compacted fibrin of the inner lining.[8]

High porosity Dacron grafts (knitted)

- Initial pannus same as woven Dacron but develops to a thickness of 100–120μm increasing to 500μm by six months.
- In dogs and other animals this inner lining replaced with a confluent layer of smooth muscle cells resting directly on the graft surface, covered by endothelium.
- These come from anastomotic ingrowth but in longer grafts endothelialization in the midgraft region fails to occur despite partial ingrowth of capillary fibroblasts from the adventitia.

Prosthetic grafts made of PTFE and Dacron can show a degree of healing by endothelialization related to the porosity of the graft. High porosity PTFE grafts promised the best endothelialization but were not marketed because of concerns regarding long-term strength and the practical difficulties of haemorrhage and serum leakage through the graft wall at implantation.

a chronic inflammatory process. Soon after implantation, the interstices become filled with fibrin and matrix similar to any early wound. Macrophages form part of a normal inflammatory response releasing cytokines to stimulate migration and proliferation of fibroblasts and endothelial cells. In the later stages however, macrophages persisting in large number may have an adverse effect on healing and ingrowth. Consistently the outer portion of the graft has high concentrations of macrophages and foreign body giant cells while the deeper layers lose these cells, probably due to the dense impenetrable nature of the fibrinous pannus. Dacron seems to be more inflammatory than polytetrafluoroethylene (PTFE) where less giant cells develop.

PHYSICAL PROPERTIES OF PROSTHETIC MATERIALS

Arterial wall pulsatility is due to a combination of elastic and viscous components inherent in the structure of the artery which can therefore be described as being viscoelastic. Most commonly this property is measured as compliance, defined as the ratio of change in diameter over change in blood pressure (percentage/mmHg $\times 10^{-2}$).

Arterial compliance is complex, having both longitudinal and circumferential components but only this latter measurement is commonly quoted when the elasticity of different materials is compared. Compliance mismatch has been implicated as an important factor in the performance of vascular grafts since 1976.[10] This mismatch should be considered to have two major components, tubular and anastomotic.

Tubular compliance

Mismatch of tubular compliance is present when there is a significant difference in elasticity between the prosthetic graft and native artery. A compliant vessel acts as an elastic reservoir absorbing energy during systole which is released during diastole giving an extra push to pulsatile blood flow. A rigid conduit will consequently diminish this secondary pulsatile energy and reduce distal perfusion. At the interface between a compliant artery and a non-compliant graft, changes in impedance (defined as the resistance to pulsatile flow) will diminish pulsatile energy by as much as 60%.[11] Furthermore, optimal organ perfusion depends on pulsatile blood flow with a change from pulsatile to static perfusion shown to increase peripheral resistance by 10%.[12] Finally, at the graft to artery interface there is wave reflection of pulsatile energy which can lead to increased velocity gradients and turbulence. As a result of these increased vibratory movements and mechanical stresses, endothelial damage and intimal hyperplasia occurs.

Anastomotic compliance mismatch

A sutured anastomosis generates a decrease in diameter and drop in compliance determined primarily by the lack of elasticity of the suture material. Interrupted sutures give a more compliant anastomosis, while a continuous technique results in a ring of non-compliant suture material – both prolene and PTFE sutures are profoundly non-elastic. Within a few millimetres on either side of the suture line, there is a paradoxical increase of compliance which is known as the para-anastomotic hyper-compliant zone (PHZ)[13] (Figure 28.1). Intimal hyperplasia develops typically in these areas of hyper-compliance.

The compliance hypothesis of graft failure

Compliance mismatch will lead to a region of excessive mechanical stress which can give

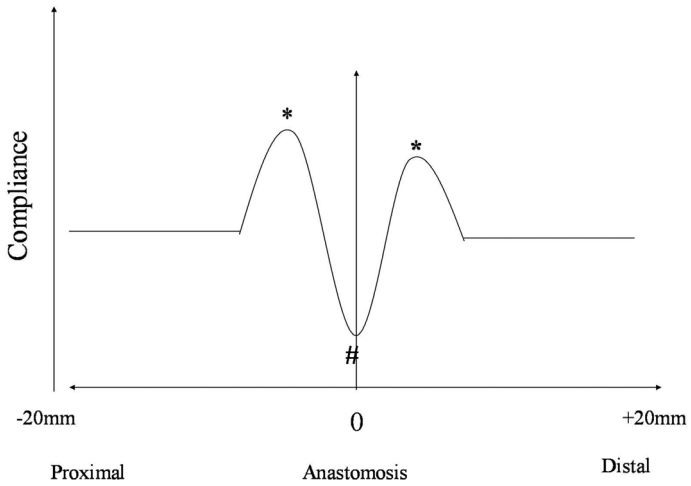

FIGURE 28.1: The peri-anastomotic hypercompliant zones (PHZ); compliance at the anastomosis is lower due to the suture (**#**) while compliance is increased compared to the vessel wall several mms from the anastomosis (*). This effect further aggravates compliance mismatch in bypass grafting.

rise to subtle arterial wall injuries and initiate the first phase of intimal hyperplasia. Cyclical stretching is known to have a positive influence on proliferation of vascular smooth muscle cells and production of extracellular matrix. This increased cyclical stretch at the zones of PHZ, will cause proliferation of the smooth muscle cells. Finally changes in compliance are known to affect flow and shear stress. Where there is turbulent flow, there will be areas of low shear stress and this is known to promote endothelial proliferation, apoptosis and reduce production of nitric oxide.

