

Analysis of Venous Blood Flow and Deformation in the Calf under External Compression

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Declaration of Originality

I Ying Wang declare that this thesis is my own work and has not been submitted in any form for another degree or diploma at any university or other institute of tertiary education. Information derived from the published and unpublished work of others has been acknowledged in the text and a list of references is given in the bibliography.

Abstract

Deep vein thrombosis (DVT) is a common post-operative complication, and a serious threat to the patient's general recovery. In recent years, there has been increasing awareness of the risk of DVT in healthy individuals after prolonged immobility, such as people taking long-period flights or sitting at a computer.

Mechanical methods of DVT prophylaxis, such as compression stockings, have gained widespread acceptance, but the haemodynamic mechanism of their action is still not well understood. In this study, computational modelling approaches based on magnetic resonance (MR) images are used to (i) predict the deformation of calf and deep veins under external compression, (ii) determine blood flow and wall shear stress in the deep veins of the calf, and (iii) quantify the effect of external compression on flow and wall shear stress in the deep veins.

As a first step, MR images of the calf obtained with and without external compression were analysed, which indicated different levels of compressibility for different calf muscle compartments. A 2D finite element model (FEM) with specifically tailored boundary conditions for different muscle components was developed to simulate the deformation of the calf under compression. The calf tissues were described by a linear elastic model. The simulation results showed a good qualitative agreement with the measurements in terms of deep vein deformation, but the area reduction predicted by the FEM was much larger than that obtained from the MR images.

In an attempt to improve the 2D FEM, a hyperelastic material model was employed and a finite element based non-rigid registration algorithm was developed to calculate the bulk modulus of the calf tissues. Using subject-specific bulk modulus derived with this method together with a hyperelastic material model, the numerical results showed better quantitative agreement with MR measured deformations of deep veins and calf tissues.

In order to understand the effect of external compression on flow in the deep veins, MR imaging and real-time flow mapping were performed on 10 healthy volunteers before and after compression. Computational fluid dynamics was then employed to calculate the haemodynamic wall shear stress (WSS), based on the measured changes in vessel geometry and flow waveforms. The overall results indicated that application of the compression stocking led to a reduction in both blood flow rate and cross sectional area of the peroneal veins in the calf, which resulted in an increase in WSS, but the individual effects were highly variable.

Finally, a 3D fluid-structure interactions (FSI) model was developed for a segment of the calf with realistic geometry for the calf muscle and bones but idealised geometry for the deep vein. The hyperelastic material properties evaluated previously were employed to describe the solid behaviours. Some predictive ability of the FSI model was demonstrated, but further improvement and validation are still needed.

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Chapter 1

Introduction

1.1 Motivation for Research

Deep venous thrombosis (DVT) is the formation of a blood clot, which usually occurs in the deep veins of leg. The incidence of DVT in the whole general population is around 5 per 10000 per annum and increases dramatically with age [1, 2]. Males are at slightly greater risk than females [3]. It has been shown that long-haul economy-class flights increase the risk of DVT [4]. As a significant and costly healthcare and social problem, DVT is of great social concern.

The occurrence of DVT is often asymptomatic, but can lead to complications with serious implications, such as chronic venous insufficiency (CVI) and pulmonary embolism. Venous hypertension caused by CVI can lead to various pathologies including pain, swelling, edema, skin changes, and ulcerations. As the almost-invariable site of initiation of thrombogenesis, venous valves are very likely to be damaged or become incompetent due to the formation of DVT, which is a major initiator of CVI. In the US, about 25 million people suffer from CVI, mainly female [5]. Pulmonary embolism occurs when the thrombus detaches and travels to the pulmonary artery, blocking it or one of its branches. In severe cases this can result in acute heart failure and death. About 10% of people developing pulmonary embolism died in hospitals [2, 6] and this rate increases to 30% at 3 years after hospital discharge [2].

It is generally accepted that the cause of most thrombi is rooted in at least one of the three aetiological factors known as the Virchow's triad: stasis, hypercoagulability, and

endothelial damage. The available modes of prophylaxis against DVT can be broadly divided into medicinal and mechanical methods. Pharmacologic anticoagulants, such as low molecular weight heparin or aspirin, have achieved considerable success, but are contra-indicated in clinical situations where bleeding is of particular concern.

Mechanical modes of prophylaxis are divided into static compression stockings and intermittent pneumatic compression devices. Notwithstanding the undoubted efficacy of compression devices in preventing DVT [7], the haemodynamic mechanisms of their action remain unclear. In order to optimize the design of compression devices, it is necessary to understand the underlying haemodynamic mechanisms, and their relation to the biochemical process of thrombogenesis.

1.2 Compression Devices

Due to the incomplete pathophysiological understanding of DVT, the design of prophylactic tools is mainly focused on preventing the initiation of coagulation rather than disrupt it once it has already begun. Development of compression devices is actually driven by the prevention of blood stasis alone. Properties of blood flow, such as its peak velocity and percentage augmentation, are employed as parameters for the assessment of compression devices. Experimental results [8-11] suggested that high wall shear stress is beneficial to the health of endothelial cells and prevention of vascular diseases, which provided certain level of support for the methodology, but these studies mainly focused on arterial thrombosis and it was suggested [12] that DVT has a different pathology.

In order to produce high blood velocity, the design of compression devices is commonly aimed at reducing the vessel volume. This is under the assumption that there is no significant change in volumetric flow rate in veins and therefore, a volume reduction can lead to a higher blood velocity according to the principle of mass conservation. Theoretical modelling studies [13] have provided some insights into the

flow within a collapsible tube. Employing finite element analysis, Dai et al. [14] and Narracott et al. [15] investigated the deformation of deep veins under different types of external compression. However, the model geometry in both studies was generalized and no validation was performed.

Recent studies of vascular endothelial cells [10, 16, 17] suggested that both velocity and pulsatility of the blood play an important role in thrombogenesis and steady flow with relatively high velocity is good for the health of endothelial cells. According to these findings, the criteria by which compression devices are designed should be reconsidered. A new methodology needs to be developed to optimize and evaluate future designs.

1.3 Research Objectives

The aim of this project is two-fold: (1) to develop a finite element model for predicting the deformation of calf muscle and deep veins under external compression, and (2) to determine the effects of external compression on haemodynamic conditions in the deep veins of calf. UK grade 1 compression stockings were used to produce the external pressure. Changes in the deep vessel geometry and venous flow were recorded by magnetic resonance imaging (MRI). The investigation is primarily focused on providing new insights into the action of the compression stocking by applying computational analysis to *in vivo* data, which may shed light on the mechanism of compression devices. In the longer term, this work will form an important component of a comprehensive modelling framework that can be used for the optimisation of future designs of external compression devices. The specific objectives covered by the thesis are:

- To develop a finite element model to simulate the deformations of calf under external compression

- To evaluate the capability of linear elastic and hyperelastic models in representing the mechanical properties of calf tissues
- To quantify the effect of compression stocking on the haemodynamic conditions in the deep venous system
- To develop a coupled fluid-structure interaction (FSI) model for predicting the dynamic responses of the deep venous system to external pressure.

1.4 Thesis Outline

In the first phase of the project, MR images of the middle section of the right calf were acquired from four healthy volunteers before and after the application of the compression stocking, using the imaging protocol presented in chapter 3. Based on these MR images, finite element analyses of the deformation of calf tissues were performed and results are discussed in two chapters, chapter 3 and chapter 4. In chapter 3, a finite element model (FEM) with different stress-strain conditions was employed to reproduce the varying compressibility of different muscle compartments. In order to improve the predictive ability of the numerical model, in chapter 4, a FEM based on a non-rigid registration algorithm was developed to evaluate the mechanical properties of calf tissues from measured deformations of the tissues and deep veins.

Subsequently, computational fluid dynamic (CFD) methods were employed for the numerical analysis of blood flow in the deep veins. Ten healthy volunteers were recruited for this purpose, and a newly developed MR imaging sequence was used to acquire not only anatomical information but also real-time flow data. Pulsatile flow analysis using subject-specific flow wave forms was performed. Details of the imaging sequences and the simulation results are presented in chapter 5.

Considering the limitation of a two-dimensional FEM in predicting the mechanical behavior of a three-dimensional structure, the two-dimensional FEM was extended to

three dimensions. An attempt was made to couple the three-dimensional FEM with a finite volume model representing the venous system to simulate the fluid-structure interactions (FSI) between the venous flow and calf tissues under external compression. Details of the FSI model are given in chapter 6.

A background section is presented in chapter 2 which covers the lower limb anatomy, the latest advances in the understanding of the pathophysiology of DVT and the empirical and theoretical studies of the effects of compression on the lower limb venous system. Final conclusions and recommendations for further research are given in chapter 7.

Chapter 2

Literature Review

2.1 Structure of the Calf

2.1.1 Overview

The lower leg contains two long bones, tibia and fibula, of which the tibia is larger. It is located in the middle of the lower leg, and runs between the knee and ankle joints, with its anterior/medial aspect close to the skin. The fibula is located on the lateral side of the tibia, with which it is connected above and below, and is the smaller of the two bones. These two bones are surrounded by skeletal muscles, except the anterior/medial aspect of the tibia.

The skeletal muscles of the calf are enclosed within a lamina of tough connective tissue known as the muscular fascia. Within the muscular fascia, functional groups of skeletal muscle are enclosed by laminae of connective tissue. There are four compartments that comprise the various muscle groups of the calf: the anterior compartment, lateral compartment, posterior compartment and deep posterior compartment (Figure 2.1). The anterior and deep posterior compartments are separated by a particularly thick lamina known as the interosseous membrane, which is anchored at either side to the tibia and fibula. Beyond the muscular fascia is a layer of subcutaneous fat and connective tissue which is in turn enclosed within the skin.

The venous system of the lower leg is composed of two distinct networks. One is the superficial venous system, which is located in the subcutaneous fat between the skin and the muscular fascia; the other is the deep venous system, which runs through the skeletal muscle. These two networks are connected at numerous locations through

perforator veins, in which the valves keep blood flowing unidirectionally from the superficial venous system to the deep veins [18].

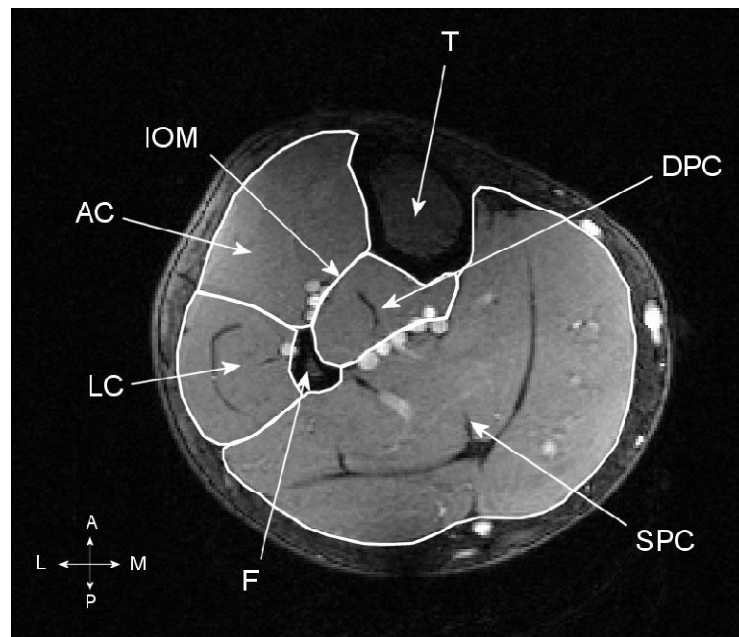


Figure 2.1 A representative MRI image of a transverse slice of the middle of the right calf. Muscle compartments are outlined in white: AC-anterior compartment, LC-lateral compartment, DPC-deep posterior compartment, SPC-superficial posterior compartment, T-tibia, F-fibula, IOM-interosseous membrane.

2.1.2 Venous System

2.1.2.1 Architecture of Veins in the Calf

In a recent MRI study [19], very comprehensive data of venous system of the calf were acquired (Figure 2.2). The deep veins system mainly includes the peroneal veins, posterior tibial veins and anterior tibial veins, also known as the axial veins. The main superficial veins are the great/small saphenous veins. Compared to the superficial veins system, the architecture of the deep venous system is less variable. Generally, these veins run alongside their corresponding arterial branches. In many cases, the artery is accompanied by two or more veins. These “vascular bundles” are located between the skeletal muscle groups and are enclosed with connective tissues.

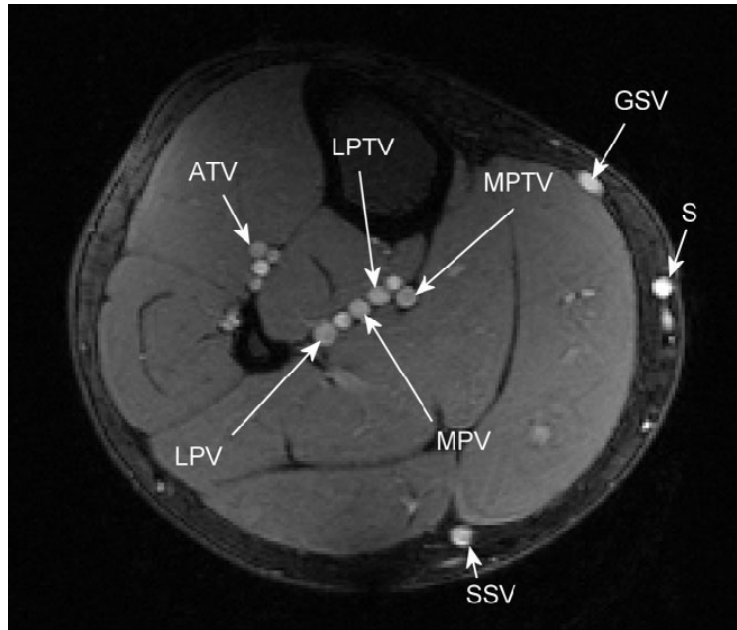


Figure 2.2 A representative MR image of a calf cross-section: ATV-anterior tibial vessels, GSV/SSV-great/small saphenous veins, S-superficial vein, LPV/MPV-lateral/medial peroneal veins, LPTV/MPTV-lateral/medial posterior tibial veins [19].

The peroneal veins arise near the lateral aspect of the heel and run up the back of the calf, behind the fibula, and join the posterior tibial veins in the upper calf. The posterior tibial veins arise from the plantar surface of the foot, and travel through the medial aspect of the calf and terminate at its joint with the peroneal veins. The anterior tibial veins are formed by the venous plexus on the dorsum of the foot, running upwards through the anterior compartment, alongside the interosseous membrane. In the upper calf, they pass through the membrane, and join the tibial/peroneal trunk to form the popliteal vein. The popliteal vein originates from the junction of the posterior tibial vein and anterior tibial vein. It ascends through the popliteal space where the shorter saphenous vein joins it. It passes through the adductor hiatus and leaves the adductor canal as the femoral vein. Belcaro et al. [20] showed that the popliteal vein, as one of the main channels for venous blood flow, carries approximately 85% of total venous blood volume from the calf and foot.

The main vessels of the superficial venous system are the great and short saphenous veins. The superficial veins of the foot and leg interconnect to form a complex network underneath the skin. These vessels drain into two major trunks: the great and short saphenous veins. The short saphenous vein (SSV) originates from the lateral aspect of the foot, and travels upwards through the middle of the posterior aspect of the calf until it joins the popliteal vein around the knee. However, Kosinski [21] studied 124 cases and found that the SSV of 33% of the individuals extended until it joined the posterior femoral vein above the knee, and 10% terminated in the great saphenous or gastrocnemial veins below the knee, while only 57% of cases were consistent with the textbook description. The great saphenous vein, which is the longest vein in the body, arises from the medial marginal vein of the foot. It runs along the medial aspect of the calf and thigh. When extending to just below the inguinal ligament in the lower abdomen, it penetrates deep into the thigh and joins the femoral vein. The femoral and the great saphenous veins merge into the external iliac vein.

2.1.2.2 Mechanism of Venous Flow in the Calf

The venous return of the calf venous system depends on the pressure gradient between the microcirculation and the right atrium, the muscle pump and the respiratory pump. The pressure at the microcirculation end can be treated as quasi-steady, while pressure at the entrance to the right atrium is pulsatile. As the right atrium opens, pressure in the inferior vena cava decreases, resulting in an expansion wave which travels distally until dissipated by viscous forces in the blood and vein walls. The distance that these waves travel is controversial. Brecher [22] suggested that venous flow is only pulsatile close to the right atrium, but Wang et al. [23] found that the transmission of waves reaches the femoral vein in dogs. However, in consideration of the physiological differences between human and dogs, the propagation distance of the waves in human may be significantly different from that in dogs.

The muscle pump depends on movement of the leg and operation of the valves. The mechanism of the muscle pump is as follows. The contraction of the muscle in the leg causes compression to the vein, which imparts momentum to the blood flow in the vein lumens and forces the blood to move towards the heart. As the volume of blood moving into the central vein increases, the pressure at the entrance to the right atrium increases. According to the Frank-Starling mechanism, enhancement of the venous return to the heart causes an increase in the stroke volume of the circulation and the pressure on the arterial side, which leads to a greater driving pressure to the blood flow through the microcirculation. When the muscle contraction is released, the pressure in the local veins is reduced, resulting in an increase in the pressure gradient between the microcirculation and the veins. During the whole process, the existence of competent valves ensures that the venous blood flow moves unidirectionally to the heart.

Respiratory activity also exerts multiple influences on venous return. Wexler et al. [24] studied blood flow in the venae cavae and found that the flow velocity is increased by inspiration and decreased by expiration. Increasing the rate and depth of respiration promotes venous return and leads to an enhancement of cardiac output. Respiratory pump affects venous return through changes in right atrial pressure, which is an important component of the pressure gradient previously mentioned. The venous flow is retarded when the right atrial pressure is increased, while a decrease of this pressure facilitates venous return. However, the effects of the diaphragmatic descent during inspiration on the intra-abdominal pressures bring conflicts to the mechanism of respiration pump. Descent of the diaphragm during inspiration tends to increase intra-abdominal pressure, potentially leading to collapse of the abdominal veins. Willeput et al. [25] showed that an increase of 5 cmH₂O (compared to the normal average value) in the abdominal pressure causes abolition of blood flow in the femoral vein. Miller et al. [26] provided a detailed study of the changes in thoracic and abdominal pressures produced by different modes of breathing and the resulting effects of venous flow in

upright humans, and their findings confirmed the earlier observation of Willeput et al. [25].

2.1.3 Skeletal Muscles in the Calf

Skeletal muscle whose contraction and shortening control the movement of bones is composed of bundles of fibres which are enclosed by a connective tissue, named as Perimysium [27]. About 80% of the skeletal muscle is water, while the rest of it is collagenous tissues (10%) and fat (3%). Because of its fibre-oriented structure, muscle displays anisotropic behaviour. It is subject to large deformations *in vivo* and the stress state in a given muscle is the result of passive and active contractions.

In previous studies, investigation of muscle force-length behaviour have been performed on cats [28], rats [29, 30] and rabbits [31, 32] and the results were highly variable. Bosboom et al. [33, 34] studied the passive transverse mechanical properties of rat skeletal muscle and indicated that it displayed viscoelastic behaviour, which was described using an incompressible Ogden model:

$$W = \frac{\mu}{\alpha}(\lambda_1^\alpha + \lambda_2^\alpha + \lambda_3^\alpha - 3) \quad (2.1)$$

where W is the strain energy function, λ_i^α is the principal stretch ratio in the i direction, and μ and α are material constants. The viscoelasticity was taken into account through a Prony series expansion:

$$S = (1 - \delta) \frac{\partial W}{\partial E} + \int_0^t \delta \frac{\partial W}{\partial E} e^{-(t-\xi)/\tau} d\xi \quad (2.2)$$

where S is the second Piola Kirchhoff stress, E is the Green Lagrange strain, and δ and τ are viscoelastic material parameters.

