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REVIEW ARTICLE

Intimal Hyperplasia in Vascular Grafts*

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Introduction

The first report of anastomotic intimal thickening after transplantation of a vein into the arterial circulation was over 90 years ago: "within a few days after the operation, the stitches placed in making the anastomosis became covered with a glistening substance similar in appearance to the normal endothelium".[1] Many reports have followed, and intimal hyperplasia is now recognised as the main cause of thrombotic complications occurring between 2 and 24 months after a vascular intervention.[2] Intimal hyperplasia causes restenosis in approximately 30–50% of coronary and superficial femoral angioplasties, 20% of carotid endarterectomies, 20–30% of femorodistal vein bypasses, 10–30% of coronary vein graft bypasses and 42–50% of the arteriovenous fistulas for haemodialysis.[2–8] The arteriovenous fistula is the lifeline for patients who depend on haemodialysis treatment. The incidence of thrombotic occlusion of these fistulas is 0.95 per patient year. Eighty per cent of these occlusions are caused by a stenosis due to intimal hyperplasia (IH). Furthermore, another 0.27 interventions per patient year are performed on stenoses to prevent occlusion.[9] Thus, intimal hyperplasia poses a significant impact on morbidity of haemodialysis patients and in the costs for treatment.

Extensive research has been performed to gain insight into the cell biology of intimal hyperplasia and to find targets for pharmacological intervention to reduce the development of IH. Also, the influence of haemodynamic forces like flow and shear stress on the development of IH has been investigated. High as well as low shear stress has been indicated as a causative factor for IH. Another possible contributing factor in the development of IH is mismatch in elastic properties between vascular grafts and native vessels. Several anastomotic designs with the use of anastomotic cuffs and patches have been used over the years to influence the haemodynamic forces or to decrease the compliance mismatch. Although some solutions have had promising results with respect to improved patencies of peripheral bypass grafts,[10] the impact of intimal hyperplasia on all fields of vascular interventions remains high.

Cell Biology of Intimal Hyperplasia

Intimal hyperplasia is thought to be due to a variety of injuries that always involve some endothelial damage.[11] It is composed of about 20% of vascular smooth-muscle cells (VSMC) that have migrated from the media to the intima and have proliferated and deposited extracellular matrix, which comprises most (60–80%) of the intimal area. Other components of the intima are macrophages and lymphocytes. The surface can be endothelialised or not, depending on the extent of and time passed since the initial damage.[11]

Research on the development of intimal hyperplasia is divided into two main regions: arterial restenosis after percutaneous transluminal angioplasty (PTA) and intimal hyperplasia after implantation of a vascular graft. After grafting into the arterial circulation or after the creation of an arteriovenous fistula for vascular

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access, veins are exposed to different haemodynamics than in the venous circulation. These altered conditions make models of femorodistal vein graft and vascular access intimal hyperplasia different from the arterial balloon injury models. However, it is generally thought that the sequence of events in the development of intimal hyperplasia in vein grafts and prosthetic grafts is similar to that in the balloon injury model, but the events inducing the start of the sequence and the speed of development might be different.[11–13] Most of the research on the sequence of events that led to intimal hyperplasia has been conducted with arterial balloon denudation models.

First wave: VSMC proliferation in the media

Endothelial cell (EC) damage induces thrombus formation. Within 24 h after thrombus formation, VSMC proliferation occurs. Normal endothelium produces factors like prostacyclin and heparan sulphate, which inhibit VSMC proliferation.[11] Damaged endothelium produces less heparan sulphate, and heparinolytic enzymes released from thrombocytes further decrease its concentration. Moreover, the production of other VSMC proliferation-inhibiting factors like nitric oxide (NO) and natriuretic peptides by the endothelium will decrease when the endothelium is damaged. Basic fibroblast growth factor (bFGF), which can be released by dying or damaged EC and VSMC, stimulates VSMC proliferation.[14,15] Angiotensinogen and the angiotensin receptor (ATI) expression are increased in IH lesions. Angiotensin II (AII) stimulates expression of PDGF-A, bFGF, TGFβ, c-myc and c-fos. These are all growth-stimulating factors.[11] Possible other mediators for VSMC proliferation are catecholamines and thrombin, all released upon injury.[16] Thus, damage of the vessel wall decreases production of growth-inhibiting factors and increases the expression of growth-stimulating factors, shifting the balance toward VSMC proliferation.

VSMC are present in two main phenotypes. The differentiated contractile phenotype mainly contains α-actin and myosin and had a low proliferation rate of <0.1%. The synthetic phenotype strongly resembles the foetal VSMC and the fibroblast, with many cell organelles and abundant rough endoplasmic reticulum, no myosin and an increase in β-actin. These synthetic cells produce four to five times more extracellular matrix than the differentiated phenotype and have an increased proliferation rate of at least 10%.[11] In intimal hyperplasia an increase in the synthetic phenotype is found at the expense of the differentiated phenotype. This results in increased proliferation and matrix deposition in the intima. In the adventitia, extensive surgical exposure and dissection damages the vasa vasorum and the autonomic nerves. This leads to de-endothelialisation within 6 h after surgery, and stimulates intimal hyperplasia.[17] Possibly this damage might also play a role in the de-differentiation of the VSMC.

Second wave: VSMC migration from media to intima

VSMC are embedded in an extracellular matrix (ECM). The extracellular matrix includes the basement membrane, the inner elastic lamina and the interstitial matrix. The inner elastic lamina is produced by the EC and mainly consists of laminin, collagen type IV and heparan sulphate proteoglycans. The interstitial matrix is produced by the VSMC and is composed of fibronectin, thrombospondin, collagen I and II, chondroitin, dermatan sulphate, proteoglycans and elastin.[18] The ECM is continuously changing by altered patterns of matrix synthesis and by the actions of matrix metalloproteases (MMPs). An intact ECM prevents VSMC migration. Injury induces the production of tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), which degrade the ECM and activate MMPs.[18] BFGF, PDGF, TGFβ and ALL, which increase after injury, all increase plasminogen activator. Heparan sulphate inhibits plasminogen production, but this inhibition is abolished because of EC damage and decreased heparan sulphate production. Fibroblast growth factors significantly contribute to the medial proliferation of VSMC, while the presence of either endogenous or exogenous PDGF promotes migration to the intima.[19,20] Several other mediators of both the tyrosine kinase (IGF-1, TGF-β, thrombin, interleukin-1) and G-protein (ALL, endothelin-1, serotonin) coupled membrane receptors have been shown to participate in these events.[21] These circumstances produce a good environment for migration. VSMC migration from media to intima starts 4 days after injury, and continues up to 1 month after injury. Recent experiments suggest that the adventitia might also play a role in delivering intimal cells. After angioplasty, adventitial myofibroblasts have been shown to proliferate and migrate to the intima as well.[22]