The clinical evidence for the compliance hypothesis is largely speculative but analysis of the clinical performance of grafts of differing compliance reveals a positive correlation between compliance and patency rates (Figure 28.2). The most commonly used prosthetic grafts, namely PTFE and Dacron are profoundly rigid over the physiological pressure range. A feature of the visco-elastic nature of human artery is compliance which diminishes with increasing pressure but which increases exponentially as the mean pressure falls below 80mmHg (Figure 28.3). The ideal prosthetic graft should share this property.

SYNTHETIC GRAFTS

The history of prosthetic grafts began in 1952 with successful placement of Vinyon –N tubes into the abdominal aorta of dogs, and subsequent human implantation in 1954 in 18 patients.[14] An explosion of interest followed with synthetic grafts being made from various textiles but their major problem was loss of tensile strength. Two materials proved to be resistant namely Dacron and PTFE, and because of their bio-durability have dominated graft development to this day.

Newer developments of dacron grafts

Heparin coating has been utilised for improving biocompatibility of Dacron. Besides enhancing the function of heparin-binding proteins, immobilised heparin also potentially reduces Dacron hydrophobicity.

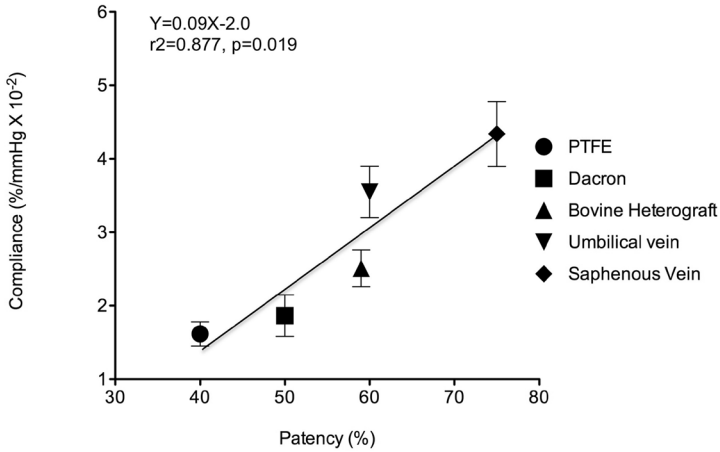

FIGURE 28.2: Correlation between typical compliance and 2 year patency of several graft materials in clinical use.

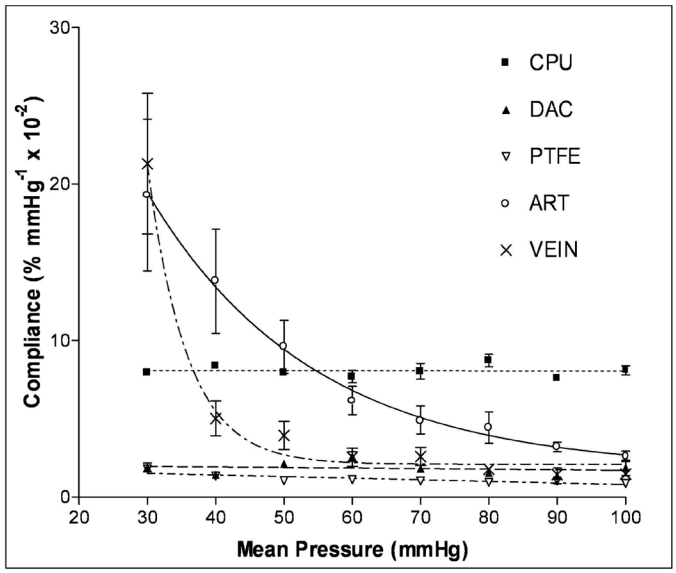

FIGURE 28.3: Compliance / Pressure curve for compliant polyurethane (CPU), Dacron (DAC), ePTFE (PTFE), human femoral artery (ART) and saphenous vein (VEIN). None of the prosthetic materials possess the visco-elastic properties of artery and vein which give higher compliance at lower pressures. CPU maintains higher compliance at all pressures compared to Dacron or ePTFE.

