

Harnessing Haemodynamic Forces for the Suppression of Anastomotic Intimal Hyperplasia: the Rationale for Precuffed Grafts†

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Objectives: standardisation of cuff geometry by manufacturing prosthetic precuffed grafts (PCG) theoretically optimises haemodynamic forces. This study was designed in order to determine whether these beneficial flow patterns are replicated in vivo in PCG.

Patients and Methods: flow visualisation and Doppler studies performed on anatomically accurate PCG models characterised in vitro anastomotic flow patterns. Thirty-two patients (median age 68 years) in whom autologous vein was unavailable, underwent bypass using PCG. Post-operative analysis included qualitative assessment of flow within the distal anastomosis using Doppler colour flow mapping. Cardiac gating techniques and assessment of velocity distribution were performed to gain additional information. These in vivo results were validated against the bench studies.

Results: a cohesive vortex was identified within the distal anastomosis of in vitro models and had an integral relationship with the cardiac cycle. This flow structure was also characterised using Doppler colour flow mapping in both longitudinal and transverse planes, confirming the location of the vortex within the body and proximal part of the anastomosis. Twenty-two patients (69%) undergoing bypass with a PCG underwent successful Doppler assessment one week post-operatively, of whom 17 (77%) had a vortical flow structure identified at the distal anastomosis, similar to that characterised in vitro. Cardiac gating verified the same integral relationship of the vortex with the cardiac cycle as that described in vitro.

Conclusion: the geometric configuration of precuffed grafts induced vortices within the distal anastomoses in 17 out of 22 patients undergoing arterial reconstruction, thereby harnessing the haemodynamic forces that may suppress anastomotic hyperplasia and improve patency rates.

Key Words: Femorodistal; Precuffed graft; Myointimal hyperplasia; Haemodynamics.

Introduction

The successful management of critical limb ischaemia involves femorodistal arterial reconstruction in over 60% of cases, and with a prevalence of 40/100 000 in the U.K., this amounts to 20 000 procedures per annum.¹ Although there is strong evidence supporting the preferential use of autologous vein,^{2,3} its absence in up to 30% of cases necessitates the use of prosthetic material, commonly expanded polytetrafluoroethylene (ePTFE). Deleterious effects upon patency and limb salvage rates are observed with prosthetic grafts, particularly

those extending below the level of the knee joint.^{4,5}

The interposition of vein at the distal anastomosis has been incorporated into the surgeons armourmentarium in an attempt to improve the situation, with numerous series reporting increased patency rates with a variety of anastomotic configurations, including the Taylor patch, St. Mary's boot and the Miller cuff.^{6–11} Stonebridge *et al.* reported the only randomised control trial comparing PTFE grafts with and without vein cuffs, and identified a significant improvement in primary and secondary patency with the Miller cuff in infragenicular bypasses.¹⁰ Several theories have been postulated as to why this may be, including the easier handling of vein at the distal anastomosis, a buffering of the compliance mismatch between native vessel and prosthetic material, and the modification of haemodynamic forces.

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The commonest cause of infrainguinal graft occlusion is the development of distal anastomotic myointimal hyperplasia (MIH), resulting in a critical stenosis, associated with a reduction in graft flow below the thrombotic threshold velocity. Sotturrai *et al.*¹² described canine end-to-side models in which ilio-femoral PTFE grafts developed MIH exclusively at the distal anastomotic heel, toe and along the recipient artery floor. How *et al.*¹³ reporting bench studies, identified these regions to be areas of low velocity and recirculation, and therefore susceptible to low wall shear stress. A modified flow pattern within the Miller cuff was described by da Silva *et al.*¹⁴ who observed the formation of a vortex within the proximal cuff, and speculated that this may increase wall shear stress at critical points, thereby potentially inhibiting the accretion of MIH. Indeed, the redistribution of hyperplasia away from the critical juxta-anastomotic regions and up towards the more capacious graft-cuff interface has been identified both angiographically and in explanted grafts.¹⁵

Further studies indicate that the geometrical dimensions of the Miller cuff also influence the flow patterns, and identify the Aspect Ratio (cuff length: cuff height) as an important factor.¹⁶ Accurate construction of dimensionally specific cuffs in an often anatomically hostile environment is difficult. If the dimensions can be standardised, however, then flow and haemodynamic forces should be optimised, thus maximising the potential benefits described for the interposition cuff. This concept has actuated the development of the precuffed graft (PCG), with pre-determined dimensions, manufactured in thinned PTFE for improved conformability, ensuring geometric precision at the distal anastomosis.¹⁷ This commercially available graft (Distaflo,™Bard/Impira) has attracted much clinical interest although, to date, the formation of potentially beneficial flow patterns remains theoretical.