Third wave: intimal expansion

The third wave of intimal expansion probably occurs as a result of VSMC accumulation through proliferation,

continued migration, or both, as well as relatively exuberant ECM synthesis. The processes of VSMC accumulation and volume of ECM production appear to be tightly linked, with fairly constant proportions of VSMC to ECM volumes, characterising the intimal lesions that arise after a variety of vascular injuries.[23] The proportional contribution of VSMC and ECM volume to the overall intimal volume remains constant except directly beneath the endothelium, where both VSMC proliferation and the relative proportion of VSMC are higher. Not much is known about the control of matrix production in the intima. Growth factors such as TGF-β and PDGF are also fibroplastic, i.e. they stimulate ECM production by VSMC. Thus, the same factors that stimulate VSMC proliferation simultaneously increase ECM production.[11]

Intimal Hyperplasia in Venous and Prosthetic Grafts

In the normal circulation a vein is subjected to low pressure, non-pulsatile flow and a shear stress of around 0.2 dyne/cm^2. Following grafting into the arterial system, the vein is exposed to high pressure, pulsatile flow and a shear stress of approximately 3–6 dynes/cm^2.[24] Arterialised vein grafts obtained from humans in the early postoperative period (<24 h) show focal loss of endothelial cells, particularly at the perianastomotic areas, and fibrin deposition on the intima.[12] This results in a loss of endothelium-dependent relaxation to acetylcholine and diminished contraction to α_2-adrenergic agonists and serotonin.[25–28] Alterations in shear stress influence the expression of endothelial adhesins. Vein grafting is followed by a rapid deposition of leucocytes, platelets and other blood components. These can release cytokines that may influence VSMC proliferation and migration.[24] Up to 2 months after implantation of vein grafts, an increased platelet activation was found.[29] Also, an increase in PDGF and bFGF production was found in the area of IH.[30]

Specimens derived from occluded human venous bypasses indicated that intimal hyperplasia occurred at the heel, toe and floor of the host artery and that it consists of myofibroblasts, fibrocollagen with cellular degeneration and proliferation.[31] Uniformly, IH occurred close to or at the anastomosis, where the veins were repeatedly handled by forceps. This trauma may have caused ischaemia or breakdown of the vein wall, producing a hyper-reaction of the vein to arterial pressure.[32]

In prosthetic grafts, the morphological sequence of the development of IH was described by Watastase.[13] He discerned six steps:

(1) early thrombosis;
(2) phagocytosis of thrombi;
(3) appearance and proliferation of fibroblasts in the pseudointima;
(4) appearance and extension of endothelial cells;
(5) appearance of VSMC and;
(6) intimal hyperplasia by proliferation of fibroblasts and production of collagen fibrils.

In contrast to healing in injured arteries, intimal thickening in vascular grafts seems to occur beneath the endothelial layer.[33] This observation provides support for the conclusion that endothelial cells might serve as a source of growth factors.[2,34,35]

However, polytetrafluoroethylene (PTFE) grafts can induce the production of VSMC growth factors in several ways:

(1) foreign body response activates macrophages which excrete growth factors;
(2) uncovered PTFE activates platelets which can release growth factors;
(3) compliance mismatch at the anastomosis may lead to excessive stretching of the VSMC, causing the VSMC to proliferate;
(4) turbulence occurs around the anastomosis, causing endothelial cell damage and release of growth factors;
(5) zones of low shear and flow separation are present around the anastomosis, causing platelet adherence and activation which release growth factors.[2,36,37]

Haemodynamic injury at the downstream anastomosis due to high flow and turbulence in AV fistulas might increase endothelial permeability to blood products, including growth factors. The combination of injury to the vein and PDGF release in the graft may provoke IH.[4,38] Although the sequence of events in the development of intimal hyperplasia in arteriovenous fistulas has not been examined in great detail, a prosthetic arteriovenous fistula can be assumed to be a combination of implantation of a prosthetic graft and implantation of a vein in the arterial circulation. Therefore, one may suggest that the mechanisms in the development of intimal hyperplasia in these separate situations can be combined to a hypothesis of the development of intimal hyperplasia in arteriovenous fistulas (Fig. 1). Implantation of the PTFE graft induces platelet and macrophage activation, which release migration- and proliferation-stimulating factors. Compliance mismatch and disturbed flow are contributing factors. The efferent vein