This change in surface chemistry might alter the proteins present at the interface, thereby influencing biocompatibility independent of the biological action of heparin. It has been shown that this is associated with exposure of the fibrinogen P2 epitope as well as the adhesion of monocytes.[18] Independent of the inflammatory response, the hydrophilic nature of the heparin coating may affect tissue interaction (reduction in cell adhesion,

growth and mobility). Overall, compared to human umbilical vein (HUV) or PTFE, heparin-bonded Dacron shows significantly better primary patency up to 2 years but not at 5 years of follow-up.[19,20]

Modifications and newer developments of PTFE grafts

The ePTFE graft has been modified in various ways. Thin wall ePTFE grafts have improved handling characteristics but still have an outer wrap to provide strength. Stretch ePTFE grafts have improved longitudinal rather than circumferential elasticity with improved handling characteristics but no other benefit has been demonstrated in clinical studies. External support, either rings or spirals, is thought to be beneficial in extra-anatomic (axillo-femoral or femoro-femoral) or below knee grafts.

A further valuable adjunct shown in prospective studies to improve below knee PTFE graft patency is an interposition vein cuff or patch at the distal anastomosis.[24] This appears to improve the haemodynamic situation at the distal anastomosis perhaps acting through minimising compliance mismatch and improving blood flow.[25]

Several reports indicate potential benefit with ePTFE aortic grafts including reduced bleeding and a lower risk of infection. The only prospective randomised comparison of ePTFE and Dacron aortic grafts, however, failed to show any difference.[26] The supremacy of ePTFE in lower limb bypass grafting has been challenged in a randomised trial which showed no difference between ePTFE and gelatin sealed Dacron.[27,28]

Heparin bonded PTFE is being widely utilised in contemporary practice. Two year primary patency and limb salvage rates were similar to autologous saphenous vein in lower limb bypass including below-knee locations.[29] While there are case series data implying that this is an effective material, results from randomised trials are awaited.[20]

Other ePTFE coating materials evaluated include citric-acid based biodegradable elastomers. In porcine carotid artery circulation, they were found to be biocompatible without causing increased risk of thrombosis, restenosis or inflammation.[31] These findings are important as this may serve as the foundation for a drug eluting vascular graft.

Polyurethane grafts

Polyurethanes are segmented polymers initially formulated in the early 60's to provide elasticity in garment materials (Lycra). These are a very large family of which the most important component is the urethane group present in repeating sequences on the main chain of the polymer. This forms the hard segment providing strength with the soft segment being the other main component (macromonomers ranging from hundreds to over a thousand Daltons). These hard and soft components have a degree of incompatibility which allows microphase separation delivering superior visco-elastic and compliant properties. Polyurethanes also possess excellent blood and tissue compatibility and are in extensive use in access catheters and linings of various prosthetic devices. Clinical experience of conventional polyurethane grafts has confirmed their superior thrombo-resistance, rapid ingrowth of living tissue and reduced anastomotic hyperplasia.[32]

Polyurethane vascular access grafts for haemodialysis have several advantages including easy cannulation, rapid compression haemostasis and early use after implantation. Disadvantages with polyurethane grafts include poor patency rates when compared with PTFE and most problematically hydrolytic degradation leading to aneurysm formation. It is this complication that has

limited their clinical use despite the advantages of good compliance[33-39] (Table 28.1).

Newer developments of polyurethane vascular grafts

Conventional polyurethanes are biodegradable at the soft segment of the polymer particularly at the ester and ether groups in poly(ester)urethane and poly(ether)urethane. Recent interest has focused on replacing these susceptible groups with other moieties in particular polycarbonate, which are more hydrolytically and oxidatively stable. One polycarbonate polyurethane is currently available for clinical use, Corvita (Corvita Inc) and also a renal access graft composed of polyether polyurethane, the Vectra graft (Bard Inc.).

Development of a compliant small calibre vascular graft has been a major goal of our unit. The focus has been on a poly (carbonate) polyurethane with a honeycomb structure (Figure 28.4) composed of an inner and outer skin enclosing a spongy middle wall thus maintaining pulsatile flow even after peri-graft tissue incorporation. Because this polymer lacks ether and ester compounds it resists biodegradation as proven both in vitro, and in long term implantation study. Comparison of this graft with artery, vein, Dacron and PTFE shows compliance similar to artery at mean pressures of 30–60 mm Hg, with very significantly superior compliance compared to Dacron or PTFE at all pressures (Figure 28.3).[42,43] Soldani et al have developed a new compliant small diameter graft with a poly (ether) urethane–polydimethylsiloxane semi-interpenetrating polymeric network and featuring two different porous wall layers; this showed superior compliance and patency rates in comparison with standard ePTFE, with the ability of remodeling in vivo being gradually replaced by natural tissue with no sign of calcification.[44]

In addition, small-diameter poly (epsilon-caprolactone) grafts represent a promising alternative polyurethane with better healing characteristics compared with ePTFE giving

