Effects of elastic compression stockings on wall shear stress in deep and superficial veins of the calf.

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Running head: Calf compression and venous shear stress.

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Abstract

The purpose of this study was to estimate wall shear stress (WSS) in individual vessels of the venous circulation of the calf and quantify the effects of elastic compression based on change of vessel geometry and velocity waveform. The great saphenous vein and either a peroneal or posterior tibial vein have been imaged in four healthy subjects using magnetic resonance imaging, with and without the presence of a grade 1 medical stocking. Flow through image-based reconstructed geometries was numerically simulated for both a range of steady flow rates and ultrasound derived transient velocity waveforms, scaled to give a standardised time averaged flow rate.

For steady flow the stocking produced an average percentage increase in mean WSS of approximately 100% in the great saphenous vein across a range of 0.125 ml s\(^{-1}\) to 1.25 ml s\(^{-1}\). The percentage increase in the peroneal/posterior tibial veins varied from 490% to 650% across a range of 0.5 ml s\(^{-1}\) to 5 ml s\(^{-1}\). In addition, application of the stocking eliminated periods of very low or zero flow from the transient waveforms. The average minimum value of WSS in all vessels without the stocking was less than 0.1 Pa. With the stocking this was increased to 0.7 Pa in the great saphenous and 0.9 Pa in the peroneal/posterior tibial veins. The pathophysiological effects of these changes are discussed.

In conclusion, the flight stocking was effective in raising venous WSS levels in prone subjects and this effect was much more pronounced in the deep vessels. The stocking also
tended to prevent cessation of flow during periods of increased downstream pressure produced by respiration.

**Keywords:** Calf veins, deep vein thrombosis, haemodynamics, numerical simulation.
Introduction

Deep vein thrombosis (DVT) is a common complication in hospitalised patients. It is often asymptomatic and resolves without intervention; however, it can lead to local injury to the vein wall and valves and is an important initiator of chronic venous insufficiency (CVI). Another more serious outcome is pulmonary thromboembolism, which is implicated in 10% of all hospital deaths (3).

Multiple forms of prophylaxis are available for DVT. Medicinal anticoagulants, such as low molecular weight heparin, are often used in conjunction with mechanical methods such as graduated compression stockings and intermittent pneumatic compression of the calf or foot. The mechanical methods are generally thought to act by the reduction of venous stasis but their biomechanical effects and influence on the underlying vascular biology have not been fully elucidated. A more complete understanding would potentially help clinicians to use them more effectively and manufacturers to improve their design.

The etiology of DVT is generally explained within the framework of the three thrombogenic factors advanced by Virchow (31): stasis, hypercoagulability and injury to the vessel wall. Injury to the vessel wall is an important factor in the arterial model of thrombosis, causing adhesion and activation of platelets and exposing them to sub-endothelial tissue factor. This chain of events is supported by the observation of a platelet rich region at the attachment point of the thrombus with red blood cell aggregates only visible at the boundaries (16).
In contrast, Sevitt has shown venous thrombi to consist of a red blood cell rich aggregate at the attachment point with platelet rich zones only visible at the boundaries (24), suggesting a different mechanism of formation. In an autopsy study of 41 limbs, Sevitt also failed to find obvious signs of vein wall injury in 49 out of 50 thrombi (24). It appears that stasis and hypercoagulability play the dominant role in venous thrombosis but the source of tissue factor, in the absence of endothelial injury, remains a matter of some debate. Current evidence points to circulating microvesicles as the most likely source (16).

The lack of platelets at the heart of the thrombus also begs the question as to how the coagulation process is activated. Tracy (30) has shown that activated endothelial cells provide a surface for the assembly of the coagulation complex which is equally efficient as activated platelets. However, there are further questions as to the stimulus for endothelial activation and the mechanism by which anti-thrombotic agents such as tissue factor pathway inhibitor and thrombomodulin are sufficiently suppressed to allow the coagulation cascade to proceed.

A possible stimulus for endothelial activation is low haemodynamic wall shear stress (WSS) resulting from stasis. It is now well known that endothelial cells are highly responsive to WSS. Regions of low or oscillating WSS have been heavily linked with formation of atherosclerotic plaques and it is generally theorised that high levels of unidirectional and pulsatile WSS promotes an anti-inflammatory phenotype (18). Much research has been devoted to the response of arterial endothelial cells to WSS but similar
mechanisms undoubtedly exist in venous endothelial cells. Eriksson et al. have demonstrated an inflammatory response in large veins to tumour necrosis factor - α, which is stronger than in their corresponding arteries (10).