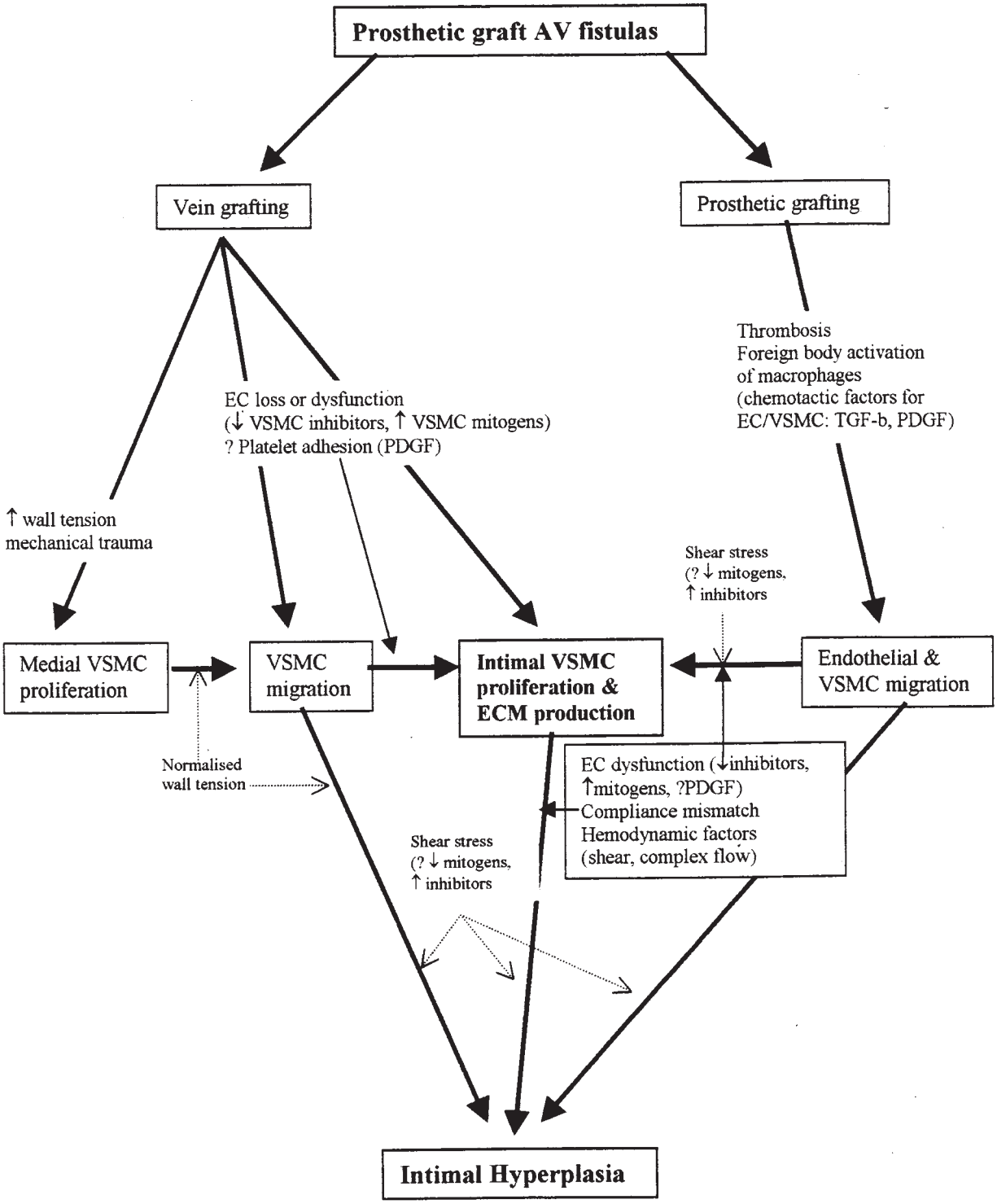

Fig. 1. Hypothesis on the development of intimal hyperplasia in prosthetic arteriovenous fistulas (modified from Kraiss & Clowes[21]). ⟶ Stimulating factors, ⋯⋯⇢ Inhibiting factors

is exposed to arterial pressure and flow, causing mechanical damage and high wall tension. The high wall tension stretches VSMC, which induces proliferation. Moreover, the mechanical trauma causes EC damage, inducing platelet adhesion and activation. The release of mediators from the involved cells induces proliferation of VSMC and degradation of ECM, promoting migration of VSMC into the

intima. The VSMC can then deposit the ECM to complete the intimal hyperplastic lesion.

Haemodynamics and Intimal Hyperplasia

Shear stress and flow

Blood flowing through a vascular segment exerts a tangential directed shear stress at the luminal surface of endothelial cells. Wall shear stress is the product of wall shear rate, i.e. the radial derivative of the velocity near the wall, and the local blood viscosity. Shear stress (τ) can be calculated according to Poiseuille's law:

$$\tau = \frac{4\eta Q}{\pi r^3}$$

where η = viscosity, Q = volume flow and r = internal vessel radius.

Wall shear stress has been shown to be an important determinant of the release of vasoactive compounds from the endothelial cells.[39,40] Several vasoactive molecules stimulate the expression of adhesion molecules and chemokines involved in intima–media thickening.[41] Wall shear stress is related to flow and inversely related to diameter. If a vein is positioned in the arterial circulation, the flow through the vein increases, but so does the diameter. Whether the actual shear stress will be increased or lowered depends on the proportional increase of diameter and flow. Since diameter is in the third dimension (see the above equation), its influence is larger and shear stress will usually be lowered. Normal vessels respond to reduced shear stress due to low flow by constricting, and this response is an endothelial dependent process. In rigid PTFE grafts where vasoconstriction cannot occur, low flow is correlated with increased intimal thickening and may represent an attempt on the part of the endothelial cells to maintain shear stress within the physiological range.[23] The hypothesis that low flow and low shear stress increase intimal hyperplasia has been confirmed by many studies. After implantation of 3-mm diameter PTFE prostheses in the abdominal aorta or inferior caval vein in albino rabbits, IH occurred much faster in the prosthesis in the venous position than in the arterial position, although the morphological changes were mostly identical.[13] Creation of an arteriovenous (AV) fistula distal from a prosthetic bypass increases the flow through the bypass. In animal studies, these high flow bypasses developed less IH than the normal flow bypasses.[23,42–44] Closure of the AV fistula or banding of the prosthesis leads to a decrease in flow. This induced an increase of IH.[23,43,45] Distal AV fistulas also lead to a better patency of prosthetic peripheral bypasses in humans.[46] In bilateral venous bypass grafts of the femoral artery in dogs, one femoral artery was left patent to induce lower flow through the venous bypass, and on both sides the mid-portion of the graft was covered with a restraining Marlex® cuff to prevent dilatation. Low blood flow was best associated with the formation of intimal hyperplasia and deformation of the vessel wall in a circumferential direction was best associated with medial thickening.[47–49] In monkeys, AV fistulas were created unilaterally to increase the flow through the iliac artery. In this study, no increase in IH was found, but the wall shear stress was equal on both sides. It was concluded that wall shear stress, and not the flow rate, might be the essential haemodynamic factor in IH.[50] Also, Zarins *et al*.[51] found no increase in intimal thickness after creation of an AV fistula on one side of the iliac artery to increase flow, although tangential wall tension and tangential wall shear stress were increased. They suggested that increased flow resulted in arterial dilatation and normalisation of wall shear stress and that artery lumen diameter might serve to regulate wall shear stress. Hofstra *et al*.[52] found low local flow velocities to be associated with stenotic lesions in human PTFE peripheral bypasses as well as in human AV fistulas. Although the above studies suggest that low flow and low shear stress induce intimal hyperplasia and high flow and high shear stress inhibit intimal hyperplasia, a number of other studies claim the opposite.