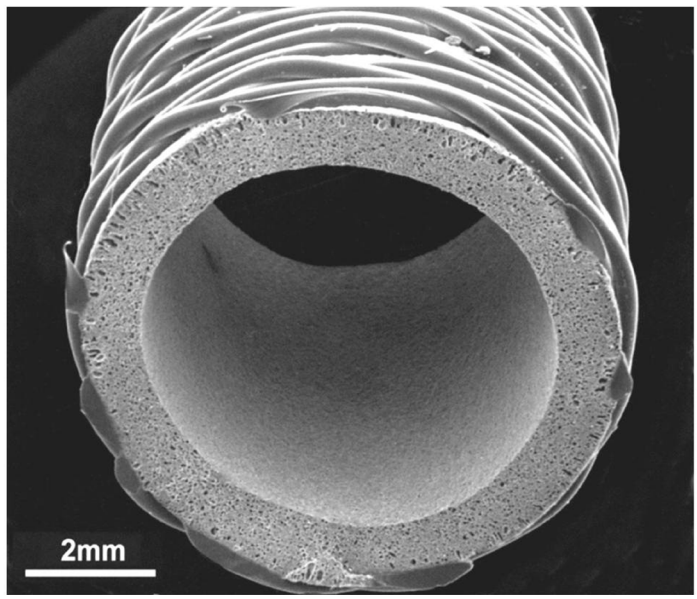

FIGURE 28.4: Compliant polyurethane graft with external support; The sponge-like structure of the wall allows pulsatile elastic recoil even with external support and after perigraft tissue incorporation has taken place.

faster endothelialisation and extracellular matrix formation, accompanied by resistance to structural deterioration during remodelling.[45,46]

Reinforced polyurethane grafts using polyester filament yarns knitted into tubular fabrics to form a composite vascular graft have been demonstrated to be 5–10 times stronger than pure polyurethane grafts.[47] A bioengineered microporous polycarbonate-siloxane polyurethane graft has been developed for coronary artery bypass grafting. Biological agents including heparin and sirolimus can be impregnated into its absorbable collagen and hyaluronan microstructure giving a unique drug-eluting graft with endothelialisation without excessive intimal hyperplasia.[48] Biodegradable polymer systems provide the opportunity for release of various growth factors to promote vascular wall regeneration. For example, fibroblast growth factor-2 (FGF-2) release from poly (ester urethane) urea scaffolds amalgamates the favourable mechanical properties of polyurethanes with the bioactivity of an angiogenic protein.[49]

Nitric oxide releasing polyurethanes reduce platelet adhesion and vascular smooth muscle cell growth, while stimulating endothelial cell growth.[50] Furthermore, the elastomeric copolymer, poly(1,8-octanediol citrate), with mechanical and degradation properties suitable for vascular tissue engineering, decreases platelet adhesion.[51] In vitro studies evaluating the biocompatibility of these materials confirm their potential for vascular graft coatings.[52]

Although tissue-engineered vascular grafts based on biodegradable polymers have yielded promising results, some drawbacks exist. 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.

Biological vascular grafts

Biografts, vascular grafts made from biological sources, have been used over many years. Allografts (sourced from the same species) in current use are primarily umbilical and saphenous vein. Xenografts (derived from other species) have a long history with disappointing results and there is no xenograft currently in clinical use.

The major problems with biografts are biodegradation and immunogenicity which can be counteracted by chemical treatment and cryopreservation. The first clinical use of an allograft was in 1948 in the treatment of aortic coarctation.[53] Arterial allografts harvested from cadavers were first used in the 1960s to perform lower limb bypass but these were prone to significant degeneration, aneurysm formation and wall calcification.[54]

Improved cryo-preservation with protectant solutions to prevent intra-cellular ice crystals on thawing, allowed the development of tissue banks to provide a ready source of allografts. Clinical use of cryopreserved allografts in the 1960s showed good short term function and the attractive possibility that cryopreservation might reduce immunogenicity.[55] Further clinical experience however revealed disappointing one year patency rates of less than 50%.[56] The stable functioning of arterial and venous grafts in human liver transplantation suggests that immuno-suppressive therapy will improve the function of these grafts. However the associated complications probably make this approach unacceptable.

Xenografts were introduced in the 1970s, most commonly the bovine carotid artery. Various chemicals including glutaraldehyde were used to cross link collagen to provide stability and reduced immunogenicity. Clinical success rates of these xenografts were poor with biodegradation after 6 months due to progressive breakdown of the collagen cross linkages.

The human umbilical cord vein was developed as a bypass graft by Drs Irving and Dardik.[57] This was stabilised using glutaraldehyde supported by an external Dacron mesh and used specifically in lower limb bypass grafting but were prone to aneurysmal degeneration. Deficiencies in the manufacturing process were corrected in the late eighties with apparent significant reduction of this problem. The graft, however, never regained popularity despite impressive results in a large series of 1,275 cases (five year secondary patency rates of 71% for femoro-popliteal and 56% for femoro-crural bypass).[58]

Newer developments of biological vascular grafts

Bacterial cellulose is a novel vascular material with the potential to reduce surface thrombogenicity. In vitro it had the slowest activation of coagulation cascade as compared to standard synthetic graft materials.[59] Bacterial cellulose has the added advantage of promoting in situ vascular tissue regeneration,[60] so it has potential as a scaffold for small bore vascular grafts.