This study was devised in order to identify the flow patterns within *in vitro* precuffed grafts, and to confirm whether they are replicated *in vivo*.

Patients and Methods

In vitro studies

In vitro bench work involved flow visualisation studies on anatomically accurate models of PCG, manufactured using rapid prototyping techniques, incorporating computer aided design and modelling (CAD/CAM) techniques previously described by

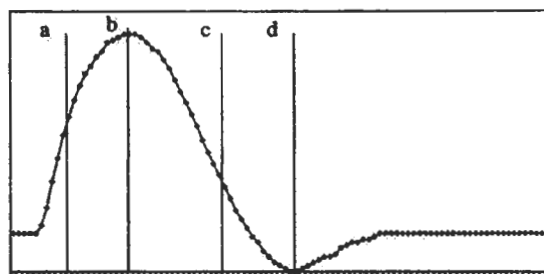


Fig. 1. Biphasic waveform (frequency=1 Hz, mean flow vol=130 ml/min) used to perfuse *in vitro* models. Flow visualisation points. (a) acceleration, (b) peak systole, (c) deceleration, (d) peak diastole.

Chong *et al.*¹⁸ The original anastomotic data was collected from a resin cast of the PCG, with the final model being either a hollow cast set within a transparent silicone rubber block, or a thin walled polyurethane mould, both with identical internal geometry. The former enabled cross illumination by a Helium-Neon laser facilitating planar particle flow visualisation, whilst the latter was echo-lucent, allowing colour flow mapping with Doppler ultrasound. Both models were incorporated into a specifically designed flow rig. A computer driven twin pump system provided the pulsatile flow which perfused the models with a blood analogue solution (40% glycerol, weight: weight, producing a dynamic viscosity, $\mu = 3.65 \times 10^{-3}$ Pa s and density $\rho = 1160 \text{ kgm}^{-3}$ at 25 °C). The flow characteristics were chosen to resemble physiological conditions at rest, derived from Doppler ultrasound measurements of *in situ* grafts and consisted of a biphasic waveform with a frequency of 60 beats per min, producing a mean flow rate of 130 ml/min (Fig. 1) corresponding to a Reynolds Number (Reynolds number = $UD\rho/\mu$, where U is the mean velocity, D the diameter, ρ the density and μ the dynamic viscosity of the fluid) of 146 in a 6 mm graft, and a mean pulsatility index (peak-peak amplitude/ mean height of the flow waveform) of 4.5. The Womersley's parameter ($\alpha = D/2[2\Pi f\rho/\mu]$ where f is the frequency of the flow waveform) was 4.24. The ratio of distal to proximal outflow was varied from 50:50 to 100:0.

Laser flow visualisation

The blood analogue was seeded with reflective particles (Rilsan blue, diameter 75–150 μm . Elf Altochem, Berkshire, U.K.) which achieved neutral buoyancy on addition of sodium chloride to the solution (approximately 7% w:w) The tracer particles, following the flow pathlines within the model, were illuminated by a thin sheet of light produced from a 16 mW helium-neon laser and line generator. The flow pattern in the longitudinal mid-line plane within the precuffed

model was recorded onto SVHS using a monochrome video camera, as well as being captured and stored as a series of single frame digital images (Cannon Powershot Pro 70 digital camera). An electronic timer, developed in-house, indicated the position in the waveform at which each frame was imaged. This facilitated qualitative analysis of the flow patterns throughout the cycle.

Doppler ultrasound studies were performed on the echo-lucent polyurethane model, which was incorporated into the same rig, under identical parameters. Orgasol particles (Elf Atochem, Berkshire, U.K.) of diameter approximately 20 microns, replaced the Rilsan blue, in order to generate a Doppler signal, and the model was submerged in a water bath to provide a suitable medium through which ultrasound could pass. A Philips CVI P700 derived a signal from a 5 MHz probe that was optimally fixed over the model, and enabled colour flow mapping and velocity profiling at the distal anastomosis. The distribution of the velocity into either antegrade or retrograde flow was deduced from the trace of the velocity profile.

In vivo study

Patients requiring infrainguinal arterial reconstruction for critical limb ischaemia or severe, debilitating claudication, in whom autologous long saphenous or arm veins were unavailable, underwent bypass with a precuffed ePTFE graft. Prospective follow-up was by means of a one week post-operative Doppler ultrasound scan (Aloka, Keymed, Essex, U.K.). Colour flow mapping provided qualitative data on the flow patterns in the longitudinal and transverse planes within the graft. Cardiac leads were used to allow gating, whereby the development of the flow patterns could be synchronised with each stage of the cardiac cycle. A 5 MHz ultrasound probe was used as standard, however deep anastomoses in oedematous limbs were better visualised with a 3.5 MHz probe. Further analysis including the velocity profile of flow within the anastomosis was possible using an in-built software package provided by the colour flow scanner, or incorporating a Philips CVI P700 doppler machine into the assessment.