There is also a strong case for hypoxia as the stimulus for endothelial activation, but since low WSS and hypoxia are both integral features of stasis it is difficult to separate the two effects in vivo. Evidence for an important role for low WSS in the formation of venous thrombi comes from the study of Goel and Diamond, where adhesion of red blood cells to platelets, neutrophils and polymerised fibrin was observed at WSS levels below 0.1 Pa but not above (12).

High WSS has also been shown to stimulate the production of various anti-thrombotic and fibrinolytic agents including nitric oxide (5), prostacyclin (11) and tissue plasminogen activator (5, 7, 8). Optimisation studies of intermittent compression devices have focused on WSS and flow rate enhancement as important parameters. Early development of these devices focussed on the generation of high peak flows, with the assumption that this would aid the mechanical break-up of thrombi. As evidence mounted that the beneficial effects may lie instead in the endothelial response to induced flows, the objectives of optimisation became less clear.

Much work has been done on this topic by Kamm and co-workers (4, 13, 14, 21, 23). Using the theoretical framework for flow in collapsible tubes developed by Shapiro and Kamm (15, 25), numerical and physical simulations were performed which shed light on
the distributed haemodynamic effects of differing modes of compression. An important aspect of modelling flow in collapsible tubes is an accurate description of the pressure/volume relationship, known as the tube law. In a further study by the same group, a 2D finite element model of a transverse section of calf was used to simulate vessel wall deformation under various circumferential pressure distributions (4). However, the model was highly idealised and, while the overall approach has provided important general insights into the underlying haemodynamics, without validation of the simulated tube law against \textit{in vivo} data it is not clear that the results are physiologically realistic.

The application of theoretical modelling to the design of graduated compression stockings has been less thoroughly pursued. The work of Sigel et al. (26) has provided an empirical basis for current designs but their main criteria was the increase in velocities at the exit of the compressed region. This is a good general indicator of the stocking’s ability to reduce stasis but gives no information on the haemodynamic conditions in the upstream vessels. This may be important as some beneficial effects of compression could be localised to only those regions directly exposed to anti-thrombotic haemodynamic conditions (4).

This study introduces the combined use of magnetic resonance imaging (MRI), pulsed Doppler ultrasound and computational fluid dynamics (CFD) to estimate the effect of static compression on WSS in the major deep and superficial vessels of the calf. Image based computational modelling has become an established tool in the study of arterial
haemodynamics and offers the potential to provide data which cannot be measured by experiment alone, in particular, WSS distribution in realistic vessel geometries.
Methods

Overview

Four healthy male subjects were studied, aged 24-32 years without any history of venous disease. The study complied with the Declaration of Helsinki and was approved by the local Research Ethics Committee. All participating subjects gave written, informed consent. Vessel geometry was acquired from MRI to provide a realistic basis for numerical simulations of flow within the vessels using CFD.

It was not possible to simultaneously measure flow rates in the reconstructed vessels, therefore the main focus of the simulations was to quantify the effect of the change in vessel geometry produced by the stocking, with time averaged flow rate assumed to remain unchanged. Steady flow simulations were performed for a range of flow rates in each reconstructed vessel to calculate the resulting WSS distributions and percentage increase in spatial mean WSS resulting from compression.

The effect of the stocking on the velocity waveform was also examined. Pulsed Doppler ultrasound data were acquired from the same subjects on a separate occasion, with the conditions mirroring those under which the MRI data were acquired as closely as possible. Difficulties arising from the presence of the stocking and the depth of tissue surrounding the deep vessels made it impractical to make direct measurements of flow in the reconstructed vessels. Flow velocity was therefore measured downstream, above the level of the stocking, in the popliteal and great saphenous veins. Representative
waveforms were then calculated for each vessel before and after compression and used to perform transient flow simulations.