Implantation of 1-cm segments of inferior caval vein into the abdominal aorta in Lewis rats caused the intima–media area of the vein graft to increase significantly with time. Re-implantation of the venous segment into the venous circulation caused a significant decrease of the vein graft intima–media area in 8 weeks.[30] AV fistulas had a higher mean blood flow and higher shear stress than venous bypass grafts in the same animals, and developed less IH.[49] Also, in PTFE AV loop fistulas created between the femoral artery and the femoral vein of dogs, intimal–medial thickness was 50% less in the banded (normal flow) than in the unbanded (high flow) side.[53] In high flow renal-artery-to-caval-vein anastomoses a significant intimal thickening occurred 3 months after implantation.[50] In humans, *in vivo* measurements of peak systolic velocities, normalised for diameter (nPSV) 2 weeks after implantation of graft AV fistulas, indicated that initial local nPSV values at the site of later stenoses were higher in the fistulas developing a stenosis than in non-stenotic fistulas.[54]

In experimental models, following exposure to the arterial environment, venous endothelial cells experience severe stretching and increased tangential stress, both of which contribute to endothelial cell damage.[12,55] Moreover, it has been observed that cyclic stretching of VSMC stimulates synthesis of collagen and other matrix components.[37] This results in wall thickening, even after re-endothelialisation has occurred. How endothelial cells or VSMC transduce shear and wall stress into a biochemical response that controls smooth-muscle growth is still unclear. Several mechanisms have been proposed, including ion channel with activation influenced by shear stress or stretch, mechanical disruption of cell–cell contacts, alteration of focal adhesion dynamics by forces transmitted via the cytoskeleton and changes in the surface concentrations of extracellular agonists.[56] Moreover, positive and negative shear stress responsive elements (SSREs) have recently been identified in the promoted regions of genes involved in the development of intimal hyperplasia, such as PDGF-A and B and TGF-b. These SSRE can either upregulate or downregulate the transcription of these genes in response to changes in shear stress.[57]

To explain the contradictory hypotheses on high and low shear stress as a cause for intimal hyperplasia, several simulation and flow visualisation models have been developed to gain more insight into the distribution of flow velocities and shear stress and the occurrence of IH *in vivo*. Fei *et al.*[58] created a 3-D numerical model with static flow. Within the anastomosis the velocity profile was skewed towards the floor with a stagnation point opposite the mid-portion of the graft lumen. A vortex was formed just upstream. Skewed velocity profiles in end-to-end (ETS) anastomoses produced low or even reversed velocities along the wall in the proximal artery and regions of anastomotic toe and heel, while producing elevated forward velocities along the distal outer wall of the artery. This coincides with flow visualisation studies in an anastomotic model created from *in vivo* peripheral anastomoses.[59] Using a higher Reynolds number to simulate high flow, high wall shear rates were found at all locations as compared to simulations with a low Reynolds number. However, recent studies on flow visualisation and numerical simulation models with pulsatile flow indicate that high temporal and spatial wall shear stress gradients, and not the absolute wall shear stress, are associated with IH.[60–62] The high flow and low flow hypotheses as cause of intimal hyperplasia do not rule each other out. It seems that there is an optimal shear stress, whether it is absolute or a gradient, at which no intimal hyperplasia occurs. High flow will induce flow disturbances at the anastomosis, inducing a high gradient of wall shear stress. Low flow will actually produce reversed flow at the anastomosis, creating a negative wall shear stress. Both circumstances are thought to increase the development of intimal hyperplasia. Moreover, regions of high wall shear stress could cause local vessel wall damage. The vasoactive substances released from these regions might exert their action in regions of low wall shear stress, where a better interaction with the vessel wall is possible due to the longer residence time.

Influence of graft geometry and compliance

End-to-side (ETS) anastomoses develop more IH than end-to-end (ETE) anastomoses.[47,63] However, an ETS distal anastomosis is usually necessary to maintain antegrade and retrograde perfusion. Lengthening of the anastomosis reduces shear stress on the floor of the arterial wall, but not the flow disturbances at the heel and toe. Since endothelial cells are orientated in the direction of the flow in a shingle-like configuration, flow disturbances can lift up the endothelium, thus exposing the subendothelium to the blood elements (platelets etc.). This could induce smooth-muscle cell migration and proliferation.[38]

Variation of graft diameter in ETS anastomoses of venous femoropopliteal bypasses in sheep had no influence on the development of IH.[64] This undermines the theory of Madras *et al.*,[65] who stated that a mismatch in diameter at the anastomosis causes energy dissipation which would lead to physical stress transmitted through the adjacent vascular wall. This stress would be cyclic, synchronous with the heartbeat, inducing VSMC proliferation. Numerical simulation models indicate that the optimal diameter ratio for graft to native vessel is 1.6–2:1.[66] The effect of graft diameter and geometry is demonstrated by Fillinger *et al.* in graft arteriovenous fistulas created between the iliac artery and femoral vein in dogs.[67] With a 4–7 mm tapered graft (4 mm diameter at the arterial side and 7 mm diameter at the venous side), significantly less IH developed at the distal anastomosis as compared to 6 mm grafts. This was explained by less flow disturbance and turbulence at the distal anastomosis of the tapered graft.

A lot of research has been conducted on the angle of the anastomosis. Thus far, no correlation has been found between the angle of the proximal anastomosis and IH.[68] In numerical simulation and flow visualisation models, a lower angle (20°) of distal anastomosis produced less flow disturbance and a lower

range of shear stress variation than higher angles (30°, 45° and 60°).[58,66,69] In a flow visualisation model, the 45° angle was found to be superior, with lowest absolute normalised shear rates and flow separation.[70]