A fibrin scaffold supported by a poly lactide mesh, and seeded with autologous arterial-derived cells prior to dynamic conditioning has been used to develop conditioned grafts with good mid-term patency and no evidence of thrombosis, aneurysm formation or calcification in vivo.[61] They also show a confluent monolayer of endothelial cells lining the inner surface of the graft. The integrated biodegradable polylactide mesh has also been used to provide temporary mechanical support during the initial period of tissue development, while an autologous fibrin cell carrier system acts as the basis of remodeling the entire graft into a viable tissue structure.[62]

The in-vivo evaluation of cryopreserved human umbilical arteries treated with poly (styrene sulfonate)/ poly (allylamine hydrochloride) has demonstrated a high graft patency after 3 months of implantation.[63] An allogenic vascular graft has also been developed from a decellularised scaffold prepared from canine carotid arteries and modified through heparin immobilisation and vascular endothelial growth factor (VEGF) coating.[64]

L'Heureux et al. have demonstrated the feasibility of assembling arterial bypass grafts exclusively from autologous cells in primate models.[65] No synthetic or exogenous materials were used; instead, the vessels were created with the use of autologous fibroblasts and endothelial cells harvested from a small biopsy specimen of skin and superficial vein. In vivo results indicated that the grafts were antithrombogenic and mechanically stable for 8 months, with histology and microscopy displaying complete tissue integration, regeneration of a vascular media, as well as elastogenesis and a collagen fibre network.

PROSTHETIC GRAFT MODIFICATIONS

Modifications to reduce graft infection

Graft infection is a devastating complication particularly in the modern era of increasing methicillin-resistant *Staphlococcus aureus* (MRSA) infection. Several different strategies have been employed to reduce the risk of infection. The simplest approach is soaking grafts coated with albumin, collagen or gelatin with antibiotics, in particular rifampicin.[66] Gelatin sealed grafts prebonded with two antibiotics have shown resistance to infection by *Staphylococcus aureus* in a dog model.[67] In vitro studies show that antibacterial levels of rifampicin will remain present for 48 to 72 hours with reduced risk of graft infection to bacterial challenge.[68]

The clinical experience of rifampicin bonded Dacron grafts relates to two randomised controlled trials the first from Italy in

aorto-femoral grafts and the second from the United Kingdom in extra-anatomical bypass grafts. There was no long term benefit in terms of reduced graft infection rate found although early wound infection rates were found to be significantly reduced.[69,70] However, these grafts should be used with caution because it has been noted that in approximately 30% of cases, microbial organisms isolated from infected grafts are resistant to rifampicin.[71]

A further approach to reducing infection is the binding of Triclosan (Irgason) to grafts. This is an antimicrobial with broad spectrum activity which in experimental studies appears to bind effectively to dacron grafts for four weeks.[72] Silver bonded PTFE grafts have been shown experimentally to reduce the risk of infection, and are currently available for clinical use[73] (Interguard Silver Graft. InterVascular, France). However, in vivo comparison in a dog model between rifampicin /gelatin sealed and silver/collagen coated Dacron grafts, revealed significantly greater resistance to infection for rifampicin bonding.[74] Silver-coated grafts did not differ from standard grafts and had no effect on reducing graft infection in a recent retrospective study.[75]

The other experimental strategies proposed include direct pre-treatment with soaking prosthetic grafts in antibiotic solution (Daptomycin) which has been dissolved in a fibrin sealant.[76] At present, all graft modifications intended to reduce the risk of infection in arterial reconstruction, although promising, lack evidence of effectiveness.[77]

Modifications to improve patency

Carbon has been used because of its lack of reactivity and potential reduction of luminal thrombogenicity with flowing blood. Experimental studies have suggested improved primary and secondary patency rates.[78] Prospective randomised comparison of carbon impregnated PTFE grafts with standard PTFE found no significant difference at 2 years but with a trend for improved patency in the carbon graft.[79]

As shown earlier heparin bonded Dacron shows only short-term advantage in improving primary patency. A commercially available graft is the Fluoropassiv (Terumo-Vascutek), a Dacron graft coated with a fluoropolymer which has been shown in experimental studies to cause less tissue reaction and to have reduced thrombogenicity.[80] There are no clinical data available to confirm any beneficial effect of this graft.