Spencer [35] proposed another constitutive hyperelastic model for fibre-reinforced composites, which was later further developed to simulate soft tissues with transversely isotropic properties such as tendons and ligaments [36], cardiac tissue [37, 38] and muscle [39]. In these models, the direction dependence on the deformation was implemented into the strain energy through a vector representing the material preferred direction.

In a recent study, Van Looke et al. developed an experimental approach [40] to characterize the passive skeletal muscle properties in three dimensions. A strain-dependent Young's Moduli (SYM) function [41], which was later combined with a Prony series representing viscoelasticity [42], was employed to evaluate the muscle mechanical properties. In the SYM model, the nonlinearity of soft tissues is represented by:

$$E_L = k_1 e^{k_2 \varepsilon} \quad (2.3)$$

$$E_T = k_3 e^{k_4 \varepsilon} \quad (2.4)$$

where E is Young's modulus, k_1, k_2, k_3, k_4 are the model parameters. Indices L and T denote the longitudinal and transverse directions, respectively. The properties of material at an angle (α) from the longitudinal direction are described as:

$$\frac{1}{E_\alpha} = \frac{1}{E_L} \cos^4 \alpha + \left(\frac{1}{G_{LT}} - 2 \frac{\nu_{LT}}{E_L} \right) \sin^2 \alpha \cos^2 \alpha + \frac{1}{E_T} \sin^4 \alpha \quad (2.5)$$

where G is shear modulus and ν is Poisson's ratio.

Although extensive investigations were performed on characterizing the mechanical properties of skeletal muscle and many attempts managed to generate good fits to experimental data under certain circumstances, it needs to be pointed out that the

mechanical behaviour of muscles, both passive and active, are still not well understood. The models developed to describe the mechanical properties of muscle are highly dependent on the subject and application environments.

2.2 Deep Vein Thrombosis

2.2.1 Pathology of Deep Vein Thrombosis

Most ideas about the pathogenesis of deep venous thrombosis (DVT) are dominated by the paradigm of 'Virchow's triad'. This model attributes thrombogenesis in veins to some combination of 'hypercoagulability', 'stasis' of the venous blood and injury to the vein wall intima, specifically the endothelium. The now-familiar 'explanation' of DVT in terms of 'hypercoagulability' and 'stasis' seems to have become entrenched [43-47] about a decade after the clinical value of anticoagulant therapy for thrombosis had been established [48-50]. Meantime, the effects of 'intimal injury' on thrombogenesis is marginalized and dismissed by many researchers. Sevitt et al. [51] indicated that direct injury to venous endothelium is rare, even with surgery. In a review of venous thromboembolism [52], it was remarked that thrombi were easier to move in the first phases of thrombogenesis, when they did not adhere as yet to the venous wall, implying that any correlation between the endothelium and the thrombus is subordinate and adventitious [53].

There is only a small amount of tissue factor in the endothelium, while much greater amounts are present in smooth muscle cells, macrophages and fibroblasts within and around the vessel walls. Damage to the vessel wall brings blood stream into contact with the tissue factor, which initiates the tissue factor pathway. The contact with tissue factor generates factor VIIa/tissue factor complexes that activate factor X. The complexes can also activate factor IX and initiate the intrinsic pathway. The activation of factor X through both routes is required for normal hemostasis. That is why deficiency of either factor VIII or factor IX leads to bleeding despite an intact extrinsic coagulation pathway (Figure 2.3).

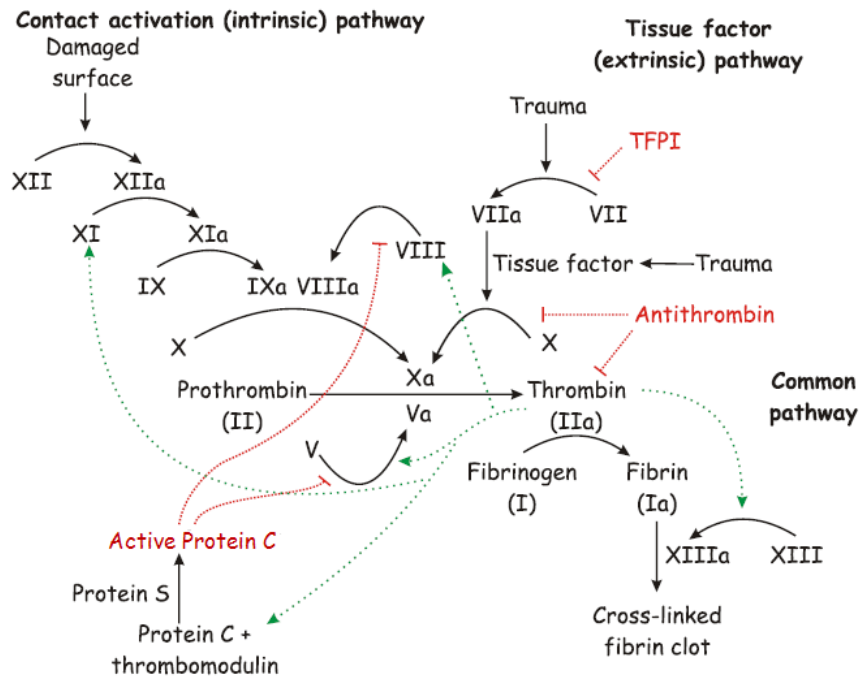


Figure 2.3 Pathways in coagulation: Anti-coagulants are shown in red, including: Protein C, antithrombin and tissue factor pathway inhibitor (TFPI). Clotting factors are represented through Roman numerals, with the subscript denoting the activated form: I-fibrinogen, II-prothrombin, V-proaccelerin, VII-proconvertin, VIII-antihemophilic globulin, IX-Christmas factor, X-Stuart-Prower factor, XI-plasma thromboplastin antecedent/ prekallikrein (Fletcher factor)/High mol wt kininogen (Fitzgerald factor), XII-contact factor (Hageman factor), XIII-fibrin stabilizing factor, Protein S. Extracted from [54].

‘Stasis’ denotes ‘impaired circulation’ rather than ‘no movement’ or ‘lower-than-normal movement’. Impaired venous return in the lower limbs certainly plays an important role in thromboembolism. In the late 19th century, it was found that prolonged bed rest could increase the risk of DVT [55]. Notwithstanding that by the 1920s, it was clear that some other factors were also involved [56, 57], the association between immobility and thromboembolism was never in doubt.

Wright et al. [58] provided experimental evidence of reduced venous blood velocity in recumbent limbs. However, according to Malone et al. [53], there is no evidence that blood velocity is a crucial factor in venous thrombogenesis, and non-pulsatility of

blood flow in the deep veins of the lower limb has more significant effects. In other words, 'impaired circulation', which represents 'stasis', should not be interpreted as 'retarded flow', but as 'non-pulsatile flow'. Actually, there is no clear correlation between pulsatility and mean velocity. Dobson et al. [59] showed that rapid or intense muscular contraction could enhance pulsatility, but at the same time, reduce the mean velocity. Knaggs et al. [60] studied the haemodynamic changes in the lower limb venous circulation during and shortly after elective abdominal surgery and noticed a significant decrease in the mean velocity in both conditions, which was accompanied by a remarkable enhancement of venous flow pulsatility. Based on the data, Malone et al. [53] predicted that deep vein thrombosis could develop when the pulsatility in the vein is seriously impaired, even if the blood velocity is relatively rapid.

Although Virchow acknowledged that intimal injury was important in thromboembolism, the role of endothelium in thrombogenesis is still debated by many researchers. Sevt [61] claimed that spontaneous thrombi were observed when the endothelium appeared intact and normal. Comerota et al. [62] said that comparing to 'hypercoagulability' and 'stasis', the role of venous endothelium in thrombogenesis was more controversial. Thomas [63, 64] indicated that the endothelium had no direct association with thrombogenesis. Nowadays, researchers still show interests in the role of the vascular endothelium in thrombosis, particularly its pro-thrombotic responses to hypoxia.

The probable involvement of hypoxic injury to the endothelium in venous thrombogenesis was established more than half a century ago [65, 66]. This issue has since been associated with ischaemia-reperfusion injury (IRI), which was first described explicitly by Hearse [67] in 1977, and has drawn intense attestations. IRI refers to damage to tissue caused when blood supply returns to the tissue after a period of ischemia. The reperfusion with fresh blood results in pathogenic responses that can induce thrombosis. The studies of IRI primarily focus on hypoxic injury to cardiac and arterial tissue, but some inferences have been applied to veins. Recently,

some cell and molecular biological research bears directly on venous endothelial hypoxia and its consequences.

It has been demonstrated that the endothelium controls venous functions by secreting prostanoids, EDRF (nitric oxide), ATP and other factors, and by regulating sodium and calcium fluxes [43, 44]. The local blood velocity and shear stress can influence the secretion process. Ten et al. [44] claimed that a web of 'signalling pathway', which is in the venous endothelial cells, is initiated by hypoxaemia, resulting in the attraction of leukocytes and platelets and subsequent fibrinogenesis. Based on these findings, which are relevant to DVT, the consensus model has been revised. Accordingly, impaired venous circulation ('stasis') leads to hypoxic injury to local endothelium, which initiates the signalling pathways that results in aggregation of platelet and leukocyte and the local activation and/or production of coagulation factors. If underperfusion continues, especially with 'hypercoagulability', this may lead directly to thrombogenesis.

Because of the fact that thrombi originate almost solely in venous valve pocket (VVP), Hume et al. [45] tried to accommodate 'Virchow's triad' to the formation of venous thrombi in VVP. Malone et al. [46] claimed that an adequate model of DVT aetiology must be able to explain why thrombi are initiated in VVP, relate the initiation of protothrombogenic nidi to recognized pathological changes in the valve cusp leaflets, account for the known morphological features of a venous thrombus, and give reasons for the marked tendency of venous thrombi to embolize when the muscle pump becomes active again after immobility. According to the criteria, he developed a hypothesis: the ischaemic-hypoxic hypothesis (IHH).

According to the IHH, thrombogenesis is initiated by non-pulsatility in the venous blood flow. Prolonged immobility, such as prolonged sitting, paresis, sustained general anaesthesia and so on, or significant hypovolaemia makes the blood flow in the deep leg veins less pulsatile, though the veins blood velocity may or may not be

significantly decreased. The importance of maintenance of normal blood volume during surgery has been demonstrated [47]. Due to the non-pulsatility, exchange of blood between the vein lumen and the VVP ceases to operate. Because the blood remains in VVP for considerably longer than would normally be the case, the available oxygen in the VVP is exhausted by the endothelial cells lining the pocket and the trapped blood cells, resulting in local hypoxaemia. Hamer et al. [48] showed that pulsatile flow is essential for ensuring adequate oxygen supply to the endothelial cells of the parietalis aspect of the valve cusp. If the non-pulsatility continues for more than 2–3 h and no fresh blood enters the VVP during that time, hypoxic injury to the endothelium of the parietalis aspect of the valve leaflet may occur. However, under this condition, there will be no further progress towards thrombogenesis because local leukocytes or platelets will also have died because of hypoxaemia.

When muscle pump starts to work again and the blood flow restores its pulsatility, the blood trapped in VVP is flushed out and the hypoxaemically-injured parietalis contacts with fresh blood. Then, the viable leukocytes and platelets of the fresh blood accumulate to repair or perhaps replace the injured endothelium. If a further cessation of pulsatile flow results in recurrent hypoxaemia, the leukocytes and platelets adhered to the necrotic endothelium will be dead. When pulsatile flow is restored again, the previous repair process is repeated and fresh leukocytes and platelets adhere to their now-dead predecessors on the parietalis. In consequence, the trapped blood in the VVP coagulates, forming an incipient thrombus tenuously anchored to the parietalis aspect of the valve cusp.

Karino [75] indicated that thrombus could cause inefficiency of operation of the valve. However, thrombus may remain its size and stays non-life-threatening unless it comes into contact with the blood flow through veins. Under this condition, the platelets and leukocytes react to their dead predecessors as to dead tissue and the thrombus starts to grow. Further fibrinogenesis ensues and the vein becomes partially and progressively occluded. Consequently, the blood velocity in the veins lumen is decreased, and some

blood cells are trapped in the lumen, which causes luminal hypoxaemia and further cell death. As a result, an irrepressible cycle of thrombus growth is initiated. Because of the growth of thrombus, the width of venous lumen becomes smaller and smaller. More and more blood cells are trapped, including erythrocytes as well as platelets and leukocytes. Therefore, in the early stage, the thrombus is white, while the more recently-formed part is mainly red. It was observed that when the oxygen supply to the veins of experimental animals was cut off, lesions similar to the white parts of naturally occurring thrombi were formed [49]. Although the velocity was decreased, the blood stream was still likely to break the thrombus's anchor to the necrotic parietal endothelium break, which resulted in formation of emboli.

2.2.2 Hemodynamic Factors

2.2.2.1 Overview

Hemodynamic forces have drawn wide attentions due to their role in regulating blood vessel structure [68] and development of vascular pathology such as atherosclerosis [69, 70] and deep vein thrombosis (DVT) [16, 17]. The coagulation system is balanced by numerous anticoagulant and procoagulant mechanisms. A numerical analysis [71] revealed that low shear conditions contribute to the procoagulant loops and facilitate the initiation of activation process. The generated product is likely to be removed from the reactive site due to an increase in velocity, and accumulates at regions with prolonged fluid residence time, such as vessel bifurcations and valve sinuses.

Goldsmith et al. conducted a series of investigations into the flow patterns in regions of bifurcation, curvature and other complex geometries and revealed the flow variations in blood vessels [72-75]. Flow conditions near the vessel wall are typically characterized by wall shear rate ($\dot{\gamma}_w$), which can be approximated by:

$$\gamma_w = \frac{4Q}{\pi r^3} \quad (2.6)$$

where Q is volumetric flow rate and r is vessel radius. The wall shear stress (τ_w), which is a product of fluid viscosity and the velocity gradient between adjacent layers of the flowing fluid, is related to γ_w through the fluid viscosity (μ):

$$\tau_w = \gamma_w \mu \quad (2.7)$$

In most of the vascular system, the shear rate is $>50/s$ and the viscosity of the blood is 3.5 mPa/s . In vessels with small diameter ($<0.3 \text{ mm}$), erythrocytes are very likely to concentrate around the centre of the vessel where blood velocity is high and a thin layer of plasma ($\mu \approx 1.1 \text{ mPa/s}$) is formed near the wall, which leads to a decrease in the apparent viscosity.

In regions where the shear rate is low ($<50/s$), the hemodynamic forces are too small to overcome the cell-cell interactions in the blood. The interactions between platelets, erythrocytes and leukocytes have been observed in low shear environments and are suggested to be responsible for the local increase of blood viscosity [76, 77] and lead to prolonged residence time of blood cells.

Throughout most of the vascular system, blood flow is laminar, although in the aorta or around a stenosis, transition to turbulent flow may occur. Nevertheless, turbulence is not expected to occur in the deep veins in the calf.

The hemodynamic forces exert influences on the vascular system by regulating a variety of functions of both blood cells and endothelial cells. Shear rate (γ_w) is often used as a flow parameter due to its relationship to both mass transport and shear stress. Extensive investigations have been performed on the effects of shear rates on blood

flow and endothelium. However, how these factors related to pathology thrombosis is not fully understood.

2.2.2.2 Effects of Flow on Blood Cells

Convection and diffusion play an important role in the transport of blood components, including platelets, red cells, leukocytes, coagulation factors and inhibitors. In most regions within a vessel, convection is much faster than diffusion and dominates the movement of the components. Only in a few microns approaching the vessel wall, due to the no-slip condition, the flow velocity is close to zero and diffusion starts to show its effects [78].

Platelets exert multiple positive influences on thrombogenesis through several activities, including adhesion (adhering to injured vessel wall), aggregation (platelets congregating), cohesion (adhering to vessel wall-bound platelets), and supporting thrombin generation on their surface. Platelet activation is mediated by shear stress and the exposure time of platelets to elevated shear stresses.

Anderson et al. [79] investigated platelet activities at high level of shear stresses (>10 Pa) and observed platelet activation after a relative long exposure time (5 min). Although shorter exposure time (30 s) could generate similar results, considerably higher shear stress was required. In a later study, under very high shear stresses (30 to 100 Pa), platelet activations were recorded in a very short period of time (0.2 to 2 s) [80]. Summarizing the former studies, Boreda [81] proposed a function to express the platelet activation:

$$\text{Platelet Stimulate Function} = \tau \times t^{0.452} \quad (2.8)$$

which indicates that platelet activation is more dependent on shear stress (τ) than exposure time (t).

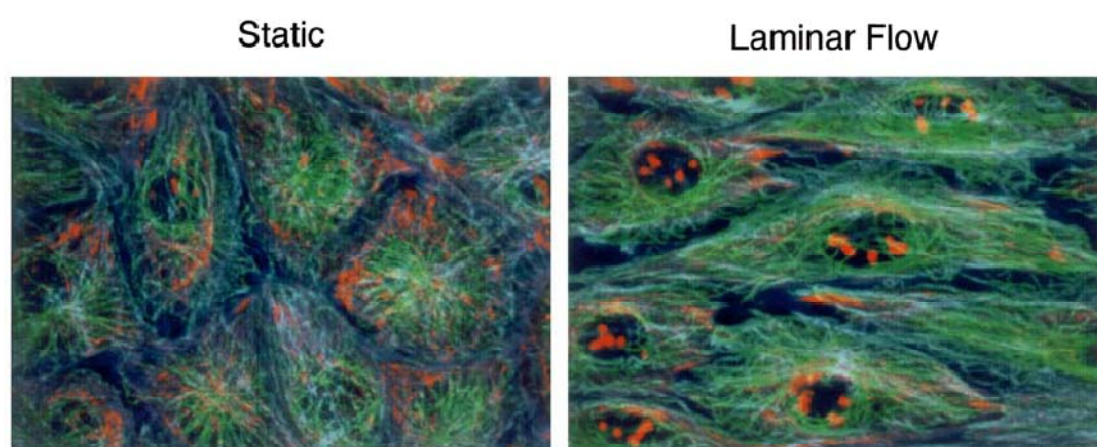
Almost half of the blood volume is occupied by erythrocytes, which significantly influence the fluid viscosity. According to classic convection-diffusion theory, the transport of platelets to the vessel surface is related to the shear rate to the one third power [82]. However, in the presence of erythrocytes, dependence of platelet movement on shear rate becomes much stronger [83]. In addition, the existence of red blood cells (RBC) enhances the concentration of platelets near the wall, which depends on the RBC deformability, shear rate ($>430/s$), and fluid viscosity [84, 85]. Erythrocytes' release of the platelet agonist, ADP, also facilitates platelet activation under high shear conditions [86]. Together, these observations indicated that through a variety of shear-dependent mechanisms, erythrocytes could enhance the interactions between the platelets and vessel wall, and promote platelet activation.

In the plasma, there are a few types of proteins, such as fibrinogen, which enhance the cell-cell bridge reactions at very low shear conditions. These interactions can lead to an increase in blood viscosity and flow resistance, and contribute to cell aggregation. Low shear stresses have been associated with cell-cell interactions involving red blood cells, platelets, and leukocytes [16, 87, 88]. Coincidence of different types of cell aggregations enhanced by low shear conditions has been observed at complex flow regions and in patients with blood stasis caused by long-term immobility [89, 90].