Another factor that might influence IH is compliance mismatch. In a flow visualisation model based on an AV loop graft between the femoral artery and vein of a dog, compliant and non-compliant PTFE grafts were tested. Anastomotic flow patterns were directly affected by the compliance of the graft conduit. In less compliant grafts, flow reversal and vortex formation were more pronounced than in more compliant grafts.[71] Comparing iliofemoral bypass grafts of greater saphenous vein (GSV) to PTFE grafts in dogs showed a larger suture line IH in PTFE than in GSV grafts, whereas the IH at the arterial floor was comparable. It was concluded that suture line IH represented vascular healing. Greater prominence of IH in prosthetic grafts may be related to compliance mismatch. Arterial floor IH was unrelated to graft type and developed in regions of flow oscillations and relatively low shear rate.[59] Decreasing the compliance of venous bypass grafts with a Dacron or Phynox[72] mesh tube resulted in an increase of IH.[64,73] Applying a tight PTFE wrap to reduce the luminal diameter and the tangential wall shear stress reduced total cross-sectional wall area, smooth-muscle cell volume and matrix deposition. A loose wrap, which did not decrease the tangential wall shear stress, did not have these effects.[74] However, Mehta *et al*. recently reported that a loose macroporous velour polyester external stent reduced intimal and medial thickening in venous bypass grafts in pigs. This reduction was associated with a reduced expression of PDGF and a reduced proliferation rate. Since the stented grafts also had a greatly increased vascularity of the neoadventitia that developed between the bypass and the stent, it was postulated that reduced intimal and medial thickening was caused by a decrease of hypoxic damage.[75]

In humans, measurement of GSV compliance before implantation as a femorodistal bypass demonstrated that a lower initial compliance increased the risk on the development of a stenosis. Moreover, GSV with pre-existent moderate-to-severe IH had lower compliance than GSV with no-to-mild IH.[76] *In vivo* measurements of elastic properties, expressed as area increase (AI) during a cardiac cycle, have been performed with ultrasound. It was found that a decline in AI occurred at the arterial anastomosis of PTFE AV fistulas, whereas an increase of AI occurred at the venous anastomosis. The authors stated that since an increase in AI is associated with flow disturbances, the mismatch in elastic properties may contribute to the predisposition of the venous anastomosis for IH.[77] However, after comparing the initial elastic properties to the follow-up data on stenosis, a better initial (2 weeks postoperative) match was found around the venous anastomosis of AV fistulas which developed stenosis as compared with the non-stenotic fistulas.[54] Numeric simulation model studies of a distensible ETS anastomosis confirmed the fact that compliance mismatch was not an important factor in the development of intimal hyperplasia. Only minor changes in overall wall shear stress patterns were observed. It is suspected that the effects of wall distensibility are less pronounced than those brought about by changes in arterial geometry and flow conditions.[60]

It is understandable that vein graft compliance does not play an important role in the development of IH when one considers that vein grafts are almost rigid at arterial pressure and the compliance of the anastomotic region resembles that of the artery rather than that of the vein.[47]

Anastomotic Cuffs and Patches

In an attempt to improve the patency of peripheral arterial bypasses, a number of different anastomosing techniques have been developed. In these techniques, venous material is used in a transverse orientation to create a gradual transition of elastic properties and to facilitate the anastomosing of two vessels of different diameter and wall structure.

Miller cuff

The venous cuff was first described by Siegman in 1979 to make a smooth connection between a venous or Dacron bypass and the thickened atherosclerotic artery and to make the anastomosis technically easier (Fig. 2a).[78] Miller adopted this technique and found that it also had a positive effect on graft patency, which he ascribed to a better transition in elastic properties.[10,79]

Although no controlled trial was conducted, the "Miller cuff" was embraced by vascular surgeons to improve the poor results of femorodistal PTFE bypasses. Multiple reports on their achievements have been published, mostly with improved patency rates as compared to the literature or historic controls. The 1-year patency rates of bypasses with a Miller cuff vary from 47% to 83% compared to 66% without a venous cuff.[80–82] Three-year patencies vary between