Nanocomposite Grafts

Recent developments in the field of nanotechnology have facilitated vascular tissue-engineering mimicking the nanostructure of native vessels. One such application is electrospinning of synthetic polymers into nanofibers.[81-84] The advantages of forming scaffolds with high porosity as well as high surface area-to-volume ratio, thus simulating the dimensions and structure of native collagen and elastin fibrils holds great promise for future off-the-shelf-grafts.[85,86]

Our group has developed a family of nanocomposite polymers-based on polyhedral oligomeric silsesquioxanes (POSS) and poly (carbonate-urea) urethane (PCU). POSS-PCU has been used to develop a small diameter bypass graft which shows matching viscoelastic properties to human arteries.[87] Furthermore, a biofunctionalised small diameter graft based on this nanocomposite polymer demonstrates the potential for relatively rapid endothelialisation from progenitor cells extracted from peripheral blood in an in vitro model.[87] An extrusion-phase-inversion technique is used to make uniform walled porous conduits from POSS-PCU. These elastic microporous grafts demonstrate

favourable mechanical integrity and are currently undergoing in-vivo evaluation of durability and healing properties.[88]

Other groups have utilised the strength and flexibility of carbon nanotubes as fillers to enhance base polymer properties but although these composite polymers decrease thrombogenicity, toxicity of carbon nanotubes remains a concern.[89,90]

ENDOTHELIAL CELL SEEDING

Achieving endothelial cell coverage is important in improving graft performance. Endothelial cells have been extracted from three main sources – vein, subcutaneous fat and omentum.[91] Further potentially promising sources are from bone marrow, circulating blood and mesenchymal stem cells. There is good experimental evidence to support the benefit of endothelial cell seeding of bypass grafts. These have better patency rates, are less thrombogenic, will tolerate low flow states and have been shown to have normal endothelial cell activity.[92] In addition seeded grafts have been shown to resist bacteraemic infection in animal models.[93-95]

Single stage seeding

Single stage seeding requires sourcing of larger numbers of endothelial cells to allow immediate seeding of the graft at implantation. With this method seeding is not expected to be fully confluent but rather is achieved over the early post-implantation period by endothelial cell replication. Herring and his colleagues in 1978 were the first to report the seeding of Dacron grafts in a dog model and showed that PTFE seeded more rapidly and completely than Dacron.[9,96] This group confirmed in an explant from a patient that endothelium was present in the mid-portion of the graft some months after implantation.[97,98] A further clinical study demonstrated reduced thrombogenicity in the endothelialised limb compared to the non-seeded contralateral limb of aorto-bi-femoral grafts.[99] The major disadvantage of one stage seeding is a lack of sources of sufficient cells to allow immediate seeding.

Two stage seeding

Two stage seeding involves harvesting a modest quantity of endothelial cells typically from a vein, and culturing sufficient numbers for confluent seeding. A group in Vienna have performed the largest and the most detailed study in man using two stage seeding with endothelial cells harvested from cephalic or jugular veins.[100] The ePTFE grafts were pre-coated with fibrin glue and then seeded with the patient's own cultured endothelial cells. This group's experience is of 213 patients with patency for below knee reconstructions of 68% at 5 and 7 years, and 65% at nine years.[101] Endothelial cell seeding has been successful in coronary artery bypass with a recent trial using two stage seeding of ePTFE reporting 90.5% patency rate at 28 months.[102] These early clinical results are very promising but two stage cell seeding is cumbersome, and not easily applicable particularly in emergency revascularisation.

VASCULAR TISSUE ENGINEERING

There are three major approaches to creating blood vessels. The first is in the addition of vascular cells to synthetic polymers of which seeding of existing graft materials forms the most basic example. The second approach is in the development of bioresorbable or biodegradable grafts made of polymers which will be absorbed to varying speeds and degrees with eventual replacement by host tissue. The third approach is that of growing

new grafts in tissue culture made from endothelial cell, vascular smooth muscle cell, collagen and matrix.

Non-degradable polymer and cell seeding

Deutsch and colleagues in Vienna showed in explants of endothelial cell seeded PTFE grafts that a neo-media develops between the prosthesis and the endothelium throughout the entire length of the graft.[103,104] The cells in the neo-media contained actin filaments and a true internal elastic membrane had developed to separate them from the endothelial layer. Probably the original inoculums of endothelial cells obtained from cephalic or jugular vein had been contaminated with some vascular smooth muscle cells or pericytes. There has been much debate in the past as to whether endothelial cells for seeding should be pure or whether there would be benefit from inclusion of vascular smooth muscle cells or pericytes. This finding of a neo-media with a well developed internal elastic membrane providing an inner structure very similar to that of a normal artery lends support to the argument that co-culturing of cells of vascular origin would be beneficial.

The reintroduction of high porosity prosthetic grafts (i.e. pores >90μm) merits further study. Impermeability at the time of implantation using established impregnation methodology avoids the risk of haemorrhage. Once the sealant is absorbed, capillary tuft ingrowth with development of a media and intima may result. An alternative approach would be to develop highly porous prosthetic grafts pre-seeded with vascular smooth muscle cells, collagen, and with a seeded inner layer of endothelial cells. The newer bio-resistant polyurethane polymers are promising materials for development of such hybrid grafts.