2.2.2.3 Effects of Flow on Endothelial Cells

Vascular endothelial cells (EC) lying between the blood and vessel wall perform many important functions by expressing proteins and factors which function as vasodilators (e.g., NO), vasoconstrictors (e.g., ET-1), growth factors (e.g., FGF), anticoagulants (e.g., heparin), and adhesion molecules (e.g., VECM-1). The luminal surface of the blood vessel and its endothelial surface are constantly exposed to hemodynamic shear stress, which regulates the structure and a variety of functions of endothelial cells, such as proliferation, apoptosis, migration, endothelial permeability and alignment [70, 91].

EC elongation and alignment in the flow direction are important for the health of EC and can be induced by shear stress [92]. Under low wall shear conditions, ECs showed random orientation and the induced inflammatory states have been demonstrated, both *in vitro* and *in vivo*, to be in a strong relationship with thrombosis [93-95]. The morphology of endothelial cells exposed to static and laminar flow has been investigated and better alignment of EC cytoskeleton was generated by laminar flow (Figure 2.4) [96]. In a later study, Nakadate observed that ECs exposed to a pulsatile flow showed even more uniform alignment [97].



(Microtubules-Green; Intermediate Filaments-Red; Actin-Blue)

Figure 2.4 Laminar shear stress induces EC cytoskeleton alignment. ECs were either kept as static control (left) or subjected to laminar flow (right) at a shear stress of 1.5 Pa for 24 h [96].

Tissue factor (TF) is a protein playing an important role in the initiation of thrombi. On the vessel surface with inflammation, wall shear stress induced augmentations of TF were observed and their activities can be increased by flow conditions which enhance the delivery of platelets and leukocytes to the endothelial cell surface [98]. However, the resulting procoagulant activities can be suppressed due to secretion of TF pathway inhibitor [98].

Endothelial cells' release of adhesion molecules induced by chemical or mechanical stimuli mediate the haemostatic and cell adhesion of the vascular system. Nagel et al. [99] investigated the influence of shear stress on endothelial expression of three adhesion molecules (ICAM-1, VCAM-1 and E-selectin). Under laminar flow conditions, time-dependent but stress-independent increases in ICAM-1 were observed, but there was no significant change in VCAM-1 and E-selectin. This finding was later proved by other studies [17, 97, 100]. Endothelial cells exposed to turbulent flow showed no variation in terms of expression of all the adhesion molecules investigated, while pulsatile flow affected surface expression in a similar manner to laminar flow.

2.3 The Effects of Compression on Venous System

2.3.1 Intermittent Compression Systems and Compression Stockings

Over the last 30 years, mechanical methods of (DVT) prophylaxis have gained widespread acceptance for surgical patients and are beginning to become popular in long-distance travel. The objective of the design of intermittent compression system is to mimic the natural action of the muscle pump, squeezing blood from the underlying veins, and prevent stasis in the veins lumen. Due to the intermittent nature of the system, periodic pulse blood flow through the deep veins is produced. The peak velocity, duration and percentage augmentation of the pulse are commonly used as parameters of assessment of different compression devices.

A common feature of compression devices is that the mechanism of their action is still unclear. Intermittent compression devices have developed into a great variety of forms, such as foot compression, calf compression, whole limb compression, and so on. The inflation can be applied in uniform pressure, or sequentially graded pressure, and can have rapid or moderate rates. However, there is little understanding of the relative efficiency of specific systems.

When intermittent compression systems inflate, the velocity of blood flow in deep veins is increased for a short time, and the velocity profile is different when using different compression systems. When using experimental methods to evaluate the velocity, the site of measurement is important because blood flow velocity in a vein is dependent on its local diameter [50]. Under normal circumstances, the greatest diameter of the popliteal vein is about 8 mm [101], common femoral vein is approximately 16 mm [101], and the posterior tibial vein is around 4 mm [102]. For instance, for a given amount of blood being ejected from the foot, it would be expected that the velocities achieved in the posterior tibial vein is higher than in the femoral vein.

Employing calf and/or thigh compression systems with pressure about 40 mm Hg, the maximum velocities achieved in the femoral vein are 35–60 cm/s [103-105], and

augmentations (maximum velocity during compression compared with maximum velocity resting) are around 50–250% [103, 105]. Under the same condition, the velocities of blood flow in the popliteal vein are around 55 cm/s. Increasing the inflation pressure to 120 mm Hg, peak velocities in both popliteal and femoral veins can reach up to more than 100 cm/s [106]. The results produced by using foot compression are more modest, about 20–40 cm/s in the femoral vein, and 30–55 cm/s in the popliteal vein [104, 105]. As expected, the velocity produced in the popliteal vein is higher than in the femoral vein.

It should be noted that there is a wide variation in venous blood flow. Fronek et al. [107] found that resting blood flow in the femoral vein changes from person to person. Many factors, including physiology, body position, respiration and cardiac cycle of the particular subject, affect the pattern of blood flow [108]. Moreover, venous blood pressure also changes; therefore, the reproducibility of velocity measurements from a particular pump, such as skeletal muscle pump or respiratory pump, in a particular individual over time is unlikely to be as good as those achieved in the arterial system.

Compression stockings are cheaper and simpler than intermittent compression devices and, for this reason, remain the most popular physical method of DVT prophylaxis. The mechanism of their action, as intermittent compression systems, is still unclear. Although some research results showed that, as DVT prophylaxis, compression stockings are not as effective as anticoagulants or intermittent compression [109], there is a growing consensus that they effectively prevent DVT [110]. It has been suggested that in certain types of orthopedic surgery, they do not function as well as in other procedures. However, the combination of compression stockings and other prophylactic methods can be more effective than any method alone [110].

Employing physiological measurements, such as Doppler ultrasound [111], it was found that compression increased resting venous blood flow velocities. The reason is that the diameter of veins is decreased under compression [19, 112]. As mentioned earlier, when there is a certain volume of blood running through a vein, the blood flow velocity is dependent on the vein's cross-sectional diameter. Therefore, compression stockings would be able to increase the velocity in the vein. Employing both MRI and Doppler ultrasound, Downie et al. [19, 113] also showed that

compression stocking produced significant volume reduction of the veins, resulting in an increase in the venous blood velocity and wall shear stress, and reducing blood stasis caused by inspiration. However, some studies using modern duplex ultrasound techniques have found no increase in resting flow velocity when stockings are worn [101, 114]. Based on evidence about changes in the diameter of veins, venous volume, and venous capacitance with and without compression stockings, Morris et al. [7] made a prediction that a significant effect of compression stockings was to reduce pooling of blood in deep veins by mechanically preventing distension of the vessels. Comerota et al. [115] observed operative venodilatation. Since there is excessive venous distension during surgery, stasis of blood flow may easily arise in patients during or immediately after an operation. Based on the results, improvements in venous pump function would be more important in prevention of DVT than dealing with immobility during surgery.

While using compression stockings, the most common problem is their fitting. Because certain types of stockings, such as thigh-length type, are difficult to apply in some circumstances, calf-length stockings are highly preferred, and have been widely used [116]. Another problem of stockings is that they are not able to produce the satisfactory pressure profile as expected. Best et al. [117] indicated that in clinical settings, 98% of calf-length stockings did not produce the pressure profile specified by the manufacturers, and 54% even generated higher pressure at the proximal end of the cuff, resulting in “reverse gradients”. Wildin et al. [118] also showed that 70% of thigh-length produced “reverse gradients”. In fact, if the stockings are poorly fitted, or have an incorrect shape and size, they may cause ischemia [119] and increase the risk of thrombosis [120].

Some manufacturers of intermittent compression systems, particularly those who also produce stockings, claimed that stockings prevented distension, whilst intermittent compression emptied veins. For these reasons, they suggested that these two types of compression should be worn together. However, there is little understanding of the haemodynamic consequence of compressions. It is difficult to evaluate the relative efficiency of different types of compression. Therefore, it is hard to ascertain if the two types of compression should be worn together or not. Scurr et al. [121] found that compared with wearing the intermittent compression alone, combination of graduated

compression stockings and graded sequential intermittent compression produced a lower rates of DVT in general surgical patients. However, in velocity studies, the same combination produced similar velocity augmentation as using intermittent compression alone, and stockings in combination with foot compression even appeared to have reduced the expected velocities [122].

2.3.2 Compression Lengths

Lower limb compression cuffs for DVT prophylaxis come in at least five varieties, foot compression, foot and calf compression, calf compression, calf and thigh compression, and whole limb compression. There would be more types if the mode of pressure application is considered (i.e., uniform/graded sequential, non-circumferential/ circumferential).

Some studies compared the velocity profiles generated by calf and thigh compression and calf compression [103, 114]. However, because compression devices were produced by different manufacturers, the differences between systems were greater than simply the length, raising doubts about the credibility of the data. Employing these two compressions from the same manufacturer, Whitelaw et al. [105] showed that the thigh length compression produced higher peak velocity and augmentation. Some studies [103, 114] compared uniform calf compression with graded sequential thigh-length compression, but the results were inconsistent. Keith et al. [114] and Vanek [109] found that there was no statistically significant difference in peak velocities produced by the two compressions, while Flam et al. [103] showed that calf compression generated higher peak velocity and augmentation. Another study, comparing calf-length uniform compression with thigh-length graded sequential compression, showed a significant difference in the number of proximal DVTs (7.2% calf-length, 2.4% thigh-length), while there was no significant difference in the calf DVT outcomes [123]. Although it might seem logical that the more of the limb the compression covers, the better the effect, there is no certain evidence to support that.

Comparing with calf compression, foot compression needs much higher pressure. The pressure produced by foot compression typically reaches up to 130 mmHg or more, compared with 40 mmHg in the calf. This is because the blood volume in the plantar venous plexus is smaller than that in the calf (20–30 mL in the foot [124], 100–150 mL in the calf [125]), and the muscles of foot are not as readily compressible as calf muscles and blood pressure at foot level is higher than that in the calf when sitting or standing. However, foot compression has become a popular alternative to calf compression in recent years because of its “out of the way” nature.

Recently, some studies [104, 105] claimed that foot compression is haemodynamically effective. Ricci et al. showed that foot compression doubles the resting peak velocity [104]. Some comparisons between foot compression and calf and/or thigh compression showed that efficiency of the foot compression devices was lower than for other systems [105]. According to limited information, it was suggested that the performance of foot compression was not as good as calf compression [106]. The venous volume ejected by foot compression is always lower [106]; therefore, even when systems are set to reduce high peak velocities, the augmentation would not be expected to last as long as that generated by other compression systems. DVT outcome studies on foot compression have been generally positive. According to Spain et al.’s study [126], foot compression has the same efficiency as graded-sequential calf compression in DVT prophylaxis. The combination of stockings and foot compression has been suggested to be more effective than stockings alone in both DVT and pulmonary embolism prophylaxis [127, 128].

2.3.3 Compression Application Protocols

The compression can be applied uniformly or graded sequentially. The action of graded sequential compression has been well described: chambers of the device are sequentially inflated from the most distal one producing the highest pressure to the

most proximal one generating the lowest pressure. It was showed that graded sequential compression was more efficient at emptying a limb than uniform compression [120]. Comparison between velocity profiles (Figure 2.5) generated by the two types of compression showed that the graded sequential compression produced longer augmentation because each bladder generated one peak, but the peak velocities produced by the systems were similar to each other. In fact, there is no evidence that one of the two systems is significantly better than the other at DVT prophylaxis [129].

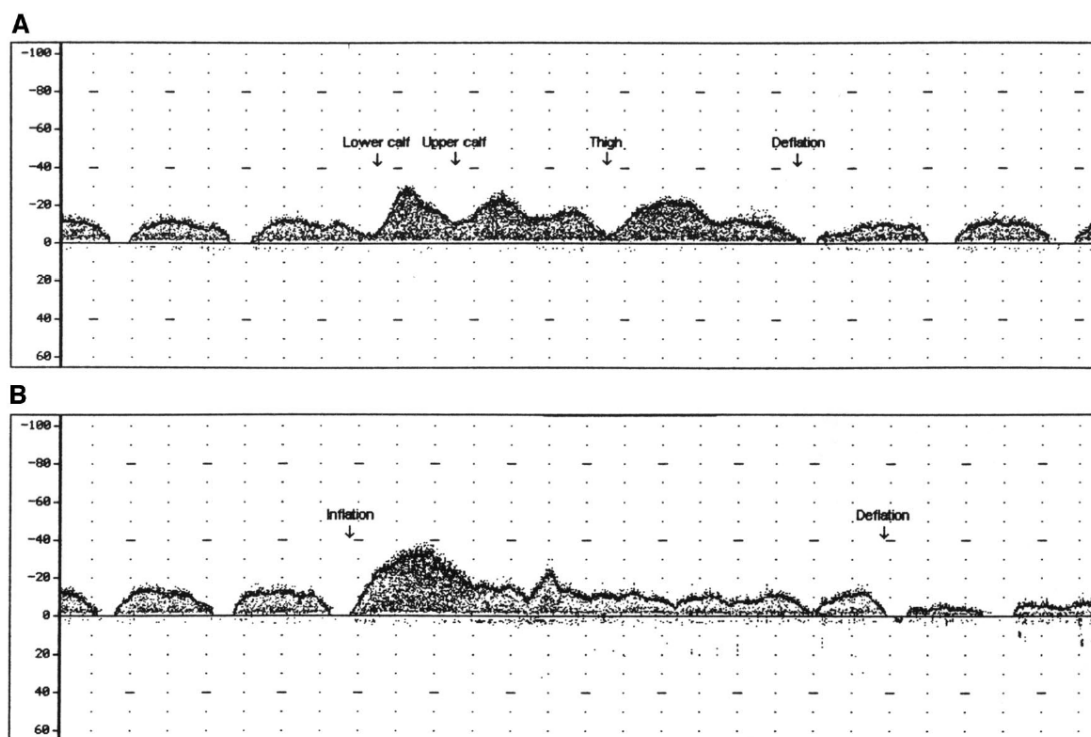


Figure 2.5 Venous blood flow velocity profiles in the femoral vein under compression of: (A) a three-bladder graduated sequential thigh-length cuff (A), and a two-bladder uniform thigh-length cuff (B). (velocity [cm/s] vs. time [1 second per vertical dotted line]). Extracted from [7].

Another way to differentiate compression systems is the extent of the air bladders. Circumferential compressions have bladders that cover the whole limb, and non-circumferential-type typically has a smaller bladder placed at the back of the limb.

Both circumferential and non-circumferential compressions have been proved to be effective at prevention of stasis and DVT prophylaxis. However, there is little research on the direct comparison between the two compression systems. Dai et al. [14] developed a two-dimensional finite-element model to simulate the deformation of lower limb under these different systems, and concluded that non-circumferential calf compression was more efficient at emptying veins than the circumferential type. However, it should be noted that the geometry of the model was idealized and no attempt at model validation was made.

2.4 Flows in Collapsible Tubes

Almost all conduits carrying fluids within the body are flexible, and interactions between an internal flow and wall deformation often underlie the biological function or dysfunction of a conduit. Comparing arteries with veins, because the internal pressure in arteries is much higher, arteries do not usually collapse but veins do, especially under external compression when the external pressure (P_e) is higher than the internal pressure (P). The difference between internal and external pressure is called the transmural pressure ($P - P_e$), whose relationship with the vessel cross-sectional area (A) is usually called the ‘Tube Law’.

In vitro experimental study [130] showed that latex tubes and veins have qualitatively similar pressure-area relationships (Figure 2.6) which differ quantitatively owing to their different elastic properties. Under positive transmural pressure ($P > P_e$) conditions, the tube cross-section remains circular and circumferential strain is induced in the wall. As the transmural pressure decreases, the strength of the tube wall becomes incapable of holding the circular shape and the tube buckles into an hourglass shape. With further reduction in transmural pressure, the tube expresses high level of compliance until opposite sides of the tube wall come into contact. The extension of the initial contact point to a line results in a reduction of wall compliance. Tadjbakhsh et al. [131] performed an analytical investigation into the buckling of circular rings. In a later study, using thin shell theory, Flaherty et al. [132] developed an analytical expression for the post contact region.

The simplest model of incompressible flow through a vascular system is the lumped-parameter model [133]:

$$Q = C \frac{dP}{dt} + \frac{P}{R} \quad (2.9)$$

where Q is the flow rate at heart, which means the inflow for arterial system and outflow for venous system, P is the blood pressure, C is the compliance of vessel wall, and R is the flow resistance at the end distal to the heart. Coupled arterial and venous lumped-parameter models have been proven a useful tool in understanding the effects of vessel compliance on blood volume shifts [134], but due to its exclusion of wave propagation effects, contribution of wave energy to the hemodynamic forces is not taken into account and significant discrepancies between the experimental data and model predictions in terms of pressure become inevitable.

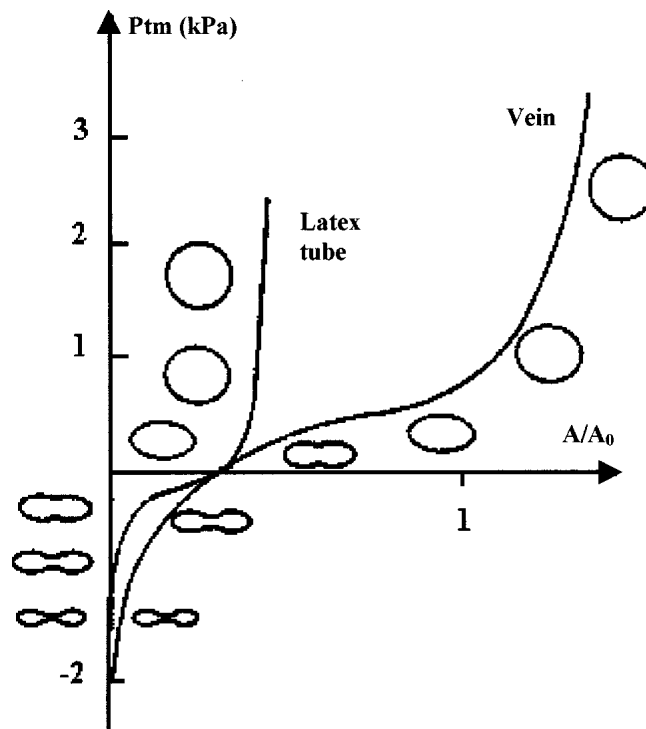


Figure 2.6 Comparison of pressure–area relation of a latex tube with the one of an excised segment of a canine vena cava. Extracted from [130].

One-dimensional models for investigating collapsible tube flows [13] are typically described through a series of partial differential equations:

$$\frac{\partial A}{\partial t} + \frac{\partial(Au)}{\partial x} = 0 \quad (2.10)$$

$$\frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} = -\frac{1}{\rho} \left(\frac{\partial P}{\partial x} + \frac{D_w \tau_w}{A} \right) \quad (2.11)$$

$$P - P_e = T - F \frac{\partial^2 A}{\partial x^2} \quad (2.12)$$

where A is cross-sectional area, x is axial distance, u is axial velocity, t is time, P is the fluid pressure, P_e is the external pressure, ρ is flow density, D_w is wetted perimeter, τ_w is wall shear stress, $T = T(\alpha)$ is the tube law characterizing the variable compliance of the tube during its collapse and $\alpha = A/A_0$, and F is the longitudinal tension.

The one-dimensional models have been shown to be a powerful tool in understanding a variety of flows in collapsible tubes and represent some hemodynamic features, such as wave propagations [135] and self-excited oscillations [136]. However, their predictions do not fit the experiments. The reason is that the derivation of Eq.(2.10) and Eq.(2.11) ignored high-order terms, which can lead to significant qualitative deviations.

Two-dimensional models have been used to reveal details of the instabilities presented in systems involving collapsible-tube flows. Investigations of Tollmien-Schlichting (TS) waves and travelling-wave flutter (TWF) revealed different mechanisms of energy transfer between flow and the wall [137-139]. Using finite element schemes, in which fluid and solid solvers are fully coupled, Luo et al. [140, 141] studied compliant wall configuration and steady flow conditions, and transfer of a steady flow to an unsteady flow with self-excited oscillations at high Reynolds number (Re). Although these instabilities are very important in many biological applications, their relevance to venous flow has not been demonstrated.

Applications of three-dimensional flow-structure interaction (FSI) model generated excellent agreement with experimental data at low Re [142]. FSI models are usually developed in finite difference, finite element or finite volume frameworks and different techniques, including Arbitrary Lagrangian Eulerian method (ALE) [143, 144], immersed boundary method [145, 146] and fictitious domain method [147], have been developed to capture the FSI interface. Three-dimensional FSI analysis has been performed on atherosclerotic plaques to determine biomechanical stresses within and around a plaque [148, 149]. Although the potential of three-dimensional models for studying the venous system has been recognised, such analyses have not been reported in the literature due to the highly variable and complex architecture of the deep venous system and its surrounding tissues.

2.5 Summary

Although the biomechanical influences of compression devices on the deep venous system have been shown to be thrombo-prophylactic, the link between the biomechanical factors and the pathology of deep vein thrombosis still remains unclear. A number of numerical studies [14, 15, 150] have been conducted to quantify the effects of external compression on the deformation of calf tissues and veins, but, as yet, no validated model has been established. The material properties of calf tissues play an important role in the load transmission of external compression to the venous system. However, these vary from person to person and are difficult to measure *in vivo*.

The influence of haemodynamic forces, such as wall shear stress, on the aetiology of vascular diseases has been demonstrated [8, 9]. Image-based 3D computational modelling has been used for the investigation of flow conditions in both the arterial and venous systems [113, 151]. However, comparing to the extensive studies of the arterial system, numerical research on the venous system is very limited. Recent development of MRI technique [152] has enabled real-time measurement of blood flow in the deep venous system. In combination with this technique, numerical simulations have the potential to determine the change in haemodynamic conditions induced by external compression and be used for the design of compression devices.

Chapter 3

Finite Element Analysis: the Effect of Compression on Tissue Deformations in the Calf

3.1 Introduction

This chapter focuses on the use of finite element analysis (FEA) to investigate the stress and strain fields induced in the calf soft tissues by the application of compression stocking. The purpose of this study was twofold: (i) to assess the capability of the finite element model to simulate the transmission of load through the skeletal muscle and onto the vein walls, and (ii) to gain more insight into the mechanical responses of the soft tissues to external pressure.

The potential of FEA to investigate the mechanical responses of calf tissues to external compression has been explored in previous studies. Employing an idealized geometry, Dai et al. [14] developed a 2D finite element model to simulate the collapse of deep vein in an idealised model of a calf cross-section under external compression, but validation of simulation results against experimental data was not performed. In a more recent study [15], the bulk deformation of calf tissues under intermittent compressions was investigated, assuming a uniform strain-stress boundary condition for all the materials of the lower leg.

The application of high spatial resolution MR imaging has been shown to be able to provide detailed information on the soft tissues in the calf [19]. The deformations of soft tissues recorded by MRI indicated different levels of compressibility for different components. As shown in Figure 3.1, there are four muscle compartments in the calf, deep posterior compartment (DPC), anterior compartment (AC), lateral compartment (LC), and superficial posterior compartment (SPC). Evaluation of the boundary

displacements of the muscle compartments showed that the displacement of DPC boundary was smaller than the other three muscle compartments (AC, LC, and SPC).

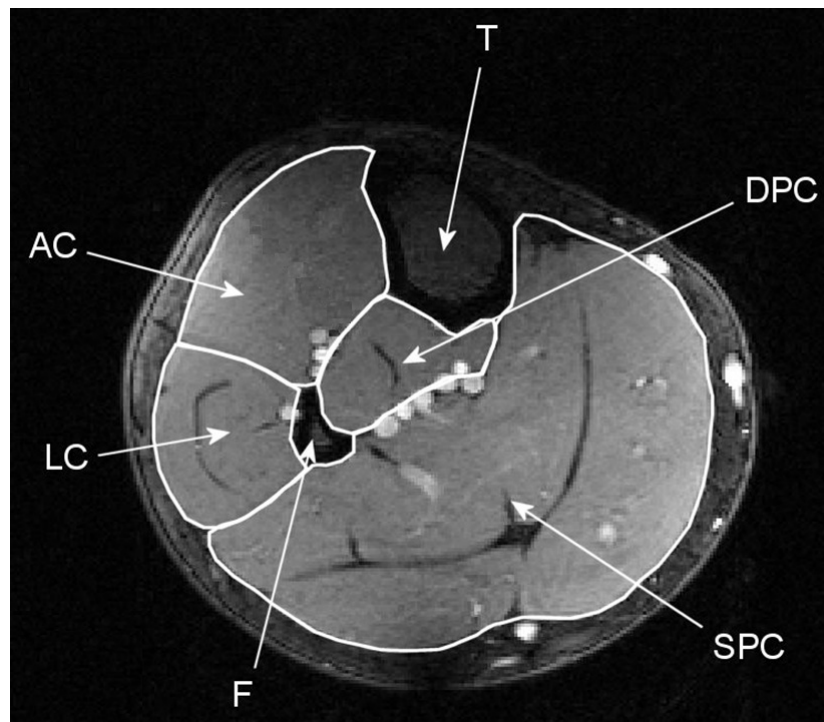


Figure 3.1 MRI image of a transverse section of calf. Muscle compartments are outlined in white. AC-anterior compartment, LC-lateral compartment, DPC-deep posterior compartment, SPC-superficial posterior compartment, T-tibia, F-fibula.

For the investigation of the mechanical responses of calf under external compression, MR image-based finite element models were developed in this study. The lower legs of four healthy subjects were scanned with, and without, the presence of compression stockings using MR imaging. In order to reproduce the observed structural behaviour of different muscle compartments to external compression, finite element models of a calf cross-section with and without restriction of the ‘out-of-plane’ deformation of DPC were built, with the plane stress condition being applied to the other three muscle compartments. Simulation results obtained using different combinations of strain-stress boundary conditions are compared and discussed in this chapter. Of

particular interests here are the area reduction of the calf cross-section and the deformation of deep veins.

3.2 Theory

3.2.1. Basic Concepts of Structure Analysis

Stress is a measure of the average force per unit area of a surface within a deformable body on which internal forces act. At an arbitrary point P on a surface whose area is A (Figure 3.2), the stress vector $\mathbf{T}$ is defined as

$$\mathbf{T} = \frac{\mathbf{F}}{A} \quad (3.1)$$

where F is the force acting on the surface. The overall stress vector $\mathbf{T}$ is acting in the same direction of the force vector. Because the force vector can be decomposed into its normal and tangential components, named as normal force and shear force respectively, $\mathbf{T}$ is composed of the resulting stress components:

$$\mathbf{T} = \sigma_n \mathbf{n} + \tau \mathbf{t} \quad (3.2)$$

where $\mathbf{n}$ and $\mathbf{t}$ are unit vectors in the normal and tangential directions of the area. σ_n is the result of normal force, named as normal stress, and τ is the result of shear force, named as shear stress.

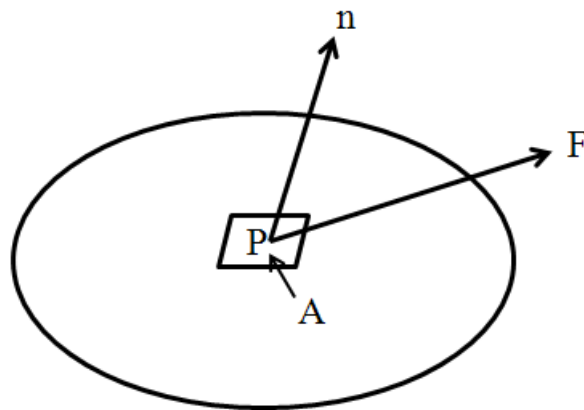


Figure 3.2 Stress in a loaded deformable body

Usually, stress is not uniformly distributed over the area and therefore the stress at a point in the region is not necessarily equal to the average stress over the entire area. An accurate definition of stress needs to consider a specific point in the body rather than a given area. Although an infinitely number of planes can be drawn through a point, the stress can be defined over an infinite small cube situated at the point (Figure 3.3). According to Cauchy, the stress at an arbitrary point in a continuum is defined as:

$$\sigma = \begin{bmatrix} \sigma_x & \tau_{xy} & \tau_{xz} \\ \tau_{yx} & \sigma_y & \tau_{yz} \\ \tau_{zx} & \tau_{zy} & \sigma_z \end{bmatrix} \quad (3.3)$$

σ is known as the Cauchy stress tensor.

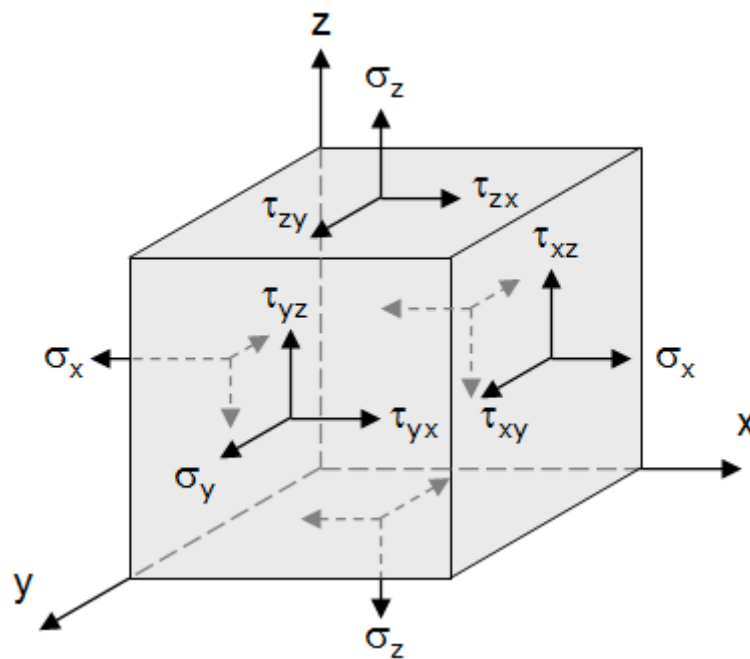


Figure 3.3 Components of stress acting on a cube.

If we only consider the stress components in the $x-y$ plane (Figure 3.4), the balance of moment about the origin point can be expressed as,

$$(\sigma_y dx) \frac{dx}{2} - (\sigma_y dx) \frac{dx}{2} + (\sigma_x dy) \frac{dy}{2} - (\sigma_x dy) \frac{dy}{2} + (\tau_{yx} dx) dy - (\tau_{xy} dy) dx = 0 \quad (3.4)$$

which reduces to

$$\tau_{yx} = \tau_{xy} \quad (3.5)$$

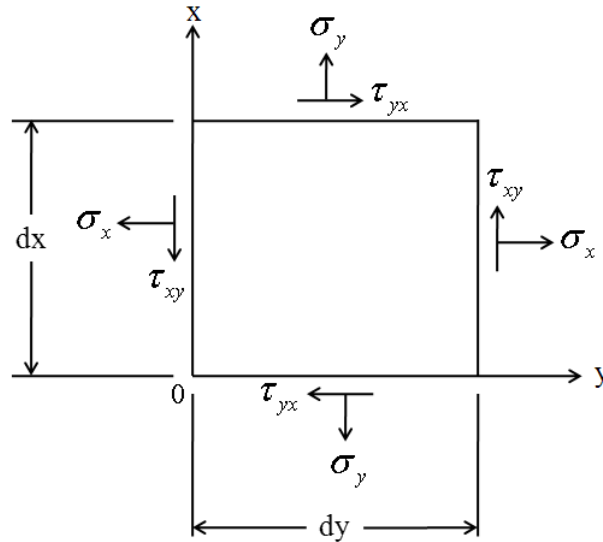


Figure 3.4 Components of stress in two dimensions.

This means that the shear stress component acting on the x plane in the y direction is equal to the shear stress component acting on the y plane in the x direction. Similarly, it can also be derived that

$$\tau_{xz} = \tau_{zx} \quad (3.6)$$

$$\tau_{yz} = \tau_{zy} \quad (3.7)$$

A strain is a normalized measure of deformation representing the displacement between particles in the body relative to a reference length. According to different deformation theories, the strain can be defined differently. Considering a bar with an initial length of l_0 under a tensile load, it will be elongated to l . The Cauchy Strain or engineering strain is expressed as the deformation per unit initial length and can be written as

$$\varepsilon = \frac{l - l_0}{l_0} \quad (3.8)$$

Obviously, the positive strain ε is associated with a tensile stress.

The logarithmic strain or true strain is defined as

$$e = \int_{l_0}^l \frac{dl}{l} = \ln \frac{l}{l_0} \quad (3.9)$$

The difference between these definitions is negligible in the small-strain region. However, when large deformations are involved, the difference becomes appreciable.

As with stress, strain can also be decomposed into its normal and tangential components. Considering now an infinitesimal deformation of an two-dimensional infinitesimal rectangular element with dimensions of $dx \times dy$, as shown in Figure 3.5 the engineering strain in the x and y directions are defined as follows:

$$\varepsilon_x = \frac{ab - AB}{AB} = \frac{ab - dx}{dx} \quad (3.10)$$

$$\varepsilon_y = \frac{ac - AC}{AC} = \frac{ac - dy}{dy} \quad (3.11)$$

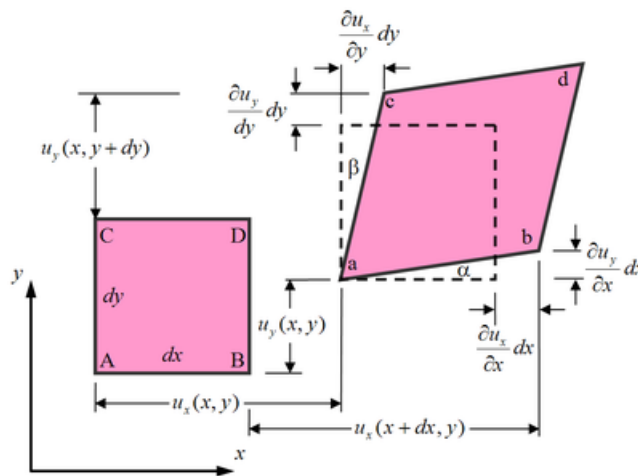


Figure 3.5 Deformation of a two dimensional infinitesimal material element.

The engineering shear strain is defined as the change in angle of the initial right angle. In the figure, it is the change in the angle between lines $\overline{AC}$ and $\overline{AB}$, namely,

$$\gamma_{xy} = \alpha + \beta \quad (3.12)$$

If considering an infinitesimal deformation, α and β will be very small, therefore

$$\tan \alpha \approx \alpha \quad (3.13)$$

$$\tan \beta \approx \beta \quad (3.14)$$

$$ab \approx dx + \left(\frac{\partial u_x}{\partial x}\right)dx \quad (3.15)$$

$$ac \approx dy + \left(\frac{\partial u_y}{\partial y}\right)dy \quad (3.16)$$

Adding these to Eq.(3.10), (3.11) and (3.12), we have

$$\varepsilon_x = \frac{\partial u_x}{\partial x} \quad (3.17)$$

$$\varepsilon_y = \frac{\partial u_y}{\partial y} \quad (3.18)$$

$$\gamma_{xy} = \frac{\partial u_x}{\partial y} + \frac{\partial u_y}{\partial x} \quad (3.19)$$

The strain-displacement relationship in two dimensions can be expressed using Eq.(3.17)-(3.19).

Obviously, in a two-dimensional strain-displacement relationship, the strain field is expressed by three strain measures, but there are only two independent displacements. In order to ensure a valid displacement, a compatibility equation is still required, which is

$$\frac{\partial^2 \gamma_{xy}}{\partial x \partial y} = \frac{\partial^2 \varepsilon_y}{\partial x^2} + \frac{\partial^2 \varepsilon_x}{\partial y^2} \quad (3.20)$$

The average rigid-body rotation of a two-dimensional element is defined as follows:

$$\omega = \frac{1}{2} \left(\frac{\partial u_y}{\partial x} - \frac{\partial u_x}{\partial y} \right) \quad (3.21)$$

This is useful when measurements are done by the moiré method.

3.2.2 Stress-Strain Relationship

Considering an infinitesimal cubic element within a loaded deformable body, the stress is related to the strain by

$$\{\sigma\} = [D]\{\varepsilon\} \quad (3.22)$$

where $\{\sigma\}$ is a stress vector defined as

$$\{\sigma\} = [\sigma_x \quad \sigma_y \quad \sigma_z \quad \tau_{xy} \quad \tau_{yz} \quad \tau_{xz}]^T \quad (3.23)$$

$[D]$ is elastic stiffness matrix and $\{\varepsilon\}$ is strain vector defined as

$$\{\varepsilon\} = [\varepsilon_x \quad \varepsilon_y \quad \varepsilon_z \quad \gamma_{xy} \quad \gamma_{yz} \quad \gamma_{xz}]^T \quad (3.24)$$

Eq.(3.22) can be inverted to

$$\{\varepsilon\} = [D]^{-1}\{\sigma\} \quad (3.25)$$

where

$$[D]^{-1} = \begin{bmatrix} 1/E_x & -\nu_{xy}/E_x & -\nu_{xz}/E_x & 0 & 0 & 0 \\ -\nu_{yx}/E_x & 1/E_y & -\nu_{yz}/E_x & 0 & 0 & 0 \\ -\nu_{zx}/E_x & -\nu_{zy}/E_x & 1/E_z & 0 & 0 & 0 \\ 0 & 0 & 0 & 1/G_{xy} & 0 & 0 \\ 0 & 0 & 0 & 0 & 1/G_{yz} & 0 \\ 0 & 0 & 0 & 0 & 0 & 1/G_{xz} \end{bmatrix} \quad (3.26)$$

where E_i is Young's modulus in the i ($i = x, y, z$) direction;

ν_{ij} is Poisson's ratio in the ij ($i = x, y, z; j = x, y, z; i \neq j$) plane;

G_{ij} is shear modulus in the ij ($i = x, y, z; j = x, y, z; i \neq j$) plane.

Also, the $[D]^{-1}$ matrix is presumed to be symmetric, so that:

$$\frac{\nu_{yx}}{E_y} = \frac{\nu_{xy}}{E_x} \quad (3.27)$$

$$\frac{\nu_{zx}}{E_z} = \frac{\nu_{xz}}{E_x} \quad (3.28)$$

$$\frac{\nu_{zy}}{E_z} = \frac{\nu_{yz}}{E_y} \quad (3.29)$$

The shear moduli G_{xy} , G_{yz} and G_{xz} are computed as:

$$G_{xy} = \frac{E_x}{2(1 + \nu_{xy})} \quad (3.30)$$

$$G_{zy} = \frac{E_y}{2(1 + \nu_{yz})} \quad (3.31)$$

$$G_{xz} = \frac{E_z}{2(1 + \nu_{zx})} \quad (3.32)$$

This is a brief description of the structure theory employed in this study. For further details, please refer to the Ansys HELP manual [153].

3.2.3 Finite Element Method for Structural Analysis

The finite element method is an approximate numerical technique for the solution of physical problems in engineering analysis and design, which typically involve an actual structure or structural component subjected to certain loads. A mathematical model expressing the physical problem is governed by differential equations, and the finite element method is used to solve the mathematical model numerically by rendering the differential equations into an approximating system of algebraic equations.

While the theory of the finite element method can be presented in different perspectives or emphases, its development for structural analysis follows the more traditional approach via the virtual work principle or the minimum total energy principle. The virtual work principle approach is more general as it is applicable to both linear and non-linear material behaviours. The principle of virtual displacement for the structural system expresses the mathematical identity of external and internal virtual work.

In order to derive the principle of virtual displacement, the general elasticity problem needs to be stated first. Consider an arbitrary three-dimensional body located in a fixed coordinated system X, Y, Z . The body is supported on the area S_u , on which all displacement components are prescribed as $\mathbf{U}^{S_u}$. The body is subjected to surface tractions f^{S_f} (force per unit surface area) on the surface S_f and externally applied body loads f^B (forces per unit volume). In this case, $S_u \cup S_f = S$, $S_u \cap S_f = 0$.

For the system described above, equilibrium dictates that the following differential equation must be satisfied:

$$\tau_{ij} + f_i^B = 0 \quad (3.33)$$

with the force boundary conditions:

$$\tau_{ij} n_i = f_i^{S_f} \text{ on } S_f \quad (3.34)$$

and the displacement boundary conditions:

$$u_i = u_i^{S_u} \text{ on } S_u \quad (3.35)$$

where the indices i and j relate to the orthogonal basis vectors, u_i is the i 'th displacement field, n_i is the i 'th component of the normal to S , τ_{ij} is the ij 'th component of the Cauchy stress tensor and f_i^B is the component of body force per unit volume in the i direction. The summation convention of repeated indices is employed here and a comma in the subscript denotes differentiation by the index which follows.

The following must then hold for any arbitrary (virtual) displacements $\bar{u}_i$ which satisfy zero displacement on S_u :

$$\left(\tau_{ij,j} + f_i^B \right) \bar{u}_i = 0 \quad (3.36)$$

Integration of this expression throughout the volume of the body and application of the divergence theorem then lead directly to the principle of virtual work:

$$\int_V \bar{\epsilon}_{ij} \tau_{ij} dV = \int_V \bar{u}_i f_i^B dV + \int_{S_f} \bar{u}_i f_i^{S_f} dS \quad (3.37)$$

The mathematical statement in Eq. 3.37 is equivalent to saying that, if the internal stress field balances the externally applied loads, the internal virtual work (left hand

side) is equal to the external virtual work (right hand side) for any continuous virtual displacement field which is compatible with the displacement boundary conditions.

For deriving the governing finite element equations, the body described above is approximated as an assemblage of discrete finite elements which are interconnected at nodal points on the element boundaries. The continuous displacements within each element are assumed to be a function of the displacements at the nodes of that element. Therefore, for one element:

$$\mathbf{u}(x, y, z) = \mathbf{H}(x, y, z)\hat{\mathbf{U}} \quad (3.38)$$

where $\mathbf{H}$ is a matrix containing interpolation functions which relate nodal displacements to the continuous displacement field within the element and $\hat{\mathbf{U}}$ is a vector of the three global displacement components U_i, V_i and W_i at all nodes of the element. Using the strain-displacement matrix, $\mathbf{B}$, which is obtained by appropriately differentiating and combining rows of the matrix, $\mathbf{H}$, corresponding element strains can be evaluated:

$$\boldsymbol{\varepsilon}(x, y, z) = \mathbf{B}(x, y, z)\hat{\mathbf{U}} \quad (3.39)$$

The element stress is calculated from the element strains:

$$\boldsymbol{\tau} = \mathbf{C}\boldsymbol{\varepsilon} \quad (3.40)$$

where $\mathbf{C}$ is the elasticity matrix of the element.

Using Eq. 3.38, the equilibrium equations corresponding to the discretised body can be derived. First, by applying the principle of virtual displacements (Eq. 3.37) to the assemblage, we obtain:

$$\begin{aligned} \sum_{n=1}^m \int_{V^{(n)}} \bar{\mathbf{e}}^{(n)T} \boldsymbol{\tau}^{(n)} dV^{(n)} &= \sum_{n=1}^m \int_{V^{(n)}} \bar{\mathbf{u}}^{(n)T} \mathbf{f}^{B(n)} dV^{(n)} \\ &+ \sum_{n=1}^m \int_{S_1^{(n)}, \dots, S_q^{(n)}} \bar{\mathbf{u}}^{S(n)T} \mathbf{f}^{S(n)} dS^{(n)} \end{aligned} \quad (3.41)$$

where m is the number of elements in the assembly and q the number of faces for element n . The superscript T denotes a transpose matrix. By substituting Eq. 3.38-3.40 to Eq. 3.41, we obtain:

$$\begin{aligned} \bar{\mathbf{U}}^T \left[\sum_{n=1}^m \int_{V^{(n)}} \mathbf{B}^{(n)T} \mathbf{C}^{(n)} \mathbf{B}^{(n)} dV^{(n)} \right] \bar{\mathbf{U}} &= \bar{\mathbf{U}}^T \left[\left\{ \sum_{n=1}^m \int_{V^{(n)}} \mathbf{H}^{(n)T} \mathbf{f}^{B(n)} dV^{(n)} \right\} \right. \\ &\left. + \left\{ \sum_{n=1}^m \int_{S_1^{(n)}, \dots, S_q^{(n)}} \mathbf{H}^{S(n)T} \mathbf{f}^{S(n)} dS^{(n)} \right\} \right] \end{aligned} \quad (3.42)$$

where $\mathbf{H}^S$ is an element surface interpolation matrix, obtained directly from $\mathbf{H}$. The nodal displacements are constants and thus the vector $\bar{\mathbf{U}}$ is taken outside the integral. Since the virtual displacements can be chosen, applying unit virtual displacements for each of the components of $\bar{\mathbf{U}}$ in turn allows us to assemble a matrix of equations relating the resultant nodal forces to the nodal displacements:

$$\mathbf{K} \mathbf{U} = \mathbf{R} \quad (3.43)$$

where $\mathbf{R}$ is the nodal load vector resulting from the integration of the right hand terms of Eq. 3.42. This method of assembling the FE equations is known as the direct stiffness method. The matrix $\mathbf{K}$ is referred to as the stiffness matrix and results from integration of the term inside the bracket on the left hand side of Eq. 3.42:

$$\mathbf{K} = \sum_{n=1}^m \int_{V^{(n)}} \mathbf{B}^{(n)T} \mathbf{C}^{(n)} \mathbf{B}^{(n)} dV^{(n)} \quad (3.44)$$

For a linear analysis the elements of $\mathbf{K}$ are assumed to be constant and, after implementation of the boundary conditions, Eq. 3.43 can be solved directly to give the

nodal displacements. The approximation inherent in the method is therefore entirely at the element level and rests in the ability of the interpolation functions (also called shape functions) contained in $\mathbf{H}$ to represent the true displacement field.

3.3 Materials and Methods

3.3.1 MR Imaging Protocol

Four healthy male subjects (24–28 years old) without any history of venous disease were included in this part of the study, which was approved by the local research ethics committee, and informed consent was obtained from all participants. The scans were performed in the prone position to avoid compressing the calf muscles against the table.

The subjects were asked to not consume any food or drink for a period of one hour leading up to the scans. None of the subjects was on any medication. The compression devices employed in this study were appropriately sized, knee-length static stockings (Mediven Travel). For each case, the first set of images was acquired without the stockings. Then, the target leg of the subject was removed from the bore to allow application of the stocking by an assistant, following which it was returned to the original position within the bore and the second set of images was acquired. In order to check the repeatability of the procedure, one subject was scanned twice in series. Each subject was allowed to take 10 minutes rest before any images were acquired. The purpose of this was to eliminate muscle tension. Throughout the entire process, all the subjects maintained a relaxed prone position.

A Siemens Avanto 1.5T scanner was employed for the scanning process. A flexible surface coil was loosely wrapped around the calf and positioned to provide a reasonable signal-to-noise ratio (SNR) at the appropriate level. The volume of the upper calf was acquired using a three-dimensional TrueFISP sequence. The TrueFISP sequence was selected because it provides reasonably good contrast between the blood in the veins and surrounding tissue, and this contrast is relatively independent of flow velocity. The TE and TR were 1.8 and 3.6 ms, respectively.

The slab thickness was 208 mm and the number of secondary phase-encoding steps was 104, giving a 2-mm slice thickness. The FOV was $200 \times 200 \text{ mm}^2$ with 320 primary phase-encoding steps and readout samples, and the resulting pixel size was therefore $0.625 \times 0.625 \text{ mm}$. No form of cardiac or other gating was used, as the pulsation in the veins was unknown.

3.3.2 Finite Element Model

A single transverse section, approximately 7 cm below the popliteal artery bifurcation, was studied in all four subjects. The MR images were segmented manually using in-house code developed in MATLAB (Mathworks Inc.). Model geometry was generated using images obtained without the stocking. Analysis of the MR images showed that the medial peroneal veins (MPV) of all the subjects had a larger cross section area compared to the other deep veins. Therefore the main focus was on the deformations of MPV in this study, in order to minimise the influence of segmentation error. Ansys 11.0 (Ansys Inc.) was employed to create the FE model.

The transverse section of the leg was assumed to be comprised of 3 components: muscle and fat, MPV, and bones. The area was meshed using 183 plane elements. Muscle and fat were treated as a homogenous material with Young's modulus of $1.2 \times 10^4 \text{ Pa}$ [14]. The wall thickness of the MPV was taken to be 0.8 mm, with a wall/radius ratio of 0.2. The Young's modulus of the veins was taken to be $1.33 \times 10^5 \text{ Pa}$ [15]. All materials were assumed to have a Poisson's ratio of 0.49. Bones were assumed to be rigid and incompressible, so that all the elements attached to the bones were fixed in space.

The deformations of calf tissues recorded by MR images revealed that the responses of different components of the calf were quite variable. The muscles of the lower leg can be divided into four compartments (as shown in Figure 3.1): the deep posterior compartment (DPC), the anterior compartment (AC), the lateral compartment (LC),

and the superficial posterior compartment (SPC). The boundary displacements of the muscle compartments indicated that DPC had smaller deformation under external compression than the other three compartments. The measured area reduction of the selected transverse sections was $3.25 \pm 1.01\%$, while the area reduction of DPC was $0.97 \pm 0.33\%$. An example is shown in Figure 3.6.

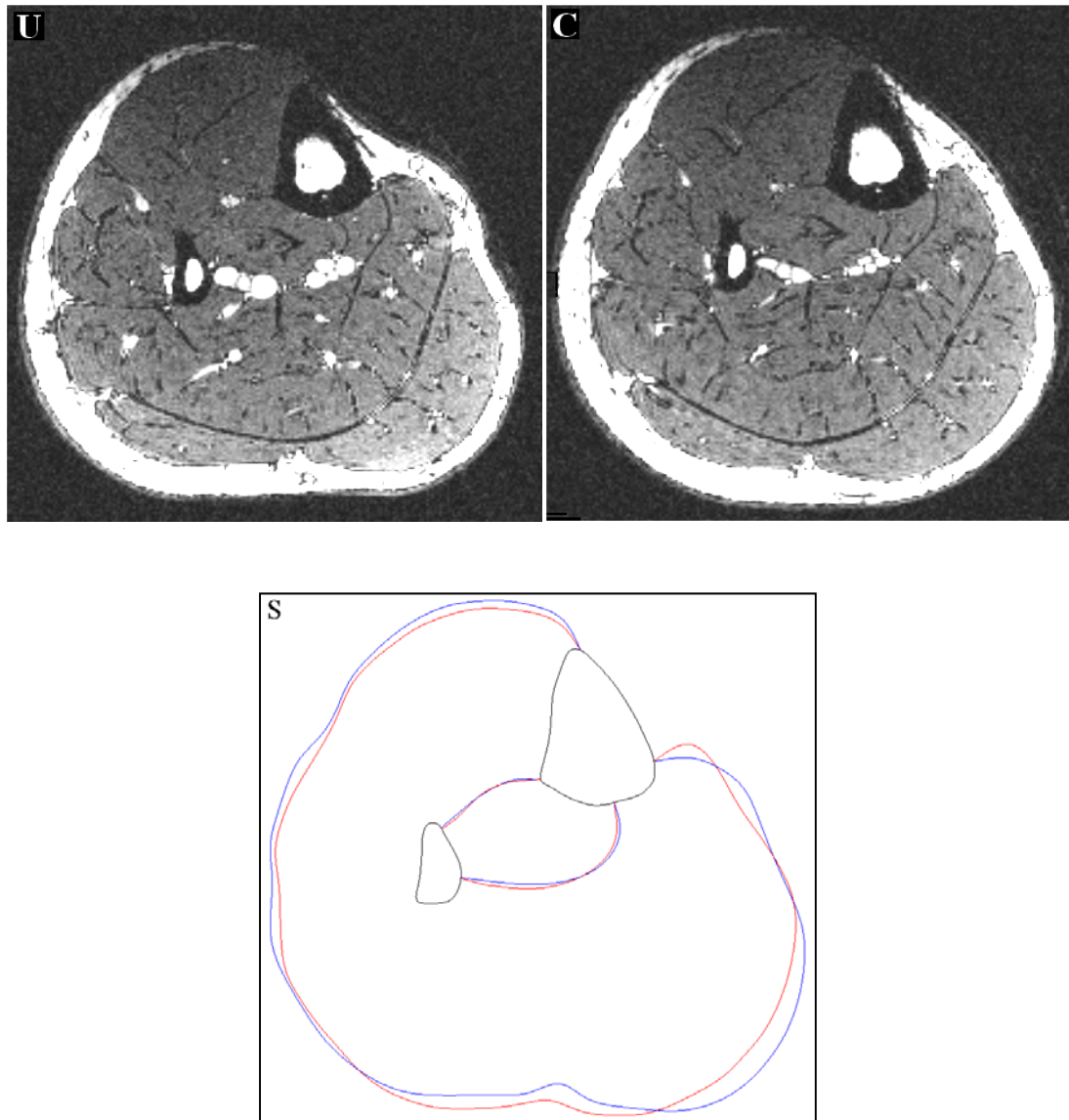


Figure 3.6 (U) and (C) are the uncompressed and compressed transverse sections of the calf; (S) is the segmented undeformed (blue line) and deformed (red line) boundaries of the muscle compartments.

Observations of the MR images showed that compared to the other muscle compartments, the DPC had smaller boundary displacements, which is likely due to several factors: (i) DPC is located deep inside the leg and enclosed by the other three muscle compartments and by the bones of the lower leg, making it less sensitive to the external pressure, (ii) DPC, located between tibia and fibula, has a relatively large area attached to the bones, restricting its out-of-plane deformation. To investigate the different mechanical responses of the muscle compartments, two finite element models (FEM) were developed and details of the stress-strain boundary conditions of the two models are given below.

Model A: Plane stress condition applied to all the components of the lower leg.

Model B: Plane strain condition applied to DPC with plane stress condition being applied all other components.

An example of mode B is shown in Figure 3.7.

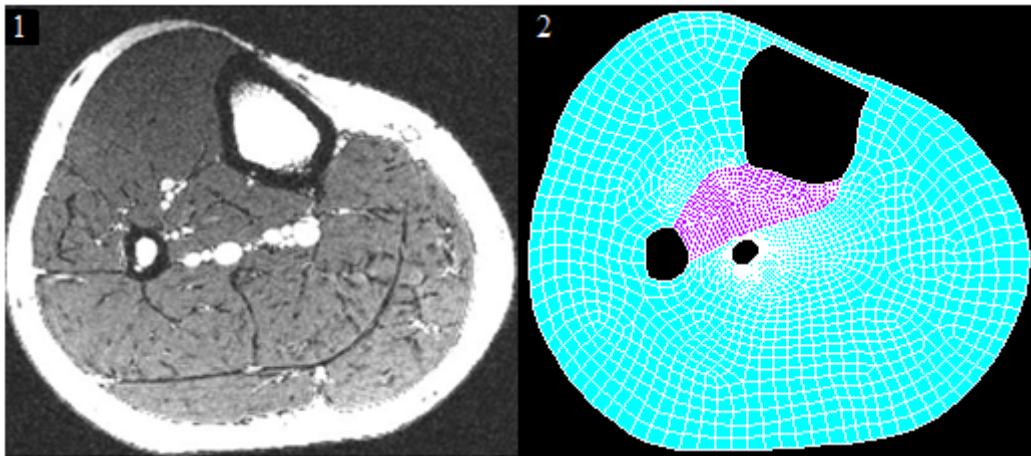


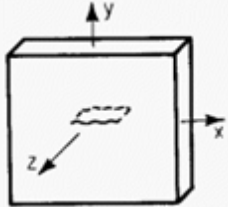
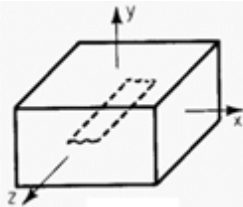
Figure 3.7 Transverse cross-section of calf of subject 1: (1) MR image of the calf, (2) Finite element model of segmented calf components: plane strain assumption for the DPC (purple), plane stress for the other regions of the section (green).

The definition of plane stress and plane strain conditions is shown in Table 3.1. Although the Poisson's ratio employed by the FEM made the material nearly

incompressible in three dimensions, the application of plane stress allows the material to be compressible in the transverse section, while the plane strain condition restricts the out of plane deformation.

A pressure load of 10 mmHg was applied to the internal surface of the MPV to simulate the blood pressure within the veins, whilst a 40 mmHg pressure was applied as the external pressure. The MPV runs alongside the boundary between the DPC and SPC, and was assumed to be located in the SPC. It was also assumed that there was no sliding at the interface between DPC and SPC, and between SPC and MPV.

Table 3.1 Definition of plane stress and plane strain conditions.

	Plane Stress	Plane Strain
		
Stresses	$\sigma_z = 0, \tau_{xz} = 0, \tau_{yz} = 0,$ $\sigma_x, \sigma_y, \sigma_{xy}$ may have non-zero values	$\tau_{xz} = 0, \tau_{yz} = 0,$ $\sigma_x, \sigma_y, \sigma_z, \sigma_{xy},$ may have non-zero values
Strains	$\gamma_{xz} = 0, \gamma_{yz} = 0,$ $\epsilon_x, \epsilon_y, \epsilon_z, \gamma_{xy}$ may have non-zero values	$\gamma_{xz} = 0, \gamma_{yz} = 0, \epsilon_z = 0,$ $\epsilon_x, \epsilon_y, \gamma_{xy}$ may have non-zero values

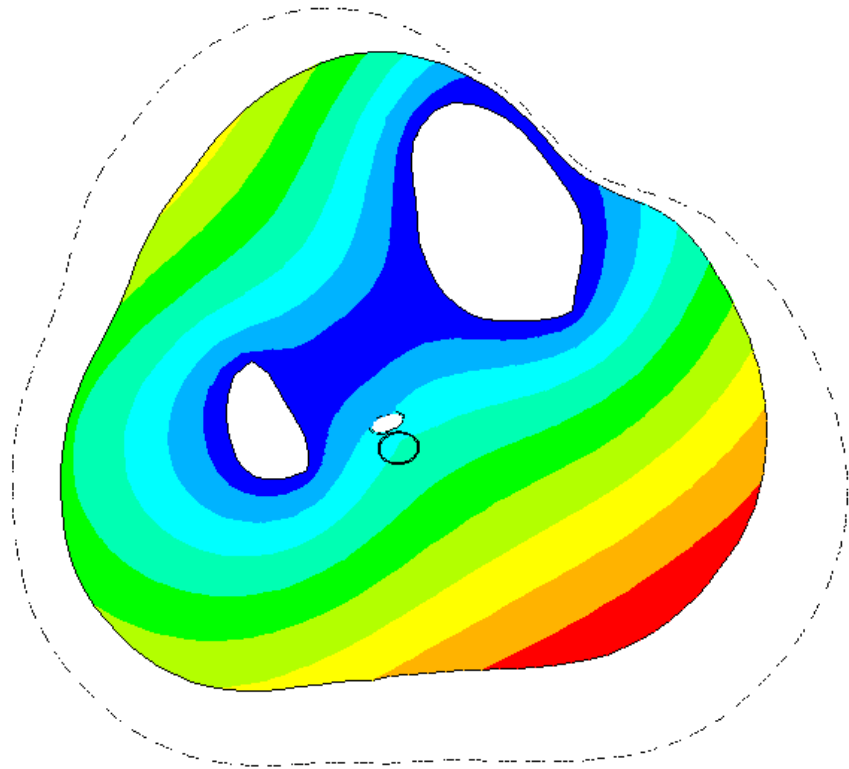
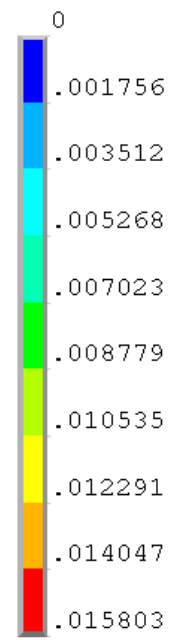
3.4 Results and Discussion

The simulated displacements within the two-dimensional transverse sections are shown in Figure 3.8. The external compression results in a change in cross-sectional area of the calf. The deep posterior compartment (DPC) located between fibula and tibia experiences the minimum deformation compared to the other parts of the calf. However, the reasons for this are different between the two models. In model A, the influence of external pressure is reduced with the increase in the distance from the outer boundary, and the rigidity of tibia and fibula limits the deformations of their surrounding tissues and prevents the external load from transmitting deeper. In model B, besides the reasons just mentioned, the restriction of out of plane deformation of DPC also plays an important role, possibly the most dominant role.

It has been indicated that muscles are nearly incompressible materials. However, because only a two-dimensional transverse section was considered in this study, stretching of the muscle in the axial direction would result in a reduction in cross-sectional area. Considering the architecture of the calf, it is very unlikely that the external pressure is uniformly distributed on the outer surface of the calf and therefore, axial displacement of soft tissues close to the stocking/calf interface is highly possible. This might be one of the reasons for the observed area reduction of calf transverse section. The collapse of vessels also contributed to the cross-sectional area reduction. Because the spatial resolution was not high enough, segmentation of all the vessels in the calf was not possible. Therefore, only the deep venous system was investigated and the results showed that the deformation of the deep vessels was on average responsible for approximately 23% (11.0% - 42.8%) of the area reduction of the whole calf transverse section.

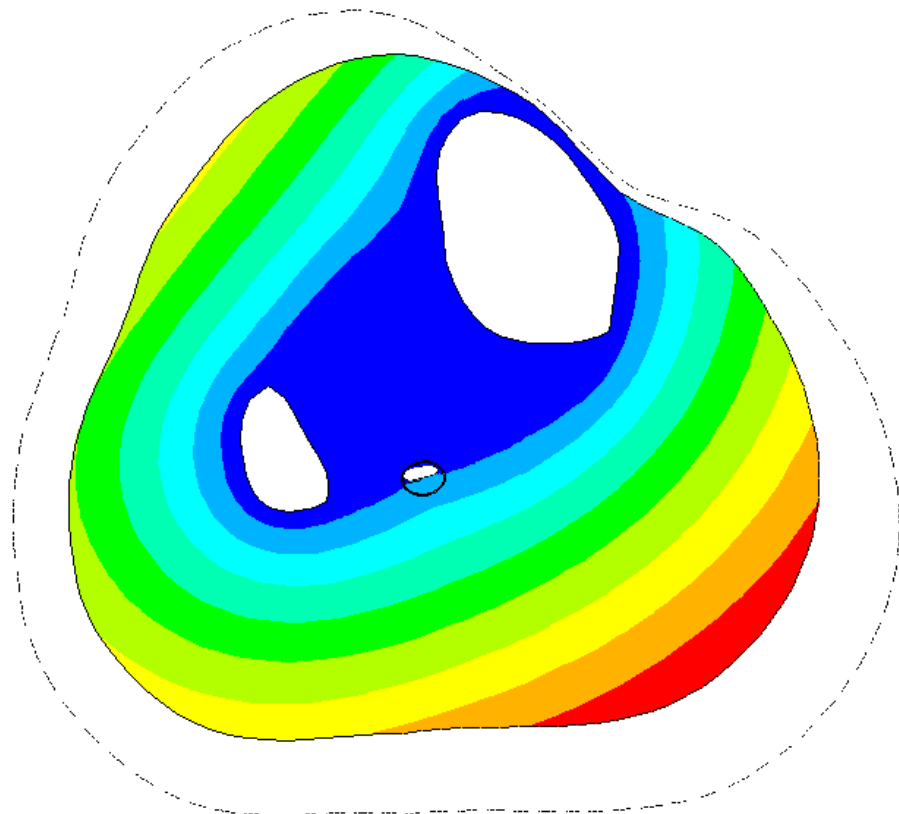
1-A

Displacement (m)



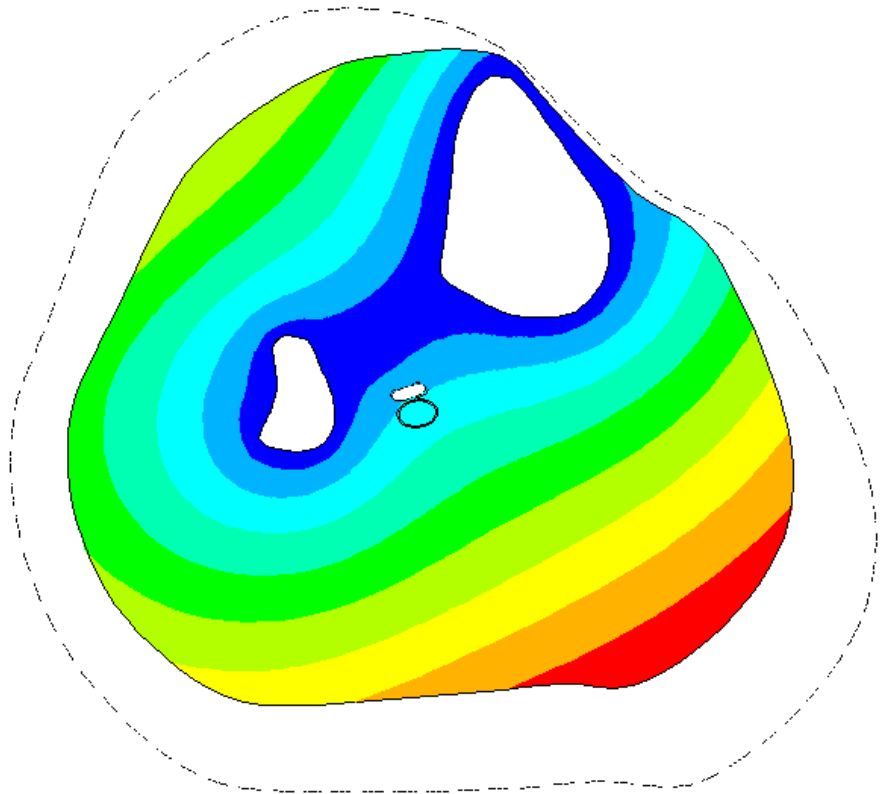
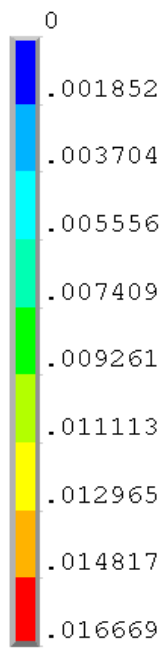
1-B

Displacement (m)



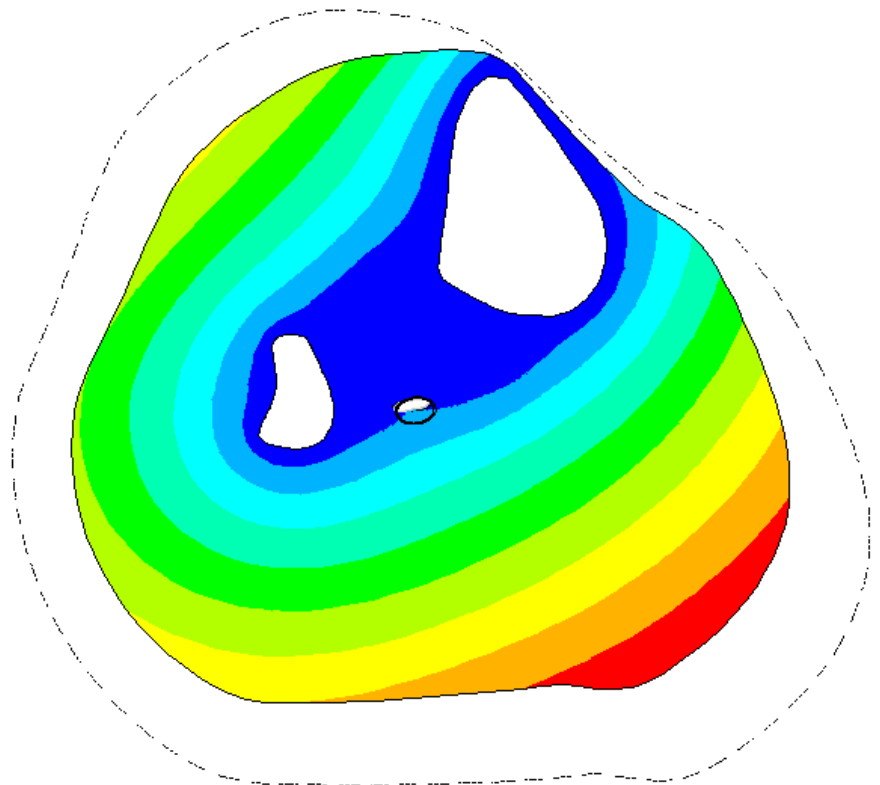
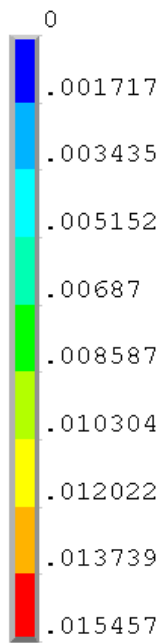
2-A

Displacement (m)



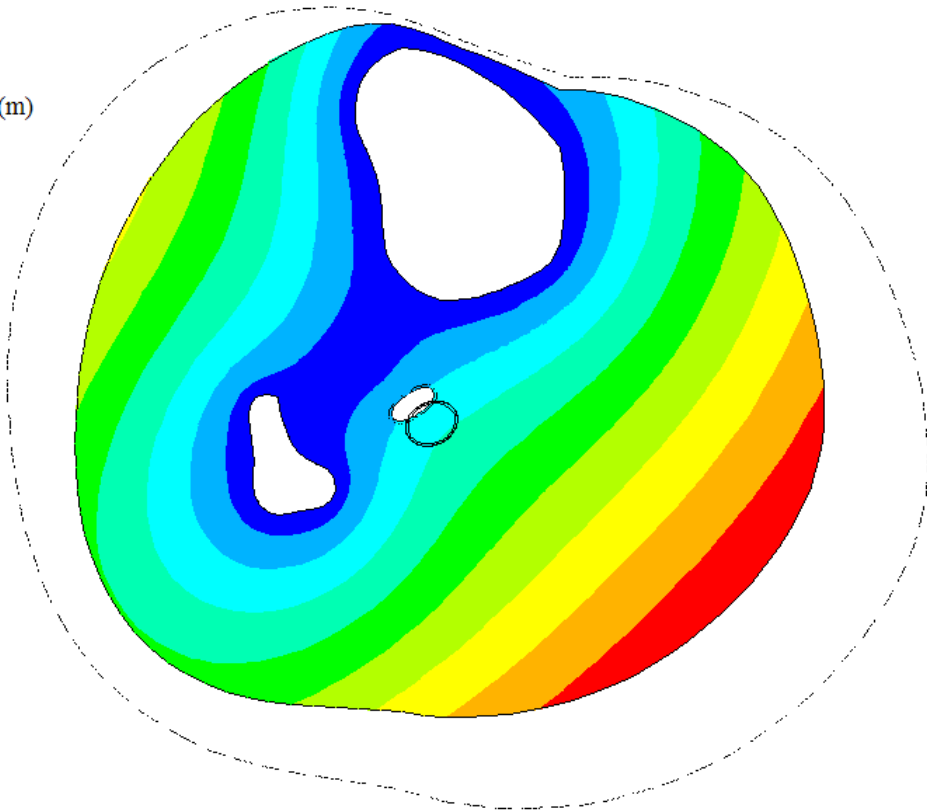
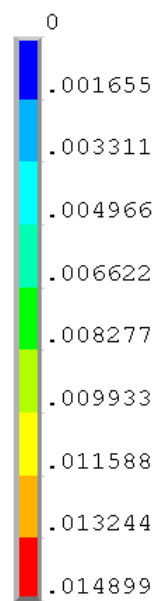
2-B

Displacement (m)



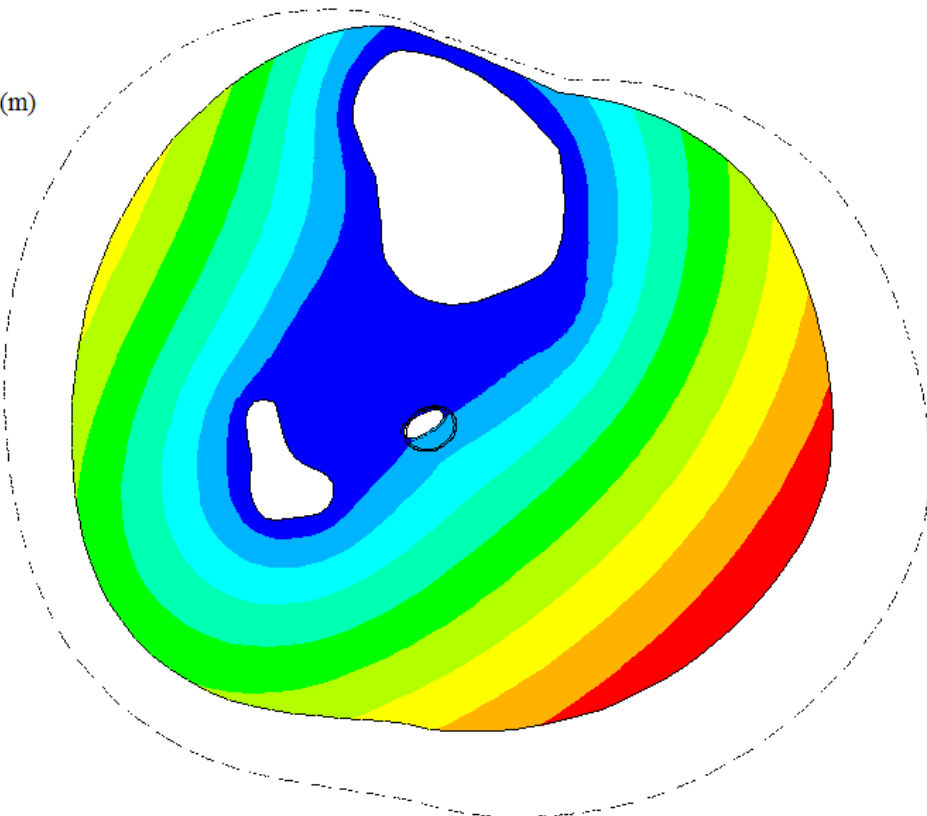
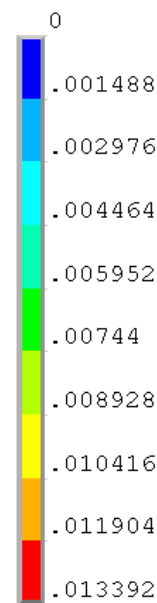
3-A

Displacement (m)



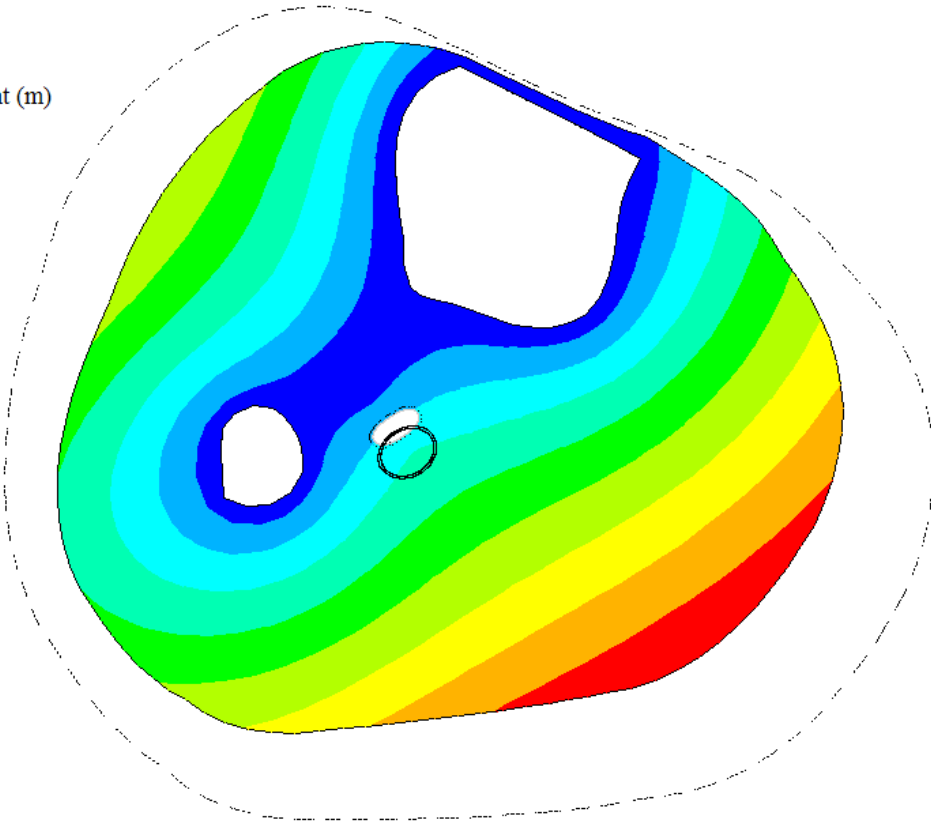
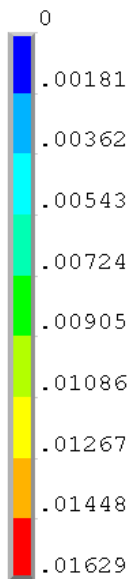
3-B

Displacement (m)



4-A

Displacement (m)



4-B

Displacement (m)

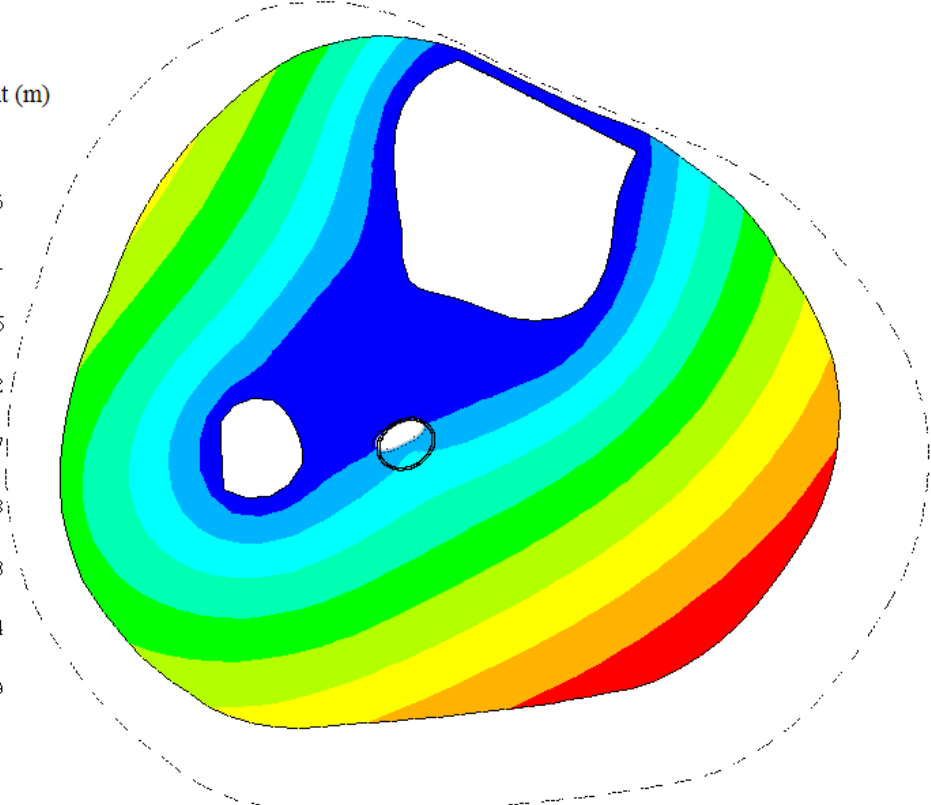


Figure 3.8 Predicted displacement contours by model A and model B, where the undeformed calf outlines are also shown (black dashed line). 1-Subject 1, 2-Subject 2, 3-Subject 3, 4-Subject 4.

Because deep veins of the calf run alongside the boundary of DPC, deformation of the DPC significantly affects the translation of the centroid of the MPV. In the simulation results of Model A, MPV moves deep into the transverse section while being compressed whereas the MPV of Model B remains at approximately the same position. Comparison of the simulation results with MR images shows that Model B (Figure 3.9-B), in which the out-of-plane deformation of DPC is restricted, produces a better agreement with segmented results from MR images (Figure 3.9-S) in terms of vein compression than Model A (Figure 3.9-A).

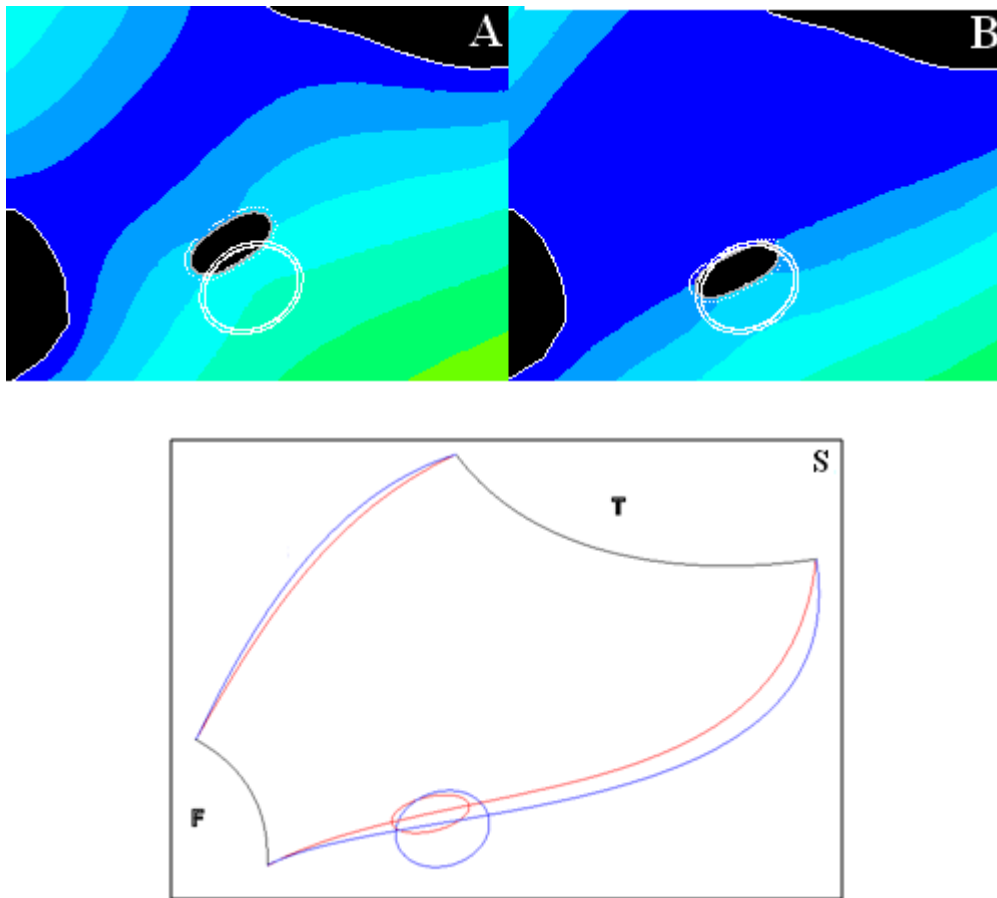


Figure 3.9 Deformation of MPV under external compression: (A)-deformation predicted by model A, (B)-deformation predicted by model B, (S)-segmented undeformed (blue line) and deformed (red line) boundaries of DPC and MPV.

Predicted area reductions of MPV using models A and B are shown in Table 3.2. For all the subjects, model B produced larger area reduction of MPV than model A. Comparing with the area reduction estimated from MR images, restricting the out of plane deformation of DPC has improved the agreement between the simulation results and *in vivo* measurements in terms of area reduction of deep veins, but both finite element models apparently underestimated the MPV area reduction.

Table 3.2 Area reduction of MPV induced by external compression

	Subject 1	Subject 2	Subject 3	Subject 4
Model A	52.2%	48.1%	39.4%	49.4%
Model B	59.0%	54.6%	48.8%	56.5%
Measurement	62.97%	55.8%	67.01%	69.37%

In order to shed light on the load transmission through the calf tissues, stress distributions were examined to search for any link between calculated hydrostatic pressure and the observed MPV area reduction. Hydrostatic pressure was chosen as the most appropriate stress measure since it relates most closely to the transmural pressure that the vein walls would be subjected to.

The obtained pressure distributions of model A show that the pressure becomes lower in the deeper area of the calf, while the DPC of model B has much higher magnitude of pressure than the other three components, even though DPC has the smallest deformation (see Figure 3.10). In order to compare with the corresponding MR measurements, the local hydrostatic pressure was calculated for each subject by segmenting the MPV outline and taking an ensemble average of all nodal values lying within. The results are shown in Table 3.3, which indicates that restricting the out of plane deformation of DPC increases the load transmission efficiency. This explains why model B generated larger area reduction of deep veins than model A.

Table 3.3 Calculated averaged hydrostatic pressure (KPa) on MPV wall.

	Subject 1	Subject 2	Subject 3	Subject 4
Model A	2.748	2.599	2.461	2.696
Model B	3.450	3.240	3.170	2.893

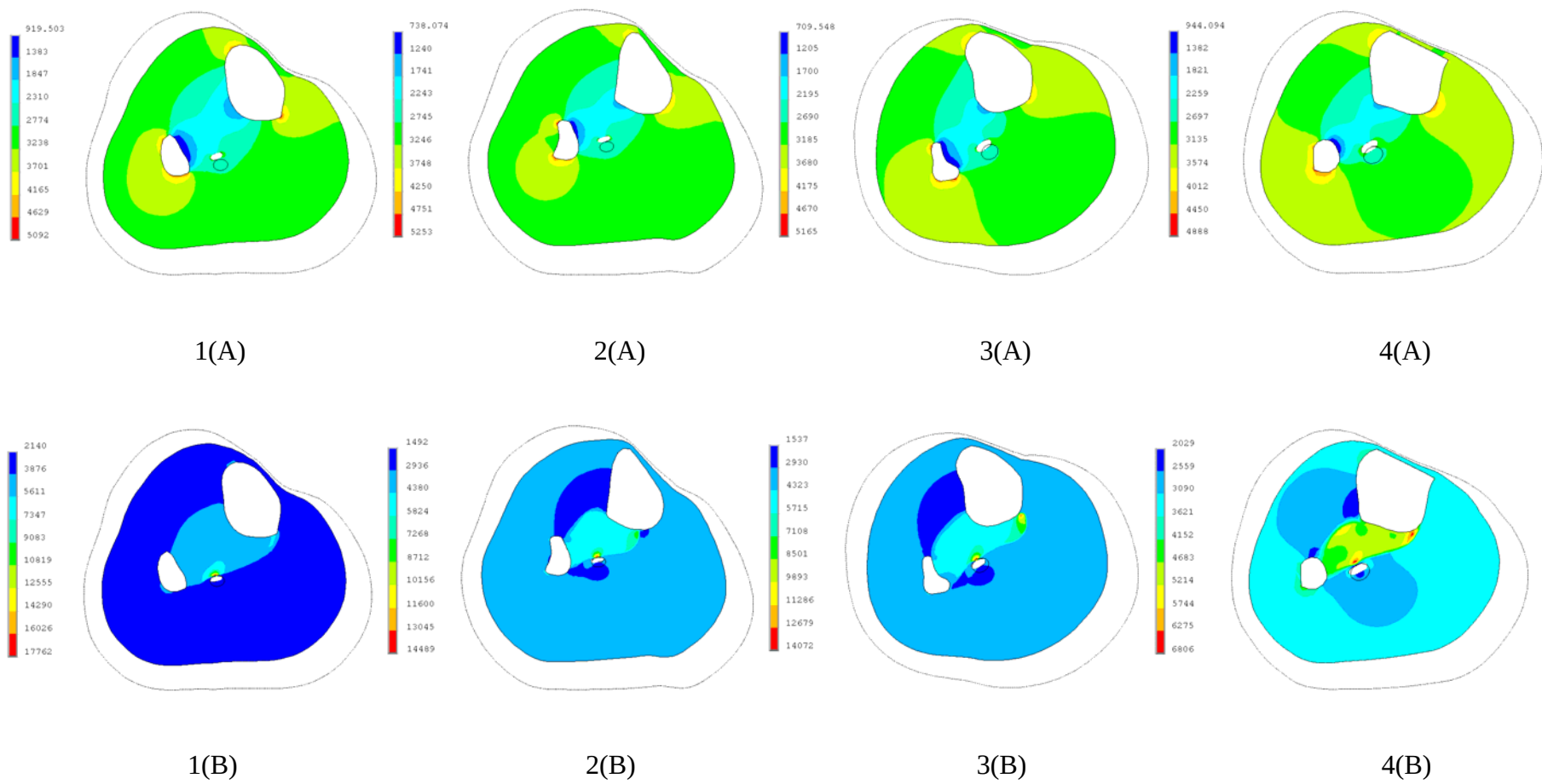


Figure 3.10 Hydrostatic pressure distribution in the transverse section of model A (A) and model B (B): 1-Subject 1, 2-Subject 2, 3-Subject 3, 4-Subject 4, undeformed calf boundary (black dashed line).

Although simulated MPV deformation under external compression showed a good agreement with the corresponding MR measurement, the deformations of the muscle compartments calculated by the FEM were much larger than the measured results. The calf cross-sectional area reductions predicted by model A and model B were $25.73 \pm 5.31\%$ and $26.91 \pm 4.88\%$, respectively, while the observed area reduction from MR images was only $3.25 \pm 1.01\%$. Although the area reduction of the calf transverse section indicated a certain degree of out of plane deformations of the muscles, the plane stress condition clearly overestimated these deformations. In practice, deformation occurs in three dimensions hence deformation in any single plane will be related to the deformation of the calf as a whole. The out of plane deformation of any cross section would be limited by its upper and lower adjacent tissues. Another reason responsible for the discrepancy was the elevated pressure load. The external compression applied to the FEM was 40 mmHg, which was higher than that specified by the manufacturer (18 mm Hg). However, the simulation still underestimated the degree of collapse of the deep veins as compared to that measured from the MR images.

Due to the observed resistance of the calf soft tissues to deformations caused by external compression, a finite element model with the plane strain boundary condition for all components was further investigated. The simulated deformation is shown in Figure 3.11 and the cross-sectional area reductions of the calf and MPV are shown in Table 3.4. The simulated area reduction of the calf is closer to the measured results, but the area reduction of the deep vein is much smaller. Although the agreement between the measured and simulated results could be improved by increasing the pressure load (>120 mmHg), it was very unlikely that compression stocking was able to produce such magnitude of external compression. All the simulation results seemed to suggest that in reality the calf soft tissues are more efficient in load transmission than that predicted by the FEM employed here, which led to the conclusion that the assumption of linear material properties for calf muscles was insufficient. Therefore, non-linear material models that can provide higher magnitude of hydrostatic pressure, such as the hyperelastic model, should be considered.

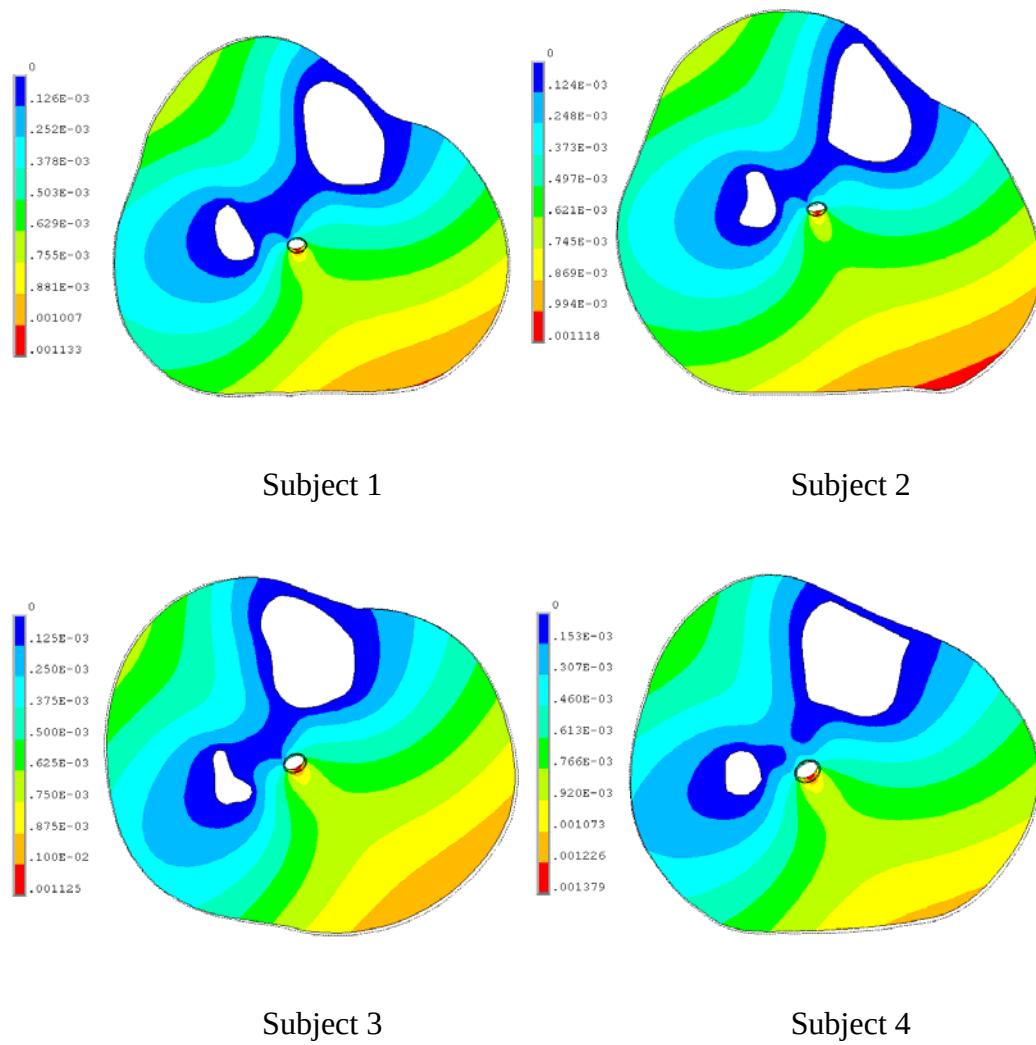


Figure 3.11 Simulated deformations of calf with the plane strain condition for all components.

Table 3.4 Simulated cross-sectional area reductions of the calf and MPV under plane strain condition

	Subject 1	Subject 2	Subject 3	Subject 4
Calf	1.39%	1.77%	1.89%	1.75%
MPV	42.35%	43.30%	38.40%	38.40%

3.5 Summary

Comparison of the MR images before and after external compression showed that the cross-sectional area of the calf under external compression was clearly reduced. Muscles have been demonstrated to be nearly incompressible, but due to the displacement of blood and interstitial fluids and out of plane deformation of the muscles, the two-dimensional transverse section investigated showed a certain degree of compressibility. Analysis of the MR images also indicated that among the four muscles components of calf, the deep posterior compartment (DPC) had smaller deformation than the other three muscle compartments.

The simulation results showed that the application of different strain-stress boundary conditions to different compartments according to their observed behaviour rather than treating the calf muscles homogenously produced the best overall agreement with the imaging results in terms of the displacement and area reduction of the deep veins. The application of plane stress condition to muscle compartments overestimated the out of plane deformation and led to a larger area reduction of the calf cross-section than that recorded by MRI, whereas the use of plane strain condition alone significantly underestimated the deformation of deep veins.

The employment of a linear elastic representation of calf tissues led to a contradiction between the deformations of soft tissues and deep veins. The comparison between the simulated and measured results suggested that the *in vivo* material behaviour of the soft tissue was more efficient at load transmission than that described by the linear elastic martial model.

Chapter 4

Finite Element Analysis: Evaluation of Hyperelastic Model with Displacement Boundary Condition

4.1 Introduction

Results presented in the preceding chapter have demonstrated clearly that linear elastic approximation of calf tissues is inadequate to simulate the load transmission and deformation of the soft tissues of lower limb under external compression. In a number of previous studies [154, 155], the mechanical behaviour of skeletal muscle was expressed using hyperelastic models, which could generate higher hydrostatic pressure than the linear elastic model under a given load. Hence, the focus of this chapter is to explore the use of a hyperelastic model for the calf muscles. The objective is to develop a suitable FEA model that is capable of predicting the deformations induced in the veins by application of external compression.

Similar to the linear elastic model adopted previously, the FEA model is restricted to two-dimensional transverse sections of the calf. A displacement boundary condition is employed, which is extracted from the corresponding deformed (with stocking) and undeformed (without stocking) MR image sets by using a non-rigid image registration procedure. All the deformations of the tissues are assumed to be in plane and, therefore, a plane strain boundary condition is applied.

The two bones of the calf, tibia and fibula, are assumed to be rigid in the FEA model. The entire soft tissue compartment is represented as a homogenous continuum with hyperelastic properties. Although anatomical information reveals that the skeletal muscle is enclosed within a lamina of tough connective tissue known as the muscular fascia and most of the deep veins lie between the connective tissues, which undoubtedly play an important role in the structural response of veins, little is known about the connective tissues' behaviour under compression and it is not clear how best

to model it. In light of this, it was decided not to include fascia in the model. This simplification will inevitably lead to errors, but without adequate model of the adipose tissue and connective tissue in the lower limb, it is believed that a simplified model would be better suited for the problem at hand than a more complicated model without reliable data.

4.2 Theory

4.2.1 Non-Rigid Image Registration

Medical images are commonly used in medical research and clinical practice, such as for diagnosis, treatment planning or monitoring disease progression. Image registration is a key enabling technology in medical image analysis, and can be used to determine the correspondence of features between images collected at different times, and often with different imaging modalities. Image registration is generally classified into types, ‘rigid’, where correspondence of images can be achieved by simple rotation and translation, and ‘non-rigid’, where due to image acquisition or biological differences, establishment of correspondence between structures in two images requires localized stretching of the images.

If $I_1 = f(x, y)$ and $I_2 = g(x', y')$ are the image intensity functions of a pair of images to be registered, which are defined in the image domains D_1 and D_2 , respectively, then the image registration problem is to find a nonlinear transformation that maps D_1 into D_2 .

The basic components of a registration procedure include the similarity measure, the transformation model and the optimization of the parameters of the transformation model. Image registration can be carried out by intensity approaches or geometric approaches. The intensity approaches make mathematical or statistical use of the intensity map to develop criteria to measure the intensity similarity between the images, and the transformation is adjusted until the similarity measure is maximized. The geometric approaches operate on identifiable anatomical features, which include surfaces, curves and point landmarks that can be matched with their counterparts in the other image. The transformation functions by mapping these corresponding features from one image to the other.

The rigid transformation model can be described compactly by 6 parameters (3 translations and 3 rotations), and can also be extended to an affine transformation with

6 additional parameters (3 stretches, 3 shears). Non-rigid transformations are more complex. The splines-based registration algorithm, using corresponding points in the source and target images and a spline function to define correspondences away from these points, has widespread applications in non-rigid transformations [156].

In the elastic model, another popular class of transformation models, the governing equations of elasticity are applied to the source image, and the image similarity measure is treated as the force that deforms the source image. Using this method, reliable physically realistic displacement fields can be generated and applied to discrete mechanical systems [156, 157].

This approach is effective in image based biomechanical modelling, where the forces acting on the boundary of a region of interest are not always known and it is not always desirable (or possible) to model the surrounding features. Boundary conditions can be derived from corresponding deformed/undeformed curves or surfaces which have been measured from the source and target images. In order to map the features in the source ($U(x, y)$) and target images ($V(r, t)$), the corresponding function is required:

$$\mathbf{U} = f(\mathbf{V}) \tag{4.1}$$

Derivation of the correspondence function can be performed by one of two general approaches (or a combination of both). The statistical approach, based on points generated using statistical shape information, is potentially more objective but does not guarantee a physically realistic result. This is because the order of the points may change during mapping. The other approach uses landmark points from the image to fit an approximate function which allows interpolation of the intermediate points. The derivation of a continuous function by enforcing correspondence at selected landmark points is potentially more subjective, particularly when there is a degree of manual input, but guarantees a smooth distribution in the calculated displacements. This is a clear advantage when applying the result as the boundary condition to an FE model.

4.2.2 Hyperelastic Materials

4.2.2.1 Overview

There are many materials, such as rubber, whose stress-strain relationship can be defined as non-linearly elastic and generally independent of strain rate. These kinds of materials are said to be hyperelastic. They are characterized by the existence of a strain energy function that is a potential for the stress.

$$\mathbf{S} = 2 \frac{\partial W(\mathbf{C})}{\partial \mathbf{C}} = \frac{\partial w(\mathbf{E})}{\partial \mathbf{E}} \quad (4.2)$$

where $\mathbf{S}$ is the Second Piola-Kirchhoff stress tensor, W is the stored energy potential, $\mathbf{C}$ is the right Cauchy-Green deformation tensor, w is hyperelastic potential and $\mathbf{E}$ is the Green strain tensor.

The existence of a strain energy function eliminates the effects of the deformation path on the work done on a hyperelastic material. The strain energy per unit reference volume in going from deformation state $\mathbf{C}_1$ to $\mathbf{C}_2$ is considered in order to illustrate the independence of work on the deformation path. Because the Second Piola-Kirchhoff stress tensor $\mathbf{S}$ and the Green strain $\mathbf{E} = (\mathbf{C} - \mathbf{I}) / 2$ are work conjugates, we have

$$\int_{\mathbf{E}_1}^{\mathbf{E}_2} \mathbf{S} : d\mathbf{E} = w(\mathbf{E}_2) - w(\mathbf{E}_1) \quad \text{or} \quad \frac{1}{2} \int_{\mathbf{C}_1}^{\mathbf{C}_2} \mathbf{S} : d\mathbf{C} = W(\mathbf{C}_2) - W(\mathbf{C}_1) \quad (4.3)$$

where $\mathbf{I}$ is the unit vector. The above equation indicates that the energy stored in the material depends only on the initial and final states of deformation and is independent of the deformation path.

The nominal stress tensor $\mathbf{P}$ can be expressed as a derivative of the potential. Because $\mathbf{P}$ is conjugate in power to the time derivative of the deformation gradient, $\dot{\mathbf{F}}^T$, $\mathbf{P}$ is given in terms of the potential by

$$\mathbf{P} = \frac{\partial w}{\partial \mathbf{F}^T} = \frac{\partial W}{\partial \mathbf{C}} : \frac{\partial \mathbf{C}}{\partial \mathbf{F}^T} = \mathbf{S} \cdot \mathbf{F}^T \quad (4.4)$$

As the deformation gradient tensor $\mathbf{F}$ is not symmetrical, the nine components of the nominal stress tensor $\mathbf{P}$ are not symmetrical.

4.2.2.2 Mooney-Rivlin Model

Rivlin and Saunders [158] developed a hyperelastic constitutive model for large deformations of rubber. The model is incompressible and initially isotropic. The stored energy (W) can be written as a function of the principal invariants (I_1, I_2, I_3) of the right Cauchy-Green deformation tensor,

$$W = W(I_1, I_2, I_3) \quad (4.5)$$

Where

$$I_1 = \lambda_1 + \lambda_2 + \lambda_3 \quad (4.6)$$

$$I_2 = \lambda_1\lambda_2 + \lambda_2\lambda_3 + \lambda_3\lambda_1 \quad (4.7)$$

$$I_3 = \lambda_1\lambda_2\lambda_3 \quad (4.8)$$

$\lambda_1, \lambda_2, \lambda_3$ are the three real eigenvalues of a second-order tensor. For an incompressible material, $I_3 = 1$, the potential can be expressed as a series expansion in I_1 and I_2 :

$$W = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \overline{c_{ij}} (I_1 - 3)^i (I_2 - 3)^j \quad (4.9)$$

where $\overline{c_{ij}}$ are constants. A simple form of this equation was derived by fitting to experimental data on rubber [159, 160], and this is expressed as:

$$W = c_1(I_1 - 3) + c_2(I_2 - 3) \quad (4.10)$$

4.3 Materials and Methods

4.3.1 Development of Non-Rigid Registration Procedure

Four healthy male subjects (24–28 years old) without any history of venous disease were scanned following the same protocol described in the previous chapter. Manual segmentation was performed to generate the corresponding deformed (with stocking) and undeformed (without stocking) geometry from the MR images. By mapping the deformed boundary curve onto the undeformed boundary curve, displacement boundary conditions were generated by calculating displacements along the boundary as a function of arc length. Corresponding points in the deformed and undeformed geometry were manually selected as landmarks. In this study, the criterion for the selection of landmarks was based on the assumption that there is no relative motion between superficial veins and skin. The procedure, shown in Figure 4.1 and originally developed by Downie [161], was adapted to suit the present study. A summary of the procedure is given below.

First, by matching stable anatomical features such as the bifurcation of the popliteal artery, a rigid registration in the z (longitudinal) direction was performed and a pair of corresponding, undeformed and deformed two-dimensional MR images was selected. Then, manual segmentation was carried out by selecting a series of points along the undeformed and deformed boundaries of the lower leg. By fitting a smooth cubic spline to the points, two curves representing the undeformed and deformed geometry were generated. The curves were parameterised as functions of U (undeformed boundary) and V (deformed boundary), with arc length chosen as the definition of the parametric variables. In order to establish the correspondence points of the deformed curves, the points on the boundaries closest to the superficial vein were chosen as landmarks under the assumption that there was no relative movement between the boundary of lower leg and superficial veins. Because of the inherent errors of the manual segmentation procedure, the landmarks were inevitably close to, but not actually on the segmented curves. They were therefore individually mapped onto the curves by translation onto the closest curve point. The other components of

the lower leg, including bones and veins, were generated using the same segmentation method.

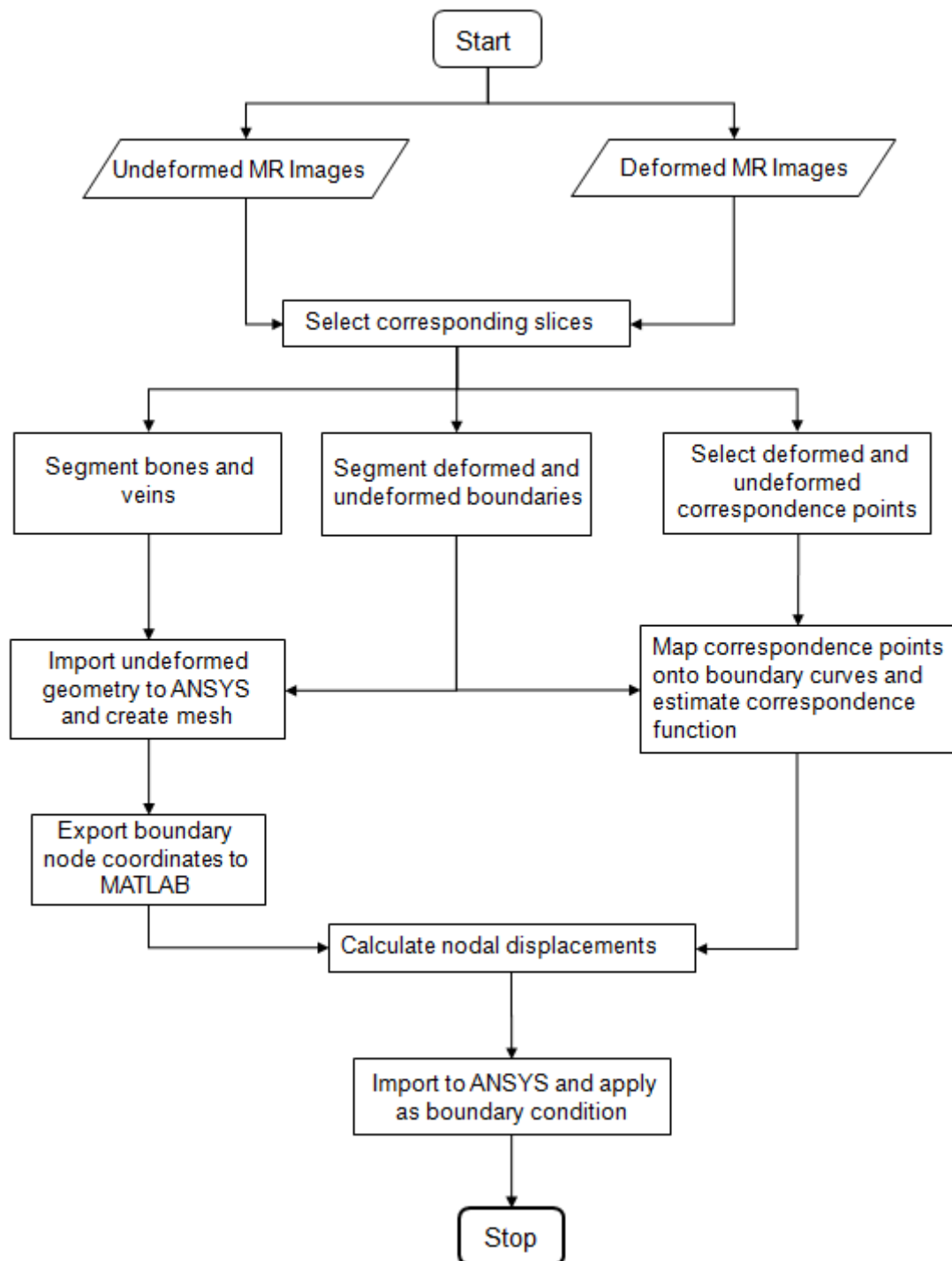


Figure 4.1 Flow of information in non-rigid registration algorithm

The relationship between the corresponding points of the undeformed and deformed boundaries were approximated with respect to $\mathbf{U}$ and $\mathbf{V}$, and the displacement along

the boundary were calculated. By importing the undeformed geometry to ANSYS 11.0 and performing meshing, a file containing coordinates of the boundary nodes was generated. Using the file and the boundary displacements function, the nodal displacements of the boundary nodes were calculated and exported back to ANSYS 11.0 to be applied as a model boundary condition.

In the FE model, tibia was assumed to be rigid, which meant that the boundary bordering this bone should remain fixed after application of the stocking, and zero displacement was applied to all nodes lying on its boundary. In some of the images, rigid body motion of the fibula (relative to the tibia) was observed. However, the displacements were small and the boundary was difficult to segment due to the surrounding connective tissue. Therefore, in the FE model, zero displacement boundary conditions were also employed along the boundary of fibula which was segmented from the undeformed image. An example of the non-rigid registration is shown in Figure 4.2.

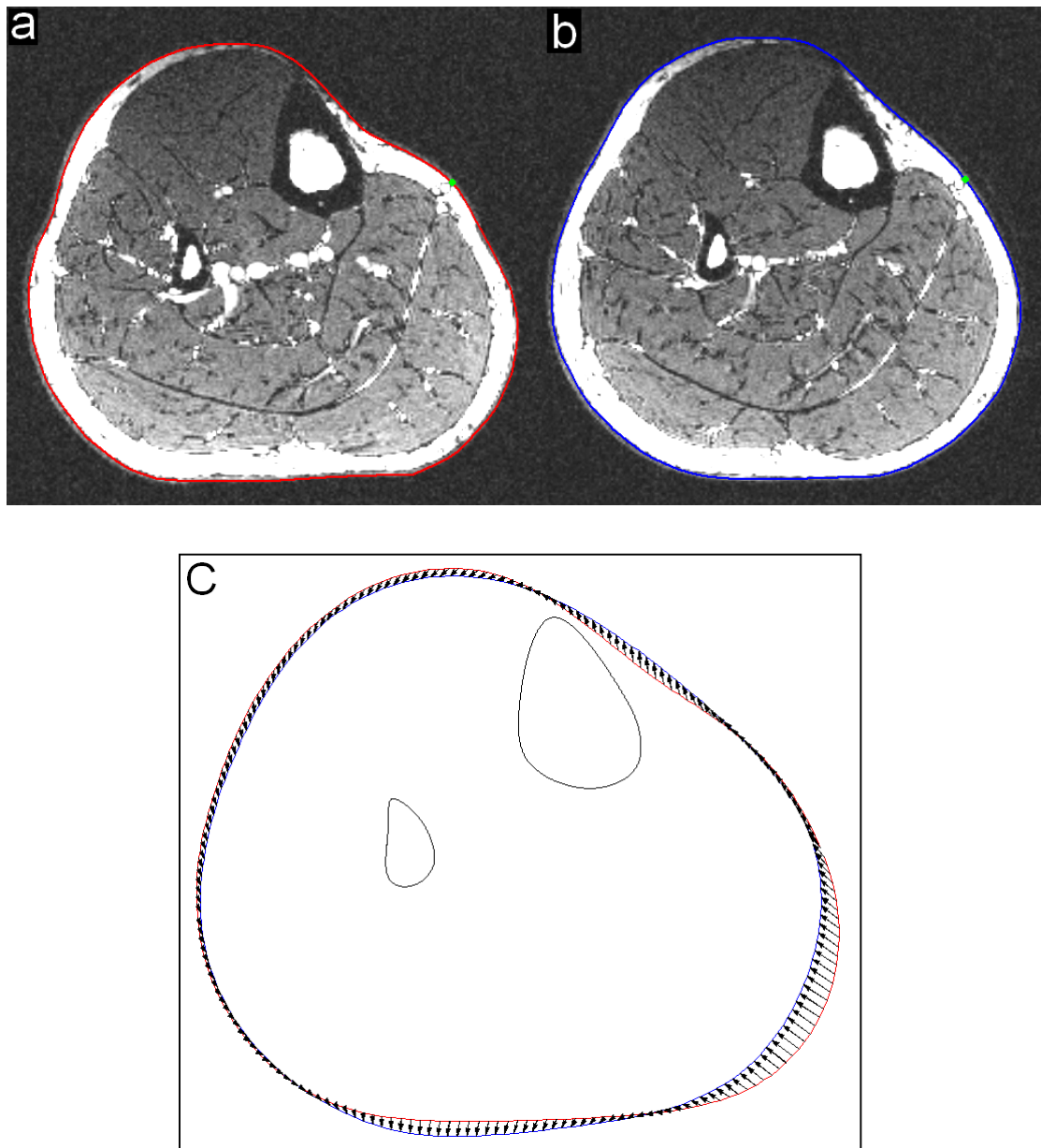


Figure 4.2 Illustration of non-rigid registration procedure: a) and b) show the undeformed and deformed images respectively, with the measured undeformed boundary (red line) and deformed boundary (blue line) along with selected landmark points (green dots). The point to point correspondence resulting from the algorithm is shown in c). Zero displacement is imposed to tibia and fibula (black line).

4.3.2 FE Model Strategy

A 3D model would provide more detailed information of the mechanical behaviour of calf. However, because the spatial resolution of MR images did not support a clear identification of the calf boundary, the extraction of the displacement boundary

condition from the images introduced a certain level of misregistration errors, which made it difficult to apply the non-rigid registration procedure to a complicated 3D structure. In addition, the capability of 2D FE model to represent 3D calf structure has been demonstrated in previous studies [14, 15]. It was decided to use a simpler model and restricted the FE analysis to a 2D transverse plane of the calf. The structure of the leg was assumed to comprise 3 parts: soft tissues, veins, and bones. The undeformed geometry was meshed using ‘Plane183’ elements (Ansys 11.0). Considering the relatively uniform compression distribution generated by the compression stocking [162], the plane strain assumption was applied to the model. Because of the irregular nature of the geometry, a free meshing algorithm was employed [163]. Comparison of the undeformed and deformed geometry showed a clear reduction in the calf volume under compression, hence large strains and non-linear material behaviour assumptions were applied. The Ansys 11.0 (Ansys Inc., USA) was employed to obtain the numerical solutions.

In the FE model, it was assumed that all muscle fibres were normal to the transverse sections where MR images were acquired so that the muscle could be treated as isotropic. As a first approximation, the soft tissues were lumped together and treated as a homogenous material described by a nonlinear hyperelastic constitutive relation [164]. The three-parameter Mooney-Rivlin model [165] was adopted, which is given by:

$$W = c_{10}(\bar{I}_1 - 3) + c