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Low wall shear stress predicts subsequent development of wall hypertrophy in lower limb bypass grafts

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Summary *Background:* Venous grafts commonly develop myointimal hyperplasia, which can lead to stenoses and, ultimately, with expression of adhesion molecules, lumenal occlusion. The aim of the present study was to investigate whether wall shear stress measured post-operatively would predict subsequent myointimal hypertrophy in lower limb venous bypass grafts.
Methods: Magnetic resonance imaging and ultrasound were performed in a cohort of patients following lower limb venous bypass graft surgery for peripheral arterial disease at baseline (1—2 weeks) and at follow-up (9—12 months). Wall shear stress was determined at baseline using computational fluid dynamics techniques and intima-media thickness along the length of the graft was measured by ultrasound at baseline and follow up.
Results: Complete follow-up was possible in eight patients, in whom low wall shear stress at baseline predicted high intima-media thickness. The relationship between wall shear stress (WSS) and intima-media thickness (IMT) was curvilinear with IMT increasing sharply at lower levels of WSS (IMT >1.0 mm at <0.3 Pa).
Conclusions: Low wall shear stress is associated with subsequent increase in myointimal thickness in lower limb venous bypass grafts. This is believed to be the first prospective study in humans to demonstrate the relationship between low wall shear stress and myointimal thickening and indicates a likely causative role for low wall shear stress in the development of myointimal hyperplasia.

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Introduction

Atherosclerosis is the leading cause of mortality in Western societies.[1] Multiple risk factors acting from early life, some of which are male sex, hypertension, elevated cholesterol, sedentary lifestyle, obesity, diabetes, smoking and genetic predisposition, have been implicated in its development.[2]

However, these 'systemic' factors cannot explain the highly focal nature of the disease and the development of atherosclerosis has been linked to local haemodynamics. In particular low or oscillating shear stress has been proposed as a localizing factor.[3,4] This hypothesis, although supported by extensive evidence in cell culture models[5] and some studies in animal models[6,7] has been difficult to test in human subjects owing to the long latency of atherogenesis and the complexity of determining shear stress in native arteries in humans.

The most successful techniques for determining realistic wall shear stresses employ anatomical and flow data acquired non-invasively in vivo via magnetic resonance imaging (MRI) and/or ultrasound from regions of interest within the circulation; these are imported into a computational fluid dynamics (CFD) code to derive parameters such as shear stress at the lumenal-endothelial interface. Such studies have demonstrated a geographical association between low shear stress and intima-media thickness (IMT), believed to be a precursor to atherosclerotic plaques.[8] They have also contributed evidence for the hypothesized connection between the recognised focal sites for atherosclerosis and local shear stress.[9,10]

In contrast to atherosclerosis which takes years to develop, vein grafts, such as those used in cardiac and peripheral bypass surgery, often fail within months or a few years as a result of stenoses arising from myointimal hyperplasia (MIH).[11] Vein graft myointimal hyperplasia and atherosclerosis share several pathological features,[12] and subsequent to MIH, vein grafts tend to express, inter alia, adhesion molecules[13] and MMPs.[14] Vein grafts can be readily imaged using magnetic resonance or ultrasound and the flow fields mapped using numerical techniques. This circumstance therefore provides an ideal setting to test whether low haemodynamic shear stress is a determinant of myointimal hyperplasia in a prospective study.

The aim of the present study was to investigate whether low wall shear stress determined post-operatively via image-based numerical analysis would predict subsequent myointimal hypertrophy in lower limb venous bypass grafts.

Methods

Ninety-six patients with lower limb arterial disease were recruited for the study. Of these, it was necessary to exclude 49 patients at the outset. Some were unfit for surgery and received angioplasty or stent; in others vein surgery was not possible and they received prosthetic grafts. The remaining 47 patients were scheduled for femoropopliteal, femoro-crural or femoro-pedal bypass grafts via the Peripheral Arterial Disease Clinic at St Mary's Hospital and participated in the study. In some of these, ultrasound examination showed some grafts with low flow or early occlusion, leaving 37 grafts in 33 patients. Subsequent exclusion criteria were complete occlusion, re-intervention following occlusion, inability to visualize the graft using ultrasound, low graft flow making 2D time-of-flight acquisition unreliable, patients unable to keep sufficiently still causing significant MR movement artefact, and inability to tolerate MRI examination (patients were too sick or suffered claustrophobia). Ultimately 18 patients underwent MRI scanning and ultrasonic Doppler measurements of blood flow for CFD modelling within 2 weeks of surgery ('baseline') and patients were re-examined 9–12 months after surgery ('follow-up'). Of these, further clinical circumstances which prevented ultrasound follow-up were patient death, graft occlusion, graft re-intervention which rendered the baseline observations inapplicable to the follow-up, presence of a previously detected AV fistula, which required re-intervention.

Following these events a total of only eight subjects (age 45–88 yrs; 6 male) were available for follow-up. The study complied with the Declaration of Helsinki and was approved by the St. Mary's Hospital Local Research Ethics Committee. All participating subjects gave written, informed consent.

Data acquisition and analysis

Anatomical data

Imaging of the graft region was performed at baseline using a 1.5 T Horizon-LX Echospeed MR scanner (GE Medical Systems, Milwaukee) equipped with a peripheral arterial coil. MR angiograms were obtained using a 2-D time-of-flight gradient echo sequence with venous pre-saturation and a series of contiguous 2mm-thick transverse slices was acquired. Field of view (FOV) for the axial image slices was 16 cm $\times$ 16 cm with 256 (frequency encoding) $\times$ 192 (phase encoding) pixel resolution, with a 256-level grey-scale intensity.

Flow velocity data

Flow velocity waveforms were obtained at baseline by pulsed Doppler using an ATL HDI 5000 ultrasound machine (ATL-Phillips, Bothell, Washington) equipped with an L12-5 linear array transducer in a 1.5 mm sample volume placed within the centre of the lumen in the proximal region of the graft at a Doppler angle of 60°.

IMT measurements

IMT of the near and far wall of the vein-graft was measured at follow-up by B-mode ultrasound, but since the accuracy of near wall IMT measurements has been questioned,[15] far wall IMT was used as the primary outcome measure in this study. All investigations were performed with the patient positioned supine after a resting period of 30 min.

The far wall IMT was measured using a digital calliper as the distance between the first echo boundary adjacent to the lumen and the next major echo contour on B-mode images. An average of five measurements was taken at each location at centimetre intervals longitudinally down the graft. (The intervals were decided on practicality; each set of five measurements at a location was considered to represent an independent data point in conjunction with the related WSS—see below.) All measurements were referenced longitudinally from one or other end on the