Patients

Between January 1999 and July 2000, a total of 32 patients underwent infrainguinal bypass using a precuffed ePTFE graft; 19 male (59%) and 13 female

(41%), median age 68 years (range 40–88). Twenty-nine patients (91%) fulfilled the criteria of critical limb ischaemia as outlined by the Second European Consensus,¹⁹ whilst the remaining three had symptoms of debilitating claudication. A total of 16 patients (50%) had undergone 23 previous ipsilateral surgical interventions for peripheral ischaemia, with a further 4 patients having required ipsilateral radiological intervention alone. Relevant past medical history included 17 patients (53%) with ischaemic heart disease, 11 (34%) suffering from either type I or type II diabetes, 13 (41%) with a history of hypertension and twenty-six (81%) either current or ex-smokers. At the time of operation the patient cohort had a median American Society of Anaesthesiology (ASA) score of 3.

The proximal anastomosis was to the common femoral artery in 25 patients (78%), the iliac vessels in 4 (13%), the above knee popliteal artery in one (3%), and previous *in situ* graft material in two (6%). The recipient artery was infragenicular in the majority of cases (87.5%), with the distal anastomosis to the above knee popliteal vessel in only 4 patients (12.5%), the below knee artery in nine (28%), and a crural vessel in 19 (59%). Thirteen of the bypasses were classified as redo procedures (41%), and there was a median number of outflow vessels of 1 (range 0–3).

Results

In vitro study

Flow visualisation (Fig. 2)

Systole begins with the acceleration phase, with laminar flow seen within the graft. As fluid moved into the cuff, the flow expanded to occupy the entire volume, with linear pathlines observed in the distal and proximal aspects of the cuff. When equal flow distribution was present there was a fluid division point midway along the recipient artery floor into the distal and proximal outflow vessels.

As peak systole was reached a region of flow separation occurred at the proximal cuff wall, which developed during the deceleration phase into a cohesive vortex, occupying approximately one third of the cuff. This highly stable vortex, exhibiting anticlockwise rotation, expanded as the velocity decreased throughout the latter stages of systole. The creation of this vortex and its subsequent expansion led to a dynamic point of flow division which moved distally along the recipient artery floor. The cuff toe and artery interface demonstrated a small region of flow separation and recirculation that extended a short