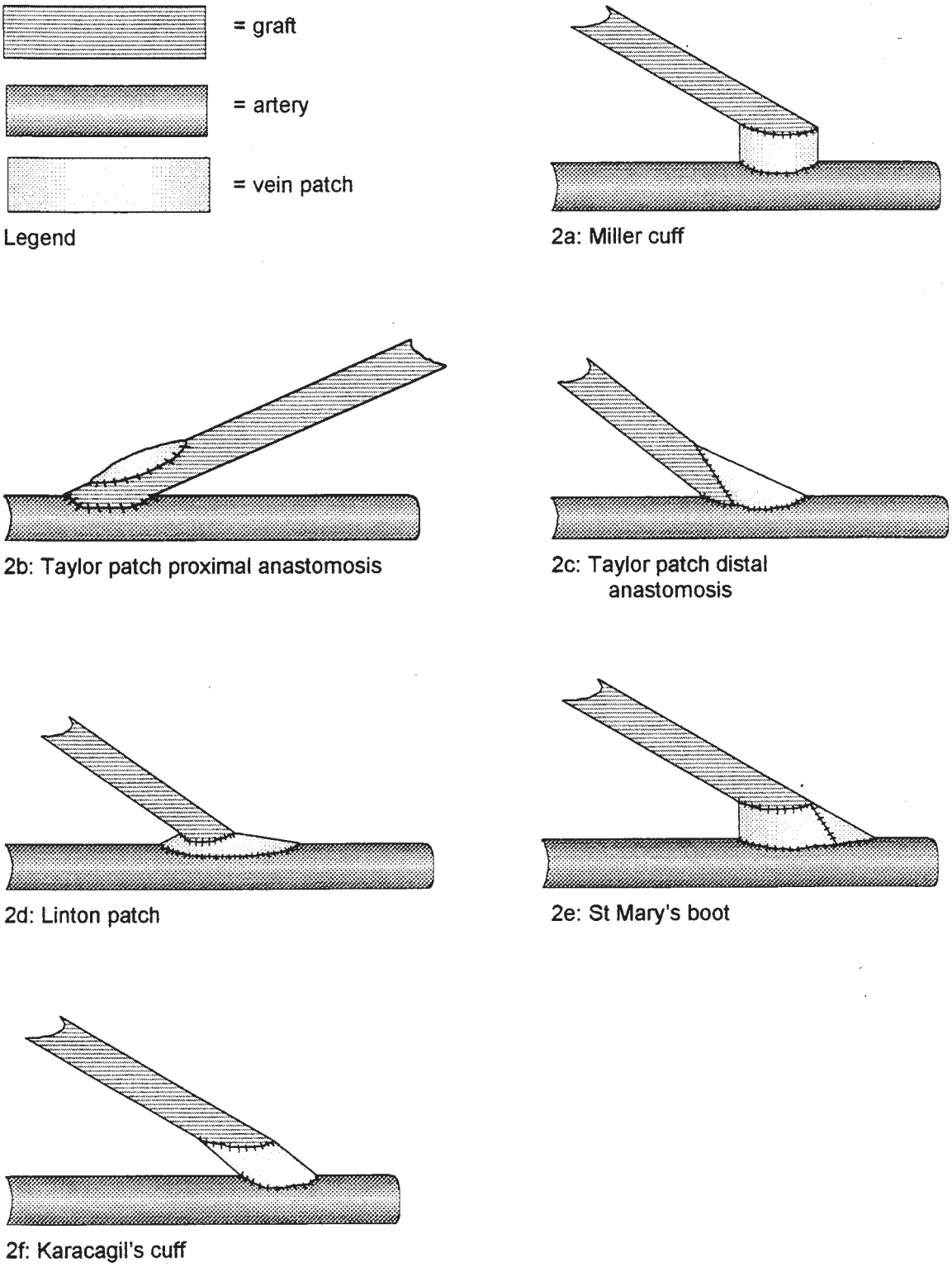

Fig. 2. Types of venous cuffs used to decrease anastomotic intimal hyperplasia.

29 and 38% with cuff and from 7 to 19% without cuff.[81,83–87] In a retrospective study an increase in 1-year patency rates was reported from 38% in PTFE bypasses with an arteriovenous fistula at the distal anastomosis ($n=76$) to 62% by adding a Miller cuff ($n=43$). It seemed that the cuff and arteriovenous fistula acted

synergistically rather than simply additively. The arteriovenous fistula increases flow, thus decreasing the risk on platelet adhesion, but it induces instability of flow and the development of intimal hyperplasia. It is supposed that the cuff compensates for these adverse effects.[88]

However, one retrospective study reported poor results with the vein cuff. Brumbe *et al*.[89] found that infragenual bypasses with PTFE and a venous cuff had a 1-year patency of 40%, whereas in normal anastomosed bypasses this was 61%. Above the knee even greater differences were found: 66% patency without and 14% with cuff. Recently a prospective randomised study showed that the Miller cuff does not improve the patency of above-knee femoropopliteal grafts, but it does improve the patency of below-knee femoropopliteal and femorocrural bypasses. This was attributed to the fact that the Miller cuff simplified the anastomosing technique of a stiff prosthesis to a small-calibre crural vessel.[90] Despite these controversies, the Miller cuff is now widely used by surgeons in various vascular reconstructions.[91,92]

Taylor patch

In the early 1980s, Taylor developed a venous patch that was stitched into the distal anastomosis to prevent intimal hyperplasia and thus improve patency rates of PTFE bypasses (Fig. 2b). Since the proximal anastomosis was also prone to develop intimal hyperplasia, a different type of patch was developed in this position (Fig. 2c).[93–95] In a subsequent publication on the causes of failures of PTFE grafts, 19% of which was due to intimal hyperplasia, Taylor states that, "The development of a technique to insert vein patches across the anastomoses appears to eliminate the significance of intimal hyperplasia".[7] However, no literature or data were shown to support this statement. Five years later Taylor published very good patency rates of PTFE peripheral bypasses (5-year patency rate of 71% for femoropopliteal and 54% for infrapopliteal grafts). These results were considerably better than published previously by others (patency 0–49% overall) and historical series from Taylor's own clinic (21 infragenual femoropopliteal grafts had a 2-year patency of 81%, the first 45 patched bypasses of 94%).[96] A sub-analysis of PTFE grafts to an isolated popliteal segment showed even better results: the cumulative patency was 84% at 1 year and 76% at 3 years, whereas the literature reports patency rates of 48–53% at 1 year and 24–35% at 3 years.[97] However, no randomisation was performed and the results of the Taylor patch are single-centre. Therefore extrapolation to the general peripheral bypass population is difficult.[98]

Linton patch

Batson *et al*.[99] described a patch technique in which the native artery is patched with a venous segment of 4–5 cm in length. In the proximal part of the vein patch, an incision is made to connect the graft (Fig. 2d). Femoropopliteal and femorodistal bypasses created with this technique had a 1-year patency of 74% and 2–4-years patency of 65%.

St Mary's boot

Although the Miller cuff and Taylor patch seemed successful in preserving long-term patency in infragenual PTFE bypasses, the development went on. The rectangular angle that connects the Miller collar to the recipient vessel produces considerable turbulence when examined by duplex scanning.

The Taylor patch has a haemodynamically smoother transition. However, it has a considerable area of PTFE connected directly to the artery. If this connection and the compliance mismatch do play a role, intimal hyperplasia remains likely at this site. Therefore, Tyrrell and Wolfe designed a new venous collar that incorporated the advantage and eliminated the disadvantages of both techniques (Fig. 2e).[100] Although their "how we do it" was published 5 years ago, no clinical results have been reported as yet. Based on the hypothesis that the geometric alteration and not the interposition of venous material is important in the supposed beneficial effect of the cuff, Brennan *et al*.[101] have developed a cuffed prosthesis by using balloon dilatation of the distal segment. Recently, a prosthesis based on this design became commercially available and the early results are promising.[102]

Karacagil's modified cuff

Karacagil, too, recognised the haemodynamically unfavourable rectangular angle of the Miller cuff and made his own modification: a V-shaped patch is sutured first to the prosthesis and then to the artery. In this way an oblique angle connection is made. Also, suturing the cuff first to the graft and then to the artery is easier than the other way

around, as is done with Miller and Tyrrell cuffs (Fig. 2f). Patency rates of the first 21 patients were 75% at 6 months and 69% at 12 months. All anastomoses were to the below-knee arteries.[103] Again, the real advantages can only be assessed by a prospective randomised study.

Research on Anastomotic Cuffs and Patches

In vitro *experiments*

Beard *et al.*[104] were the first to examine the haemodynamics of the Miller cuff *in vitro*. They embedded anastomotic complexes of PTFE prostheses to cadaver internal mammarian arteries with or without a Miller cuff into silastic foam and perfused it with whole human citrated blood through a hydraulic system. Flow was measured proximal to the anastomosis. Anastomoses with a Miller cuff had significantly higher blood flows than standard anastomoses, especially when the recipient artery was smaller than 2 mm. The investigators hypothesised that this haemodynamic advantage was caused by the compliant vein cuff that allowed more distension of the anastomosis and reduced anastomotic resistance.