**Vessel Geometry**

**Image Acquisition**

The MR images were acquired from a Siemens Avanto 1.5T scanner, using a 3D true FISP sequence, as described previously (9). The images were acquired with and without the presence of a grade 1 medical stocking. Subjects were imaged in the prone position to avoid compressing the muscles of the calf against the table. After entering the bore, a period of 5 minutes was allowed to pass before the proximal third of the subject’s right calf was imaged. The subject was then partially removed from the bore to allow application of the stocking while remaining prone. A period of 10 minutes was then allowed to pass before imaging the same section of calf.

**Image Processing**

The venous system of the calf is separated into the superficial system (external to the muscular fascia) and the deep system (internal to the muscular fascia). The major veins of each system are the great saphenous vein (superficial) and the peroneal and posterior tibial veins (deep) which are generally four in number and run alongside the peroneal and posterior tibial arteries before joining to form the popliteal vein.

In each subject a segment of the great saphenous vein and one other deep vessel (a peroneal vessel in three subjects and a posterior tibial vessel in one) were selected for
analysis based on the clarity of the MR images and the presence of a reasonable length of vessel free from bifurcations. All segments studied here were 4 cm long apart from the great saphenous vein in subject 4 where only a 3.2 cm segment met the necessary criteria. All segments were located in the proximal third of the calf, below the level of the popliteal venous confluence.

The vessel cross sections were segmented manually using in-house software written in MATLAB (version 7.0.1, The Mathworks, Natic, USA) and these were then used to reconstruct the full 3D geometry. A smoothing function was applied in MATLAB during geometry reconstruction to reduce imaging artefacts and small manual errors from the segmentation process in order to facilitate mesh generation. The curve fitting algorithm “csaps” was employed for this purpose; firstly to smooth the cross sections (smoothing parameter = 0.9) and then to smooth along the axial direction (smoothing parameter = 0.7).

**Velocity Waveforms**

**Ultrasound Data Acquisition**

The subjects were asked to lie in the prone position and perform diaphragm-dominated respiration, as described by Miller et al. (19), regulated by an analogue metronome with a period of approximately seven seconds (one full respiration cycle). Once regulated respiration had commenced measurements were made after a five minute interval.
Due to the depth of tissue surrounding the peroneal and posterior tibial vessels and the presence of the stocking in half the measurements, it was not possible to measure flow directly at the site of the vessels segmented from the MR images. Flow velocities were therefore recorded by pulsed Doppler ultrasound in the popliteal and great saphenous veins, just above the level of the stocking, using a Philips ATL 5000 Doppler ultrasound machine equipped with a 6MHz linear array transducer. Digital data were transferred to a PC and analysed using commercial software (HDI Lab version 1.19, ATL-Philips, Bothell, Washington).

Doppler waveforms were recorded over a period of 50 s in both vessels, initially without the stocking. The insonation angle was 60° and the entire vessel cross section was included in the sample volume as has been shown previously to be optimal for venous flow measurements (20). Following this an identical stocking to that used in the MRI scans was applied to the subject’s right leg and measurements were repeated after a ten minute interval.

**Signal Processing**

The peak velocity waveform was extracted using HDI Lab and used to calculate a representative waveform by segmenting the entire waveform into individual respiration cycles and taking an ensemble average of 6 cycles. Since the period was not accurately controlled; in each case the segment length was optimised in order to give the minimum root mean square value when the representative waveform was subtracted from the
original waveform. Any remaining high frequency noise was then removed using a low
pass filter with a cut off frequency of 0.5 Hz.

The presence of valves (if competent) in the venous system will cause flow to come
abruptly to a halt rather than become reversed. Such discontinuities cannot be
approximated well with low frequency harmonics and mathematical artefacts introduced
to the waveform during filtering may falsely imply that reverse flow is taking place.
Reverse flow was not observed in any of the measurements so for the duration of such
artefacts, flow was set to zero. A sample comparison of computed representative
waveforms against the raw data output from HDI Lab is shown in Fig. 1.

(Figure 1)

CFD Analysis
Simulations were performed using the commercial CFD code CFX10 (ANSYS Inc.).
Blood was modelled as a Newtonian fluid with density 1060 kg m\(^{-3}\) and viscosity 3.5
mPa s. The Reynolds number fell within the laminar regime in all simulations so no
turbulence model was used. Spatial discretisation was performed via a hybrid 1\(^{st}\)/2\(^{nd}\) order
scheme, whilst temporal discretisation was performed via an implicit 2\(^{nd}\) order backward
Euler scheme.