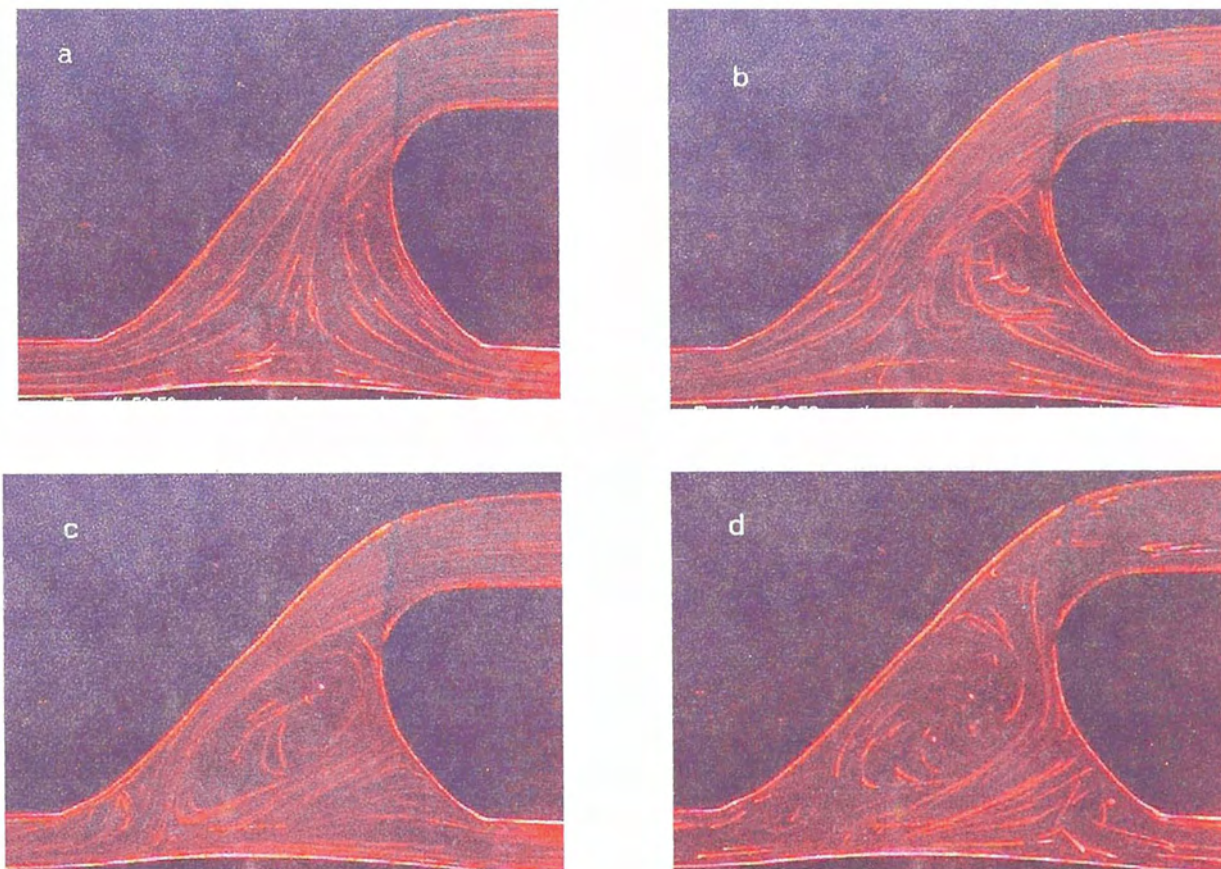


Fig. 2. Flow visualisation within a precuffed graft model. (a) acceleration, (b) peak systole, (c) deceleration, (d) diastole.

distance along the superior wall of the artery and persisted from deceleration until the onset of diastole (approximately 0.1 s), whereupon the retrograde flow eliminated it.

Onset of diastole was characterised by reverse flow within the run-off vessels. Fluid from the distal outflow passed along the artery floor, inferior to the vortex, and ascended up the proximal cuff wall, where it was joined by flow from the proximal vessel. The direction of diastolic flow within the cuff perpetuated the anti-clockwise rotation of the vortex, and created a short-lived flow division point along the roof, where graft becomes cuff.

There was little net outflow in the latter stages of diastole, however the vortex persisted, behaving in a characteristic manner, expanding as it rotated. The arrival of the next cardiac cycle completely removed all the flow particles from the cuff.

A monophasic waveform, with continuous low velocity forward flow throughout diastole, produced similar flow patterns, with a stable vortex developing in the deceleration phase and persisting throughout the cycle.

Outflow distribution imparted some minor changes, with purely distal outflow reducing the size of the vortex; otherwise flow remained similar (Fig. 3).

Doppler studies (Fig. 4)

The acceleration phase of the cardiac cycle was characterised by purely antegrade (red) flow within the graft and cuff in a longitudinal plane. As the cycle moved from peak systole into the deceleration phase, an area of retrograde flow, signified by blue, was seen to develop within the proximal aspect of the cuff. This expanded to occupy the proximal half of the cuff. This flow structure persisted for the rest of the cardiac cycle. A view through the transverse axis of the graft and cuff verified the position, direction of motion, and relationship to the cardiac cycle of this flow structure (Fig. 5a).

A velocity profile of flow through the cuff, from top to bottom, clearly indicated an antegrade flow component within the superior cuff, changing to a retrograde component within the inferior cuff (Fig. 6a) representing the rotational flow of a vortex.