Bioresorbable and biodegradable polymers

The concept of degradable or absorbable graft materials providing initial vessel integrity but in time replaced by the host's own tissues has been under development for some time.[105,106]

Polyglycolic and polylactic acid are the two bioresorbable polymers which have been most fully investigated. In addition to polydioxanone, these are the polymers which have FDA approval and for this reason are the preferred materials.[107] Polyglycolic acid is susceptible to in-vivo hydrolysis after 2–4 weeks. Polylactic acid is more resistant to hydrolysis in-vivo and in the form of, L-polylactic acid, has high mechanical strength. Copolymers of these two substances are in wide use as absorbable sutures and are better known as vicryl and polyglactin 910 (PG910). Polydioxanone, otherwise know as PDS, is a much more slowly reabsorbed compound. The first fully bioresorbable vascular graft was made from sheets of vicryl but became aneurysmal.[108]

Greisler's group in Chicago has contributed significantly in this field initially making grafts from woven polyglycolic acid for a rabbit model.[109,110] Four weeks after implantation a confluent layer of endothelial cells with a medial layer of myofibroblasts surrounded by dense collagen fibres was found. Ten percent became aneurysmal early on probably because of reabsorption before adequate ingrowth of host tissue. Grafts made of polydioxanone (PDS) were more slowly reabsorbed for up to six months. Similar tissue ingrowth as in the previous experiments with full endothelialisation over a neo-media was found. These were strong grafts able to withstand very high static bursting pressures (600-2000 mmHg).[111]

Greisler's group then reported a composite bioresorbable graft of 74% PG910 and

26% PDS which at one year in a rabbit aorta model had 100% patency with no aneurysmal degeneration. Complete reabsorption of PG910 took place within 2 months and PDS within 6 months. These arteries withstood up to 800mmHg of pulsatile pressure.[112] Composite partially resorbable grafts were next looked at in two grafts, the first constituted of 69% PG910 and 31% polypropylene, and the second of 70% PDS and 30% polypropylene. In a dog aorto-iliac interposition model, one year patency rates of 90% for the former graft and 86% for the latter graft were found.[113] Despite these experimental successes, so far no bioresorbable small diameter graft has been produced for human implantation.

Combined bioresorbable and tissue engineered grafts

Later work focused on the concept of a graft composed of autologous vascular cells with a bioresorbable scaffold providing sufficient strength during tissue ingrowth and replacement.[114] The first report was of smooth muscle cell seeding onto polylactic acid scaffold in a rat model where a neomedia with vascular orientation of cells was found.[115] Langer and Vacanti reported the successful development of a tubular scaffold made of woven polyglactin as an outer layer and an inner layer of non-woven polyglactin onto which autologous cells were seeded. After seven days of culture the vessels were implanted into sheep pulmonary artery with 7 grafts remaining patent for up to 3 months. The polymer scaffold was found to be replaced as expected by host cells and matrix, but these grafts dilated.

A more robust graft was produced using a composite scaffold of polyglycolic acid as an inner layer designed to degrade by two months, and polyhydroxy alkanoate as an outer non-porous layer, designed to degrade much more slowly. This graft was implanted into sheep abdominal aorta with full patency and no dilatation being found at up to 150 days and complete replacement by host tissue. A normal endothelial layer and a vascular media containing collagen and elastin were found.[116,117]

Surface modulation of polyglycolic acid polymer with 1N NaOH increases absorption of seeded smooth muscle cells.[118] The RGD peptide, a component of fibronectin, is known to promote endothelial cell attachment and also influence cell differentiation.[119] Much work is now focused on the incorporation of RGD peptide sequence onto polymer surfaces to enhance endothelial attachment. A further promising approach is the incorporation of biologically active substances, for example vascular endothelial growth factor and basic fibroblast growth factor in order to stimulate and modulate the differentiation of the seeded cells into functional phenotypes.[120]

Mechanical conditioning of seeded vascular cells

The exposure of smooth muscle cell seeded scaffolds to physiological and pulsatile pressures results in orientation into multilayers with collagen fibrils in the extracellular matrix.[121] Elastin and proteoglycans are also released into the extra-cellular matrix after 8 to 16 weeks of exposure to arterial circulation.[122] Furthermore conditioning of seeded endothelial cells by exposure to pulsatile flow and shear stress has been shown to improve proliferation and adhesion.[123]

Alternative scaffolds

Biocompatible and biodegradable synthetic polymers made by recombinant DNA technology are under development. Examples include the elastic protein-based polymers

such as poly (GVGP), a repeating sequence in the elastin molecule. Carboxy-amides are chemical moieties which will hydrolyse at varying times depending on the amino acid sequence. By selection of carboxy-amides for inclusion in the structure of the poly (GVGPV) polymer a planned degradation rate can potentially be incorporated. Differential degradation, resorption and replacement by host tissue of several layers of a graft can therefore be achieved while maintaining its structural integrity.[124] These polymers have excellent elasticity and proven optimised cell attachment due to incorporation of RGD sequences.[125]

Decellularised vessels have well preserved collagen fibres theoretically ideal for ingrowth. Good long term results from allogenic decellularised biological scaffolds have been reported with minimal immunoreactivity[126] but this initial promise was not maintained in further experimental studies. Xenografts would be practical for human implantation but unfortunately even decellularised scaffolds maintain a significant degree of immunogenicity and inflammatory response sufficient to destroy elastin.[127] Endothelial cell seeding with autologous cells has not been successful in reducing their immunogenicity and thrombogenecity.[128] Although a very promising concept the continuing problems of antigenicity make their clinical application unlikely.