However, Tyrrell *et al.*[105] could not reproduce these results. One of the possible explanations is that, in the *in vitro* setting as described above, there always is suture-line leakage. As the suture line of the Miller cuff is longer than that of the standard anastomosis, the former would have more leakage. Flow measurements proximal to the anastomosis, as carried out by Beard *et al*., could have been biased by this leakage. Tyrrell *et al*. measured flow in the recipient artery to overcome this problem and found no difference in flow. The volume flow was correlated to the diameter of the vessel at the toe of the anastomoses with a Miller cuff and a Taylor patch, but not in the direct anastomosis. The authors concluded that the direct anastomosis has an increased resistance to flow as compared to the anastomosis with a Miller cuff or a Taylor patch. To assess this, silicon casts of the anastomoses were manufactured, and maximal and minimal diameter were measured. The roundness of the anastomoses was calculated by division of these two dimensions. As a perfect circle has the greatest cross-sectional area for any given circumference, less roundness indicates a higher resistance. The median roundness was less for direct anastomoses (81%) than for either the Miller cuff (92%) or patch (93.5%) anastomoses.[106,107] The direct anastomoses had a higher resistance, which may lead to a reduced volume flow and may cause more flow disturbances.

Local haemodynamics within a Miller cuff were also studied in an *in vitro* model. During most of the cardiac cycle a unidirectional coherent vortex developed in the cuffed anastomosis. This vortex had a high velocity with greater shear stress exertion on the vessel wall than laminar flow. In view of the hypothesis that low shear stress would induce intimal hyperplasia, the increase in shear stress could explain the beneficial effect of a cuff on anastomotic IH.[108] In numerical simulation models, the Taylor patch had a less disturbed flow and a lower wall shear stress gradient than a standard anastomosis. This was associated with larger anastomotic surface areas, smoother curvatures at and near the anastomosis and smaller anastomotic angles, with approximately 10° being superior.[66] Another feature of the cuff was examined using greater saphenous vein specimens. Pressure-dependent changes in diameter indicated that the fresh long saphenous vein was anisotropic, with a mean longitudinal strain 7.2 × that of the circumference. Cutting the vein lengthwise and stitching it decreased this ratio to 1.95. The Miller cuff and Taylor patch are likely to take maximum advantage of these mechanical characteristics, since the long axis of the vein and arteriotomy are aligned. This may improve PTFE graft patency.[106,109] A cuff or patch at the venous anastomosis reduces anastomotic resistance, which could increase volume flow and reduce flow disturbances. Also, due to the better transition of mechanical characteristics, less flow disturbances are expected.

Animal studies on mechanical properties and histology

In a study on the development of intimal hyperplasia in the infrarenal aorta of rabbits, prosthetic patches induced more intimal hyperplasia than venous patches. The largest intimal hyperplasia was induced in regions of the arterial wall that were subjected to the highest stress. According to the Law of Laplace (wall stress $= \frac{1}{4} \Delta \times p \times r$) the arterial wall stress increases with patch width. To limit intimal hyperplasia, venous patches should be used and they should not increase the total circumference by more than 30%.[79] In a canine model, Taylor-patched anastomoses of prosthetic arteriovenous fistulas developed less intimal hyperplasia than standard anastomoses.[110]

Suggs *et al.*[111] implanted PTFE bypasses in carotid arteries of dogs, with venous cuffs on the proximal and distal anastomosis at one side and normal anastomoses on the other side. The average diameter 1 mm distal to the graft toe was significantly smaller in non-cuffed than in cuffed grafts. The authors stated

that inhibition of stenosis formation by the vein cuff might be caused by inhibition of proliferation of smooth-muscle cells due to a wider distribution of kinetic energy (less compliance mismatch) or due to interposition of venous endothelium which offers a humoral protection.

The effect of the mechanical properties of the Miller cuff on the development of intimal hyperplasia was studied in bilateral PTFE carotid artery bypasses in dogs.[112] On one side the expandability of the vein cuff was limited by making a PTFE jacket around it, on the other side a normal Miller cuff was created. No difference in intimal hyperplasia thickness was found. To assess whether the angle played a role, a Miller cuff anastomosis was created on one side with a vein and on the other side with PTFE. Bilateral graft thrombosis occurred in 80% of the animals, suggesting that the perpendicular anastomotic angle was not protective. From these results the authors concluded that the protective effect of the vein cuff was not mechanical in origin. Possibly the autogenous endothelium provided a humoral protective effect. This might also explain the effectiveness of the Taylor patch, since, in the Taylor patch, part of the prosthesis is directly connected to the native artery.[112] This part would not benefit from a mechanical effect of the vein patch. However, if the venous endothelium releases substances that decrease IH, the whole anastomotic area might profit.

Sottiurai[38] performed a series of experiments to assess the cause and prevention of distal anastomotic intimal hyperplasia. Using a Linton patch, he found that, in the rigid standard PTFE grafts, Doppler waveforms and patency were better than with a direct anastomosis. In thin-walled PTFE grafts, the Doppler waveforms and patency were adversely affected by a cuff. Intimal hyperplasia did occur in the cuffed rigid PTFE anastomoses, but was less pronounced compared to prostheses without a venous cuff.[113]

Risk Factors and Pharmacological Interventions

Factors associated with failure of vascular reconstructions include patient-related factors like continued smoking of cigarettes and hyperlipidaemia, and local factors like reconstruction of relatively small vessels with low blood flow, excessive vessel distension during preparation of the conduit (vein graft) or substantial injury during the reconstruction.[2,33,114]

In animal studies, pharmacological interventions had variable success in diminshing the development of IH. Dietary supplementation with L-arginine in hypercholesterolaemic New Zealand white rabbits reduced intimal thickness by 24%. EC function improved, but not the hypercholesterolaemia-associated VSMC phenotype.[115] The antioxidant Lazaroid decreased the mean intimal-thickness increase by 41% in New Zealand white rabbits with an external jugular vein interposition bypass in the carotid artery. However, the luminal diameter and medial thickness did not alter, nor did the 3H-thymidine incorporation in VSMC *in vitro*.[116]