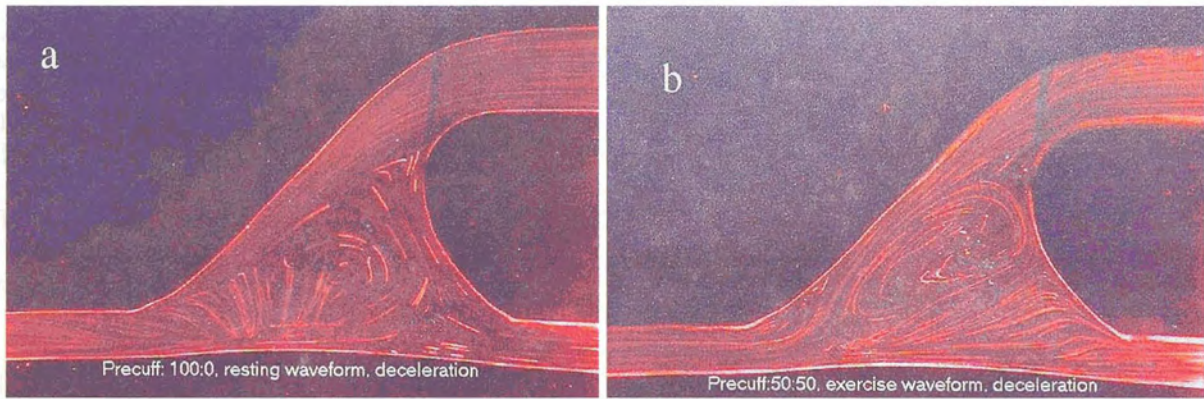


Fig. 3. Flow visualisation within precuffed graft model. A vortex demonstrated with (a) purely distal flow and (b) monophasic waveform.

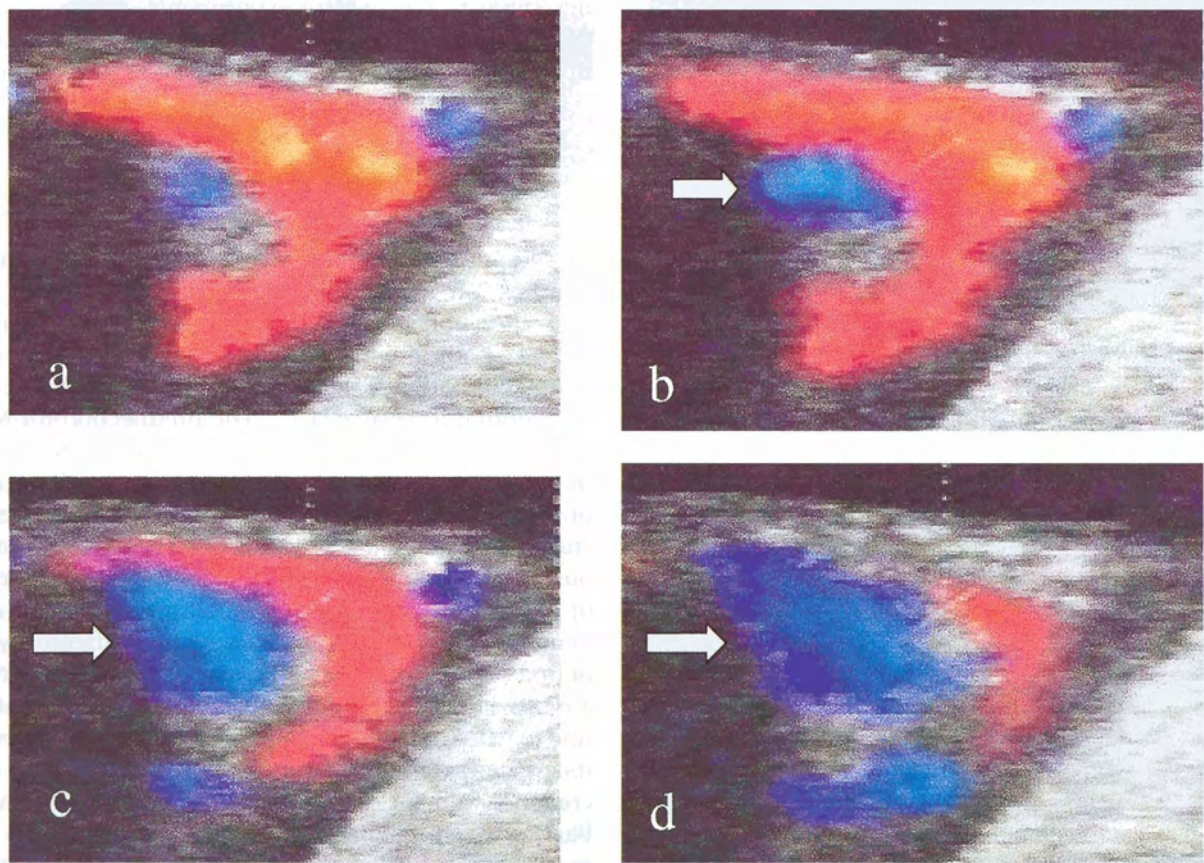


Fig. 4. Doppler colour flow mapping of *in vitro* precuffed models demonstrating the relationship of the vortex (arrowed) to the cardiac cycle. (a) acceleration, (b) peak systole, (c) deceleration, (d) late diastole.

In vivo study

Thirty-two patients underwent infrainguinal arterial reconstruction using a PCG, of which 22 (69%) were successfully scanned after the first post-operative week. 10 patients did not have Duplex assessment including one patient with graft occlusion who died on the third post-operative day due to myocardial infarction, 4 patients whose grafts occluded within

one week, 2 patients with extensive ulceration of the lower limb precluding accurate assessment and 3 patients prematurely discharged.