A poly-L-lactide/poly-epsilon-caprolactone scaffold releasing heparin by a combination of electrospinning and fused deposition modeling technique has been used. This particular scaffold design allowed the generation of both a drug delivery system amenable to surmount thrombogenic issues and a microenvironment able to induce endothelial differentiation.[129] Silk-based fibroin grafts have been developed and they provide excellent patency when implanted in smaller vessels.[130] The fibroin graft gradually degraded with formation of an artery-like structure by endogenous endothelial cells and smooth muscle cells. Fibroin may hold the promise to generate vascular prostheses for smaller-diameter arteries.

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.[131] Growth-regulating substances, growth factors or antimigratory and antiproliferative drugs have been incorporated directly into prosthesis wall or delivered through drug-eluting stents, catheters and perivascular collars.[132,133] Artificial materials releasing nitric oxide (NO) are also being developed, consisting of synthetic polymers incorporated with NO donors such as diazeniumdiolates and S-nitrosothiols.[134]

Tissue-engineered grafts

Blood vessels made purely from biological materials and vascular cells have the major potential advantage of a vasoactive biological conduit which can both heal and remodel according to changing environment. In Japan Hiraj and Matsuda developed a graft from canine vascular cells and collagen which proved resistant to physiological pressures only with a dacron backbone.[135] In 1998 the Quebec group reported the first successful totally biological graft made from cultured human umbilical vein cells which withstood physiological pressures.[136] The addition of a period of pulsatile culture following an initial static culture of smooth muscle cells and collagen reliably produces grafts

which are strong and resistant to supra-physiological burst pressures.[137,138]

All work in this field has been based on young cells. The successful translation of these promising developments to clinical application requires proof that adult or senile vascular cells will behave similarly. Such cells will have to come from each individual vascular patient until such time as pluri-potential, non-immunogenic cells can be sourced.

GRAFT MATERIALS FOR AORTIC ENDOGRAFTS

The endografts in current clinical use are mainly made from either thin woven polyester (Dacron) or ePTFE. Sac enlargement after endovascular aneurysm repair (EVAR), without evidence of endoleak, has been attributed largely to endotension or material porosity. The first-generation Gore Excluder graft allowed serous transudate contributing to continued sac pressurization. AneuRx grafts had a higher incidence of microleaks, or persistent transgraft blood flow, occurring through the thin graft material. The Excluder and AneuRx devices modified their graft material in 2004 with subsequent reduced permeability.[139] Stent and graft materials have different mechanical properties and any repetitive movement between them may damage the fabric. Stronger sutures and tighter weaves have made current designs more stable, but none is yet free from fabric graft failure.[140]

Research has also been targeted to improve the delivery profile of endografts, which is a main limiting factor in utilisation of these grafts for thoracic aneurysms. One such approach is to use thin-film Nitinol (NiTi) and early in vitro results have confirmed its feasibility.[141] This device is presently being tested in animal models.

With the availability of new materials, reducing mismatch in aortic stiffness and compliance may become important in future EVAR grafts. Indeed, some differences in presently used materials have already been observed by van Herwaarden and colleagues finding differences in compliance between Gore Excluder and Medtronic Talent stent-grafts at the level of aneurysm neck.[142] In the next decade, we can expect continuing improvements in device design. Plasmid-loaded cationized gelatin (CG) hydrogel-coated stent grafts offer transduction of therapeutic genes into the vascular wall facilitating the biologic healing between the aorta and graft.[143] Novel graft materials such as POSS-PCU have the potential to deliver compliance, antithrombogenicity, biocompatibility and spontaneous endothelialisation to provide better configurations and reduce the risk of complications.

THE FUTURE

Over the next 5 years improved prosthetic grafts will become available with the introduction of biodurable and compliant materials. Lumen modulation by anticoagulant molecules, cell ligands and growth factors will further enhance performance thus adding thromboresistance to compliance. Attachment technology will allow Dacron and PTFE to be similarly modified although these can never be sufficiently compliant to abolish compliance mismatch.

New compliant graft materials will be developed using novel spinning technologies to incorporate collagen and elastin polymers resistant to degradation. The technology for totally bioresorbable grafts is already in clinical use for paediatric cardiovascular reconstruction and its applicability to adult use is under study. Similarly the development of totally autologous tissue engineered grafts is in its infancy. Endothelial cell seeding is clinically proven but cumbersome. With ongoing development to match as closely as

possible the mechanical characteristics and functions of normal human arteries there is real potential for new graft development within the next decade.

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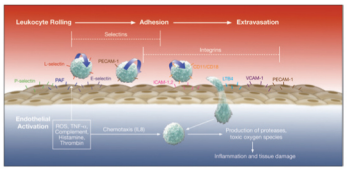

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Edited by Robert Fitridge and Matthew Thompson

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