Dobrin *et al*.[47] found a significant decrease in intimal area in vein femorodistal bypass grafts in dogs treated for 3 months with aspirin and dipyramidole as compared to non-treated animals. However, the ACE-inhibitor Cilazapril, given to baboons with aortoiliac bypasses, did not decrease IH at the site of graft anastomosis.[117] In a sheep model, low molecular weight heparin reduced formation of IH on a Dacron graft inserted in the common carotid artery.[118]

In humans, a reduction of the incidence of restenosis following PTCA *in vivo* has been achieved with an antibody to GPIIb-IIIa, an adhesion molecule, necessary for platelet aggregation.[119] However, antithrombotic approaches in humans using drugs like aspirin, dipyridamole, ticlopidine, dextran, and coumarin have produced little or no benefit.[2]

Treatment of Stenosis Due to Intimal Hyperplasia

Since neither improvement of graft geometry nor pharmacological therapy has yet led to prevention of intimal hyperplasia, treatment of stenoses and thrombotic occlusions remains the most important means to maintain graft patency.

Current methods of graft salvage are either surgical or endovascular. Surgical techniques include thrombectomy and graft revision with patch angioplasty or jump graft extension.[120] If the stenosis is near the anastomosis and sufficient graft length remains, a reanastomosis can be performed. Other short stenoses can be treated with removal of the hyperplastic tissue and closure of the vessel wall with a venous or prosthetic patch. Lesions that are long or difficult to reach can be bypassed with a jump graft extension.

Percutaneous endovascular techniques have a number of advantages over surgical treatment: due to their technical simplicity and there being no need for general anaesthesia, hospital stay and morbidity are reduced. Moreover, they can be applied in patients in bad physical condition, in whom surgery is contraindicated.

However, the use of PTA is limited to stenoses

shorter than 5 cm. Occlusions can be treated pharmacomechanically or mechanically by atherectomy,[121,122] although this has less success and less long-term patency and a greater number of complications. Complications include haemorrhage and pseudoaneurysm formation at the puncture site, subintimal dissection or performation at the angioplasty site and distal embolisation.[123] Recurrence or recoil of the stenosis can be treated with an intravascular stent.[124]

In animal experimental studies, radiation therapy suppressed the development of intimal hyperplasia.[125] Recently, endovascular brachytherapy has been introduced clinically to reduce restonosis after PTA. The results are promising, although no prospective trials have been published yet.[126]

Summary

At present, the only approach for treatment of IH is surgery, angioplasty and possibly brachytherapy.[2]

However, IH not only poses a mechanical obstruction. Assuming that the vessel wall has lost its normal endothelial layer, at least transiently, and that the VSMC are transformed from a quiescent contractile state to a proliferative non-contractile phase, many normal physiological functions of the vessel wall are also altered.[127] To diminish endothelial dysfunction, endothelial cell injury, endothelial denudation and smooth-muscle cell injury, the "no touch" technique should be applied, where there is minimum manual and instrumental contact with the vessel.[128] However, this does not influence the effects of flow, shear stress and compliance on the endothelium. There is still controversy as to whether high or low shear stress induces IH. The high shear stress and low shear stress theories are probably not mutually exclusive. The stresses in the high shear regions may induce IH in the low shear regions by causing EC to secrete growth factors that accumulate in the low flow regions.[70] Possibly there is an optimum for flow and/or shear stress with minimal development of IH, whereas anastomotic hyperplasia does occur when flow is unusually slow or rapid. This hypothesis was postulated in the early years of research on intimal hyperplasia and it seems to be still topical.[129] Moreover, rather than the absolute wall shear stress, the temporal and spatial gradient of wall shear stress might be of great importance. Based on this hypothesis, numerical simulation models have calculated an optimal anastomotic design with minimal flow disturbance and low wall shear stress gradient. The optimal anastomosis has a 1.6–2: 1 graft-to-artery diameter, a heel angle of between 10° and 15° and at the toe a gradual transition in curvature and cross-sectional area.[66] However, there are no clinical data available on this design.

A number of different anastomosing techniques have been introduced over the last 40 years to influence the haemodynamic conditions. All seem to have their own advantages and disadvantages, with different clinical results. There is a wide variability in indication for operation, site of distal anastomosis and quality of the runoff. Also there is a marked difference in reporting the results, which were mainly retrospective and sometimes reported as only primary, or also secondary patencies. A number of *in vitro* and animal studies were performed trying to resolve the mystery of cuffs and patches. Less oval distortion of the anastomosis, better compliance match and interposition of venous endothelium were mentioned as possible positive effects. Since the actual causes of intimal hyperplasia are still unclear, these are mere speculations. Only a prospective randomised trial can resolve the controversy that still exists as to whether the different anastomotic techniques improve patency and what technique induces the best patency results. Taylor has challenged Tyrrell and Wolfe to perform a randomised trial to compare the Taylor patch to the Miller cuff.[95] In a letter to the editor, John Ligush convoked vascular surgeons to perform prospective randomised trials on the effect of the Taylor patch, using the experience gained from the large carotid endarterectomy trials.[98]

Although more authors have announced prospective studies with different types of cuffs,[88,89] only one trial has been published and found improved patency in femorocrural bypasses but not in femoropopliteal bypasses.[90] The Columbus Vascular Surgery Society Taylor Patch Study is also conducting a prospective trial. The objective is to compare 5-year patency rates of infragenual PTFE grafts with or without Taylor patch. Until February 1996 about one-third of the target number of patients (225) were included in 18 months.[130] Results of this study are not yet published.

Intimal hyperplasia remains one of the major obstacles to long-term graft patency. It appears to be the response of the vascular smooth-muscle cells to a combination of physical, cellular and humoral factors accompanied by dysfunctional endothelial regulation.[2,50] It is now apparent that any form of endothelial trauma will produce a thickened neointima as part of the healing response. It has to be appreciated that neointimal hyperplasia occurs at different sites following different procedures, but will not always have the same sequelae.[127] Given the multifactorial nature of the aetiology of intimal hyperplasia, it may

be that a single pharmacological agent will not prove capable of controlling smooth-muscle cell proliferation. However, since the geometry of the ETS anastomosis induces IH, and this geometry cannot be easily altered, pharmacological control of IH might be the only way to actually prevent IH.

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