The orientation of images are the same as *in vitro*, with inflow on the left and distal outflow on the right. Qualitative analysis by colour flow mapping typically showed the presence of a flow structure closely related to that seen *in vitro*, with antegrade (red) flow along the hood of the cuff, and a retrograde (blue) component

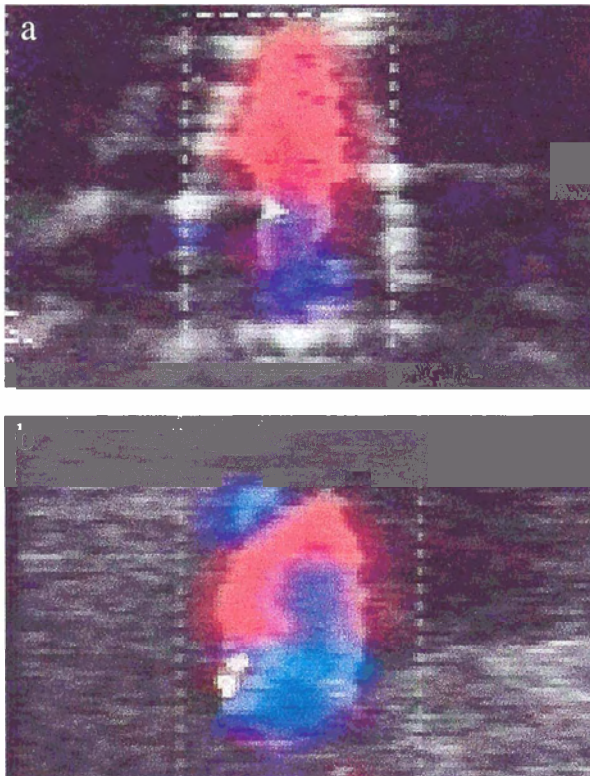


Fig. 5. Colour flow mapping in the transverse plane. (a) *in vitro*, (b) *in vivo*.

within the body and proximal aspect of the cuff (Fig. 7). The location of this flow structure was reiterated when viewed in the transverse plane (Fig. 5b). The bi-directional features of this flow were confirmed by assessment of velocity distribution in the longitudinal plane (Fig. 6b).

Cardiac gating identified unidirectional flow through the cuff during the acceleration phase, developing into a bi-directional flow structure at peak systole and during deceleration, characterised by the red and blue colour mapping (Fig. 7). This structure, with antegrade and retrograde flow components, persisted throughout the remainder of diastole.

This characteristic flow structure typified the vortex described in the *in vitro* experiments, and was identified within the body and proximal aspect of the cuff in 17 of the 22 grafts (77%) assessed by Duplex scan.

Discussion

The hypothesis behind the precuffed graft is that of suppression of intimal hyperplasia through optimisation of haemodynamic forces, and is based upon strong experimental evidence of an inverse relationship between mean wall shear stress (WSS) and myointimal hyperplasia.²⁰⁻²³ The predilection for MIH deposition at the heel, toe and recipient artery floor of an end-to-side anastomosis correlates with regions of flow separation and low wall shear stress in bench studies.¹³ This concurs with work reported by Bassiouny *et al.*,²⁰ which in addition identified the presence of suture line intimal hyperplasia in both PTFE and venous grafts. Such findings imply that different types of juxta-anastomotic hyperplasia may exist, indicating a multifactorial aetiology. MIH occurring in the suture line may be in response to surgical trauma,²¹ although its greater prominence in prosthetic material may add credence to theories relating to compliance mismatch. Bassiouny speculated that such differences in the mechanical properties of the artery and graft may create an anastomotic sinus that induces secondary flow patterns in the vicinity of the suture line, interacting with biomechanical and humoral factors to modulate suture line intimal thickening. In contrast however, Sottiurai described a series of animal experiments in which end-to-side anastomoses to canine femoral artery were created using PTFE with and without a venous collar, autogenous vein and autogenous artery. Histological examination identified the presence of intimal hyperplasia at the heel, toe and **along the recipient artery floor in all cases, including those where no compliance mismatch existed.**²²

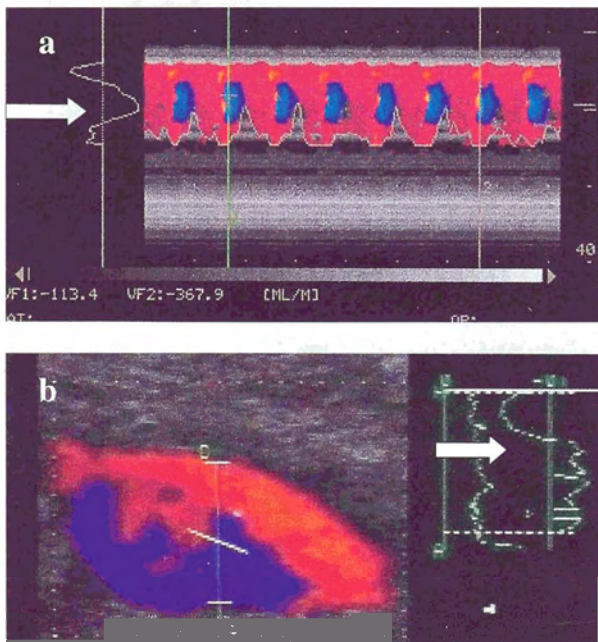


Fig. 6. Velocity profiles at the distal anastomoses of (a) *in vitro* and (b) *in vivo* precuffed grafts. Different scanners are used, however antegrade and retrograde components of vortical flow are demonstrated in both (arrows).

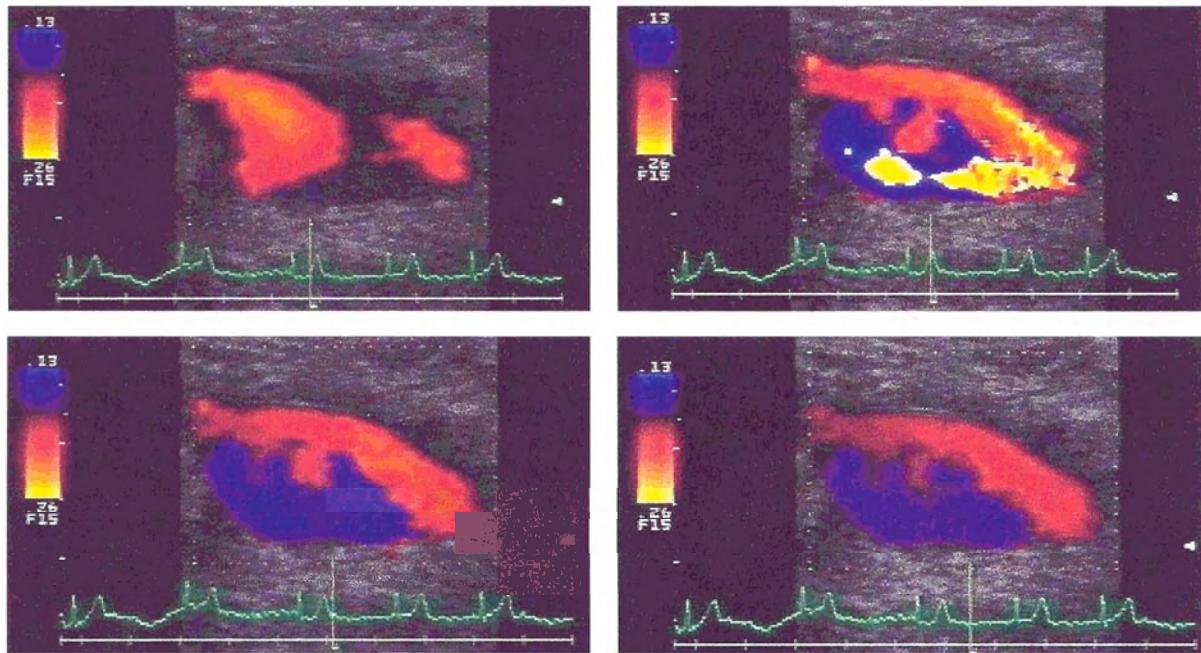


Fig. 7. Duplex of *in vivo* precuffed graft. Cardiac gating identifies the vortex forming at peak systole, and persisting through diastole. The vertical line indicates the point in the cardiac cycle.

Whether the easier handling of either vein or the precuffed graft over standard PTFE diminishes the extent of vascular injury is a subjective quantity. The suture line hyperplasia identified by Bassiouny may be anticipated to be more prominent in the precuffed graft than vein, due to the physico-chemical boundary that exists between the artery and the non-autologous PTFE. This, however, may be self-limiting and abate once intimal remodelling has resolved the surface irregularity.

Myointimal hyperplasia not directly related to the suture line, but occurring along the artery floor, has been shown to appear in equal volumes in both venous and PTFE grafts, which suggests that it accrues predominantly in response to haemodynamic forces experienced within the anastomosis.^{20,22,23} The relatively static flow division point reported by How *et al.*¹³ in end-to-side models was shown to create a region of low wall shear stress, and corresponds to the location of this MIH. The primary intention of anastomotic engineering therefore, is inhibition of this type of MIH through harnessing of haemodynamic forces, namely wall shear stress. Our experiments have identified that the precuffed graft accurately reproduces the anticipated flow patterns, particularly a vortex, within the anastomoses of both *in vitro* and *in vivo* grafts. It has been shown that the presence of a similar vortex within the Miller cuff leads to the redistribution of mean WSS at critical points in the recipient artery¹³

and we believe that such benefits can be extrapolated to apply to the precuffed graft. We also observed that the flow division point in our model was dynamic, moving distally as the vortex forms during systole, a flow characteristic also described in the Miller cuff.¹⁴ This potentially removes the region of very low wall shear stress associated with a static flow division point along the artery floor.

Further benefit may be imparted by a vortex in the form of improved mixing of blood products. The rotational motion persists throughout diastole, encouraging mixing during a period of the cycle when stasis may be expected. Platelets undergoing stasis and with prolonged periods of exposure to injured endothelial surfaces, are activated and mediate the release of mitogenic and chemotactic factors which play an important role in the development of MIH.²⁴

The shape of the precuffed graft may also have additional advantages besides that of generating a vortex. The redistribution of MIH in the Miller cuff up to the graft/cuff junction may be a function of compliance mismatch, but flow visualisation has also identified a region of flow separation at the toe of this junction, which may be anticipated to demonstrate low shear stress. Our earlier studies on cuff geometry suggest that the degree of flow separation is dependant upon the dimensions, with particularly prominent areas observed in long cuff models. We have attributed this flow phenomenon to the creation of a "shoulder"

effect at the anastomosis between the PTFE and the vein cuff.¹⁶ The conical shape of the precuffed graft negates this, and no areas of flow separation within the cuff were observed. This is perceived to be beneficial, and corroborates with previous speculation in connection with the St Mary's boot.¹⁵

The toe of a distal end-to-side anastomosis, known to be susceptible to MIH, demonstrates large areas of flow separation and low wall shear stress.¹³ Flow visualisation studies in the Miller cuff indicate a region of transient flow reversal along the superior wall of the outflow vessel, immediately distal to the cuff toe, and a similar pattern is found in the precuffed graft. These flow patterns are short lived however (0.1–0.2 s) and explanted Miller cuff grafts have not demonstrated this to be a site of adverse hyperplasia. Nevertheless this is a critical point in any anastomosis and requires further Duplex surveillance of *in vivo* grafts, and histological examination of explanted grafts before any conclusions may be drawn.

This study incorporated modern Doppler techniques in the form of Duplex colour flow mapping and velocity profiling in order to demonstrate the consistent replication of the vortex *in vivo*. Whilst it is possible to deduce the velocity distribution across the anastomosis from the profile (Figs 6a and 6b), caution must be exercised in deriving quantitative velocities because of the potential for large errors. The magnitude of the velocities obtained are highly dependant on both the user and the instrument settings.

Early graft occlusion within the first month is commonly due to technical difficulty in creating a satisfactory anastomosis between non-compliant ePTFE and the small distal vessels. The easier handling of a vein cuff certainly affords less technical error in forming this anastomosis and may explain some of the observed benefit of the Miller cuff. The distal end of the precuffed graft is created from thinned PTFE, which improves conformability whilst maintaining tensile strength. It is the authors' experience that a satisfactory distal anastomosis was achieved in all 32 patients, including the five whose grafts occluded within the first post-operative week. Graft failure in these patients was attributed to the severity of the existing disease, with all five patients undergoing redo procedures to a single crural vessel. The graft occlusion in the patient who died may be attributed to the significant hypotension endured following a myocardial infarction. In addition to the satisfactory handling, there is an issue of operation time. The precuffed graft obviates the need to harvest vein and create a geometrically precise cuff. The potential to reduce the operation time in patients who are often systemically

unwell (our cohort demonstrated a median ASA of 3) can only be beneficial.

Conclusion

In vitro studies with a precuffed graft demonstrated potentially beneficial flow patterns, with a vortex created within the body and proximal part of the cuff. This vortical structure, which has been found to be associated with a redistribution of WSS in the recipient artery, was subsequently shown to be closely replicated in the majority of precuffed grafts used clinically. The precuffed graft may therefore be able to harness haemodynamic forces in such a way as to suppress the development of distal anastomotic intimal hyperplasia. Clinical evidence supporting this and the anticipated improvement in patency rates over other prosthetic grafts is now required in the form of controlled trials.

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Mr P. L. Harris acts as a consultant for Bard/Impra.

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