Steady flow simulations were run for a range of flow rates between 0.5 and 5 ml s\(^{-1}\), in
the case of the deep vessels, and 0.125 to 1.25 ml s\(^{-1}\) in the case of the great saphenous
vein. Since the inlet geometries were arbitrary, with irregular cross sections, velocity profiles could not be determined directly. To provide a consistent inlet boundary condition, the model inlet was therefore extended upstream by ten hydraulic diameters and the velocity profile was allowed to develop from an initial flat profile.

Grid dependency tests were run for one subject. Refining the mesh from 74,000 nodes to 540,000 nodes produced a change of less than 5 mPa in wall shear stress. A mesh size of 140,000 nodes was determined to provide a discretization error of less than 1.5 mPa, relative to the wall shear stress calculated from the 540,000 node mesh and was used throughout. Transient simulations were performed for three respiration cycles and the results were taken from the final cycle. Uniform mean flow rates of 1 ml s$^{-1}$ in the deep veins and 0.25 ml s$^{-1}$ in the great saphenous vein were used for each subject. A study of the time step dependency revealed that increasing the time steps from 100 to 200 steps per cycle gave a RMS difference of less than 0.1 mPa in wall shear stress and so 100 steps were used throughout.
Results

Geometry Reconstruction

The volume of all reconstructed vessels was reduced by the stocking but the effect was more pronounced in the deep veins than in the great saphenous vein. On average the deep veins were reduced in volume by 59% while the great saphenous vein was reduced by 40%. Elastic recoil in the vessel wall, implied by the reduction in vessel circumferences, was observed in all vessels. Bending of the vessel wall was more evident in the deep veins than in the great saphenous veins, with their cross sections taking on an approximately ellipsoid shape (further details are available from (9)). Sample geometrical reconstructions from a peroneal vein and the great saphenous vein of subject 2 are shown in Fig. 2.

(Figure 2)

Velocity Waveforms

In the absence of the stocking during diaphragmatic breathing, velocity waveforms in all vessels showed a similar pattern to those observed by Miller et al (19). During inspiration, flow was greatly reduced, often to below measurable levels, as the descending diaphragm increased intra-abdominal pressure (though an initial period of reversed flow was not observed during our measurements). As the expiration phase began and intra-abdominal pressure dropped, flow rapidly resumed and continued until the next inspiration phase. With the presence of the stocking the response was markedly different. The overall pattern of respiratory flow modulation remained but the magnitude was much decreased.
During inspiration, flow slowed somewhat but did not fully halt in any of the cases (see Fig. 3).

The effect was quantified based on the pulsatility index ($PI = \text{maximum velocity minus minimum velocity over mean velocity}$), which was calculated from the representative waveforms since the flow rate was not consistent from cycle to cycle. Without the stocking, the mean and standard deviation of the PI were $1.56 \pm 0.31$ in the popliteal vein. With the stocking, this was reduced to $0.56 \pm 0.35$. A similar magnitude of effect was seen in the great saphenous vein, with a PI of $1.47 \pm 0.60$ reduced to $0.48 \pm 0.38$ upon application of the stocking.

(Figure 3)

**Steady Flow Analysis**

Flow simulations were performed for the great saphenous and deep veins using geometries reconstructed from MR images acquired before and after application of the stocking, for a range of physiologically relevant flow rates derived from the literature. No qualitative change in flow and WSS patterns was found with the increase in flow rate, although quantitative variations were observed. Spatial distribution of WSS in the great saphenous vein was relatively uniform, both with and without the stocking. More variation was seen in the deep veins as illustrated in Fig. 4. Without the stocking, bulges in the vessels (possibly indicating the presence of valves) gave rise to very low values of WSS in some regions. With the stocking, WSS tended to be higher near the proximal
ends of the reconstructed segments, approaching the junction of the peroneal and posterior tibial veins.

Table 1 gives a summary of spatial mean WSS values averaged among the four subjects, before and after compression, along with the corresponding Reynolds number at the segment inlets. The increase in WSS with respect to flow rate was approximately linear in the case of the great saphenous veins, giving a value of 100%. In the case of the deep veins the percentage increase varied from 490% to 650% across the range of 0.5 ml s\(^{-1}\) to 5 ml s\(^{-1}\). In both cases a quadratic expression was required for an exact fit between WSS and flow rate.

(Figure 4)

(Table 1)

**Transient flow analysis**

The transient simulations were performed using subject-specific velocity waveforms acquired before and after compression, assuming constant time-averaged flow rates (0.25 ml/s for the great saphenous vein and 1 ml/s for the deep veins). The results showed slightly higher values of time-averaged WSS but very close (within 1%) to that in the steady flow simulations at the same flow rate. Despite the reduced pulsatility of the velocity waveforms in the compressed vessels, the range of spatial mean WSS experienced by the vessel during a respiration cycle increased by approximately 100% in the deep veins. In the great saphenous vein the WSS range was decreased by
approximately 35% due to the lesser reduction in vessel volume. Temporal variations in spatial mean WSS are shown in Fig. 5 with maximum and minimum values given in Table 2.

(Table 2)

(Figure 5)
Discussion

Segments of the great saphenous vein and either a peroneal or posterior tibial vein have been reconstructed from MR images in four subjects, before and after application of a grade 1 compression stocking. The increase in WSS levels produced by the change in geometry has been derived from CFD analysis for a range of steady flow rates. Two flow rates were selected and used to scale velocity waveforms measured downstream in the great saphenous and popliteal veins during diaphragmatic respiration. These data were then utilised in a transient CFD analysis.

The reconstructed vessel geometries demonstrated a marked difference between the deformation of the great saphenous and major deep veins. Not only was there a much greater reduction in volume in the deep veins (59 % compared to 40 %) but there was a greater degree of bending of the vessel wall, implied by the alteration of the cross sectional shape under the influence of the stocking.

Since the flow rates in the reconstructed vessels at the time the MR images were acquired could not be measured directly, a range of steady flow rates was analysed with the intention of providing data across a physiologically relevant range. The ranges of flow rates studied in the great saphenous and deep vessels were relatively wide. This was partly in recognition of the uncertainty resulting from the inability to measure this parameter during the course of this study, and partly due to the high level of variability in lower limb venous flow.
No direct measurement of peroneal or posterior tibial vein flow could be found in the literature but data exist for popliteal flow and for great saphenous flow close to the sapheno-femoral junction. Delis et al. (6) have demonstrated the strong dependence of lower limb venous flow rates on posture, making measurements from subjects in the horizontal position the most relevant to this study. Lurie et al. (17) examined 12 subjects and found an average flow rate of 3.8 ± 0.6 ml s\(^{-1}\) (mean ± s.d.) in the popliteal vein and 3.9 ± 0.3 ml s\(^{-1}\) in the great saphenous vein 5 cm upstream from the sapheno-femoral junction. An earlier study by the same investigators (20) did not measure popliteal flow but found an average great saphenous flow rate of 0.6 ml s\(^{-1}\) among 25 subjects, again acquired just upstream from the sapheno-femoral junction but this time in 30° reverse Trendelenburg’s position (legs down on tilted table). Delis et al. (6) found an average popliteal flow of 1.7 ml s\(^{-1}\) (estimated from figure in (6)) in a study of 26 limbs from 13 healthy subjects in the horizontal position.

Given the range of popliteal flow values reported from the literature it seems likely that, in the horizontal position, resting flow rates in the peroneal and posterior tibial veins are less than 1 ml s\(^{-1}\). From the steady flow results, this implies that normal WSS levels (without compression) in this position are less than 0.2 Pa. In their study of the effect of WSS on secretion of tissue plasminogen activator, Diamond et al. (7) showed that WSS levels above 0.4 Pa were required to stimulate increased secretion. Our results indicate that, under the action of the stocking, a flow rate of just 0.34 ml s\(^{-1}\) would be sufficient to generate this threshold level of WSS in the segments of deep vessel studied here. In the uncompressed vessel geometries, the same flow rate would give an average WSS level of
0.07 Pa. Without the stocking, a flow rate of less than 0.52 ml s\(^{-1}\) would generate WSS levels under 0.1 Pa, at which Goel and Diamond observed adhesion of red blood cells (12). With the stocking, a flow rate of 0.52 ml s\(^{-1}\) gives a WSS value of 0.61 Pa.

It must be emphasised that since these flow rates have not been acquired simultaneously with the imaging of the vessel geometries, the values presented should be viewed as illustrative. However, the results indicate that for an equivalent flow rate before and after compression, the stocking was effective in raising WSS. It is particularly interesting to note the difference in response between the deep vessels and superficial vessels. WSS increased in the peroneal and posterior tibial veins by an average of between 490% and 650%, across the range of flow rates examined, compared to just 100% in the great saphenous vein, illustrating the difference in compression of the deep and superficial veins. This assumes an unchanged mean flow rate which may not be the case.

Studies have shown that static external compression can produce a reduction in femoral vein flow rates (22, 27). This effect will reduce the beneficial impact of the stocking on WSS and stasis in general, though from the steady flow simulations it would require a flow rate reduction of 51% in the great saphenous vein and 83% in the peroneal/posterior tibial vessels to negate the influence of the stocking on WSS entirely. The results of Sabri et al. (22) suggest that a reduction of around 10% in femoral vein flow rate could be expected for a grade 1 stocking.
The velocity waveforms obtained without the stocking showed similar behaviour to that reported by Miller et al. (19). The oscillations in downstream (proximal) pressure caused by the movement of the diaphragm periodically slowed the flow velocity to very low values, often causing it to cease entirely (or at least reducing it below measurable levels). The effect of the stocking on the waveform was unexpectedly pronounced. The magnitude of the modulation was dramatically reduced and a continuous flow towards the heart was always maintained. As far as the authors are aware, this phenomenon has not been described previously and an explanation will be suggested based on the theoretical model advanced by Takata et al. (29).

As the diaphragm descends, it tends to compress the abdominal veins. Assuming retrograde flow is prevented by the venous valves and a low resistance pathway to thoracic veins is maintained, this will tend to displace blood centrally without much change in local venous pressure in the abdomen. However, if the external pressure increases to the point where internal venous pressure is not high enough to prevent collapse of the inferior vena cava, then a high resistance pathway to flow from the abdominal region is created. The implications of this are not straightforward but by consideration of mechanical equilibrium at the throat of the collapsed portion, we can assume that local venous pressure must have increased to a value close to that of the external abdominal compartment.

This increased back pressure will reduce the outflow from the upstream veins and, if sufficiently high, will hold the upstream valves shut preventing outflow from the leg.
This causes venous pressure to rise exponentially towards an asymptotic value (32). The situation will be maintained until either the rising upstream pressure reverses the pressure gradient across the valve leaflets and re-establishes flow or the diaphragm ascends during expiration, removing the back pressure, and flow resumes with a transitory increase as the walls of the leg vessels recoil, expelling the blood volume which has accumulated during the period of increased back pressure.

The effect of the stocking may be two-fold. The reduction in cross section of the veins under the stocking will increase the local vascular resistance. An accurate prediction of the effect of a change in resistance in one vessel in a flow network requires consideration of the resistance of all vessels in the network and is beyond the scope of this study. However, evidence exists in the literature to support an increase in local venous pressures. Spiro et al. have shown that the application of external pressure to the hind limb of a dog produces a pressure increase in the femoral vein; at 15 mmHg of external pressure an internal pressure rise of 8 mmHg was observed (27). An increase in venous pressure in the calf could explain the change in waveform since it would reduce the effect of the increase in downstream pressure produced by inspiration and could help to maintain a continuous flow.

In addition, the rate at which venous pressure rises when outflow is prevented is determined by the compliance of the system. The presence of the stocking should reduce the compliance of the vessels in the calf, since the compliance of the deep veins is dominated by the surrounding skeletal muscle and the blood will have to do more work to
expand the vessel wall against compressed skeletal muscle. When the outflow from the leg decreases below the inflow from the microcirculation, pressure in the calf therefore rises faster than that in the thigh, potentially maintaining a continuous flow into the femoral network.

The main purpose of the transient analysis was to assess whether the changes in respiratory modulation of the velocity waveform induced by the stocking would alter the time averaged WSS. Time averaged transient WSS, with and without the stocking, was found to be the same as for an equivalent steady flow rate in the corresponding vessel geometry. The elimination of periods of very low or zero WSS in the presence of the stocking may be important though.

At the flow rates investigated; without the stocking, WSS periodically dropped to an average value of less than 0.1 Pa in all vessels, with the stocking, the average minimum values were 0.7 Pa in the great saphenous vein and 0.9 Pa in the peroneal/posterior tibial vessels. Not only did the stocking tend to prevent the cessation of flow but, in the deep veins, the resulting reduction in cross sectional area increased the range of WSS experienced during the respiratory cycle. A continuous flow would also hold the venous valves open, maintaining a constant vortical flow behind their leaflets, a frequent site of thrombus formation. The effect has only been shown here in prone subjects and may not apply with the limb in a dependent position such as seated in an airplane. However, the transient effects of static compression probably deserve greater attention.
The improvement in the methodology used here over previous studies, such as that of Sigel et al. (26), is the ability to examine haemodynamic conditions in the specific veins where thrombi are known to initiate. The main limitation is the difficulty in the measurement of flow rate in the deep veins. The depth of the surrounding skeletal muscle makes Doppler ultrasound unsuitable for this purpose and MRI sequences for the measurement of venous flow will require some effort to develop. The degree of repeatability in venous waveforms is too low to allow a gated approach, meaning that real time imaging would probably be required to capture transient effects.

Even with the potential to make simultaneous measurements of vessel geometry and flow, further effort will be required if the methodology presented here was to be extended to clinical studies or the optimisation of stocking design. Endothelial phenotype varies throughout the cardiovascular system (1) and it is not yet clear what a healthy level of WSS in the large veins of the calf would be. It appears that very low values may promote (either actively or passively) the adhesion of red blood cells and that endothelial production of anti-thrombotic agents is stimulated above some threshold level, but the specific values obtained from the studies of Diamond et al. (7) and Goel and Diamond (12) may not be applicable to the vessels studied here.

Nevertheless it is important that methodologies are developed in order to take advantage of developments in our understanding of the pathophysiology of venous thrombosis. In future studies it would be desirable to improve the resolution and clarity of the MR images in order to allow the reconstruction of the smaller intra-muscular veins of the
soleus and gastrocnemius muscles, a frequent site of thrombosis (2). In the longer term, efforts should be made to include fluid structure interaction between the blood and vessel wall and eventually to include the venous valves.

The subjects used in this study were all young and healthy. A possible focus for future clinical study using this methodology would be haemodynamic differences between young and old populations. Stanton et al. have reported that older subjects tend to exhibit “saccular dilatations” in the veins of the calf (28). This observation may be linked to the increased incidence of DVT in older populations and would make a valid target for investigation via this methodology.

In conclusion, these results indicate that, in prone subjects, grade 1 compression stockings are effective at increasing WSS in large deep and superficial veins in the calf, based solely on change in vessel geometry, and the effect is more pronounced in the deep vessels. The presence of the stocking also seems to decrease the reduction in local flow velocities induced by periods of increased downstream (proximal) pressure, which acts to ensure that WSS is prevented from dropping to near zero. Both of these effects may play important roles in the overall mechanism by which compression stockings provide their clinical benefit.
References


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Figure Captions

Figure 1: Comparison of sample representative waveforms (thick continuous lines) shown superimposed on the raw data trace output from HDI Lab (thin dashed lines). Data are taken from the great saphenous vein in subject 3, with (bottom) and without (top) the presence of the stocking.

Figure 2: Reconstructed vessel geometry from subject 2: top left - compressed peroneal vein, top right - uncompressed peroneal vein, bottom left - compressed great saphenous vein and bottom right - uncompressed great saphenous vein. Cross sections at 1 cm intervals are shown either side of the vessels.

Figure 3: Representative samples of ultrasound velocity profiles with (continuous lines) and without (dashed lines) the presence of the stocking; for ease of comparison velocity has been non-dimensionalised by the respective mean velocity and time by respiration cycle period.

Figure 4: Colour contour maps showing spatial distribution of wall shear stress in the deep veins, calculated using a flow rate of 1 ml s$^{-1}$. Each subfigure shows the vessel in uncompressed (U) and compressed (C) states from two aspects; perpendicular (left) and parallel (right) to the boundary of superficial and deep posterior compartments. Subject specific scales are shown to the right of each subfigure; a quadratic scale has been used to allow comparison between compressed and uncompressed vessels.
Figure 5: Transient simulation results showing time dependent spatial mean wall shear stress in the peroneal/posterior tibial veins (left column) and great saphenous veins (right column) in all four subjects. The time scale has been normalised by the period of the respiration cycle.
Table 1

Table 1: Subject averaged values of spatial mean WSS and Reynolds number in great saphenous and deep veins.

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<th>Flow rate (ml s⁻¹)</th>
<th>0.5</th>
<th>1</th>
<th>2.5</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re_u</td>
<td>34.43</td>
<td>68.87</td>
<td>172.17</td>
<td>344.33</td>
</tr>
<tr>
<td>U WSS (Pa)</td>
<td>0.10</td>
<td>0.19</td>
<td>0.49</td>
<td>1.00</td>
</tr>
<tr>
<td>Re_c</td>
<td>48.87</td>
<td>97.75</td>
<td>244.37</td>
<td>488.74</td>
</tr>
<tr>
<td>C WSS (Pa)</td>
<td>0.57</td>
<td>1.20</td>
<td>3.33</td>
<td>7.54</td>
</tr>
</tbody>
</table>

U WSS – Uncompressed spatial mean WSS (without stocking), C WSS – Compressed spatial mean WSS (with stocking). Re_u/Re_c – Reynolds number at inlet of uncompressed/compressed geometries, based on hydraulic diameter.
Table 2: Transient WSS values for great saphenous and deep veins.

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Subject</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Great Saphenous Vein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without stocking</td>
<td>Max. WSS (Pa)</td>
<td>0.92</td>
<td>0.54</td>
<td>0.70</td>
<td>0.54</td>
<td>0.68</td>
</tr>
<tr>
<td>With stocking</td>
<td>Max. WSS (Pa)</td>
<td>1.25</td>
<td>1.11</td>
<td>0.74</td>
<td>1.20</td>
<td>1.08</td>
</tr>
<tr>
<td></td>
<td>Min. WSS (Pa)</td>
<td>0.14</td>
<td>0.00</td>
<td>0.01</td>
<td>0.21</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Min. WSS (Pa)</td>
<td>0.71</td>
<td>0.45</td>
<td>0.68</td>
<td>0.95</td>
<td>0.70</td>
</tr>
<tr>
<td>Deep Vein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without stocking</td>
<td>Max. WSS (Pa)</td>
<td>0.29</td>
<td>0.20</td>
<td>0.42</td>
<td>0.34</td>
<td>0.31</td>
</tr>
<tr>
<td>With stocking</td>
<td>Max. WSS (Pa)</td>
<td>1.17</td>
<td>1.17</td>
<td>1.40</td>
<td>2.28</td>
<td>1.51</td>
</tr>
<tr>
<td></td>
<td>Min. WSS (Pa)</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Min. WSS (Pa)</td>
<td>0.76</td>
<td>0.47</td>
<td>1.13</td>
<td>1.29</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Maximum and minimum values of transient WSS for the great saphenous and deep veins in all four subjects, calculated using time averaged flow rates of 1 ml s⁻¹ in the deep veins and 0.25 ml s⁻¹ in the great saphenous vein.
Figure 1: Comparison of sample representative waveforms (thick continuous lines) shown superimposed on the raw data trace output from HDI Lab (thin dashed lines). Data are taken from the great saphenous vein in subject 3, with (bottom) and without (top) the presence of the stocking.
Figure 2: Reconstructed vessel geometry from subject 2: top left - compressed peroneal vein, top right - uncompressed peroneal vein, bottom left - compressed great saphenous vein and bottom right - uncompressed great saphenous vein. Cross sections at 1 cm intervals are shown either side of the vessels.

387x630mm (600 x 600 DPI)
Figure 3: Representative samples of ultrasound velocity profiles with (continuous lines) and without (dashed lines) the presence of the stocking; for ease of comparison velocity has been non-dimensionalised by the respective mean velocity and time by respiration cycle period.
Figure 4: Colour contour maps showing spatial distribution of wall shear stress in the deep veins, calculated using a flow rate of 1 ml s⁻¹. Each subfigure shows the vessel in uncompressed (U) and compressed (C) states from two aspects; perpendicular (left) and parallel (right) to the boundary of superficial and deep posterior compartments. Subject specific scales are shown to the right of each subfigure; a quadratic scale has been used to allow comparison between compressed and uncompressed vessels.
Figure 5: Transient simulation results showing time dependent spatial mean wall shear stress in the peroneal/posterior tibial veins (left column) and great saphenous veins (right column) in all four subjects. The time scale has been normalised by the period of the respiration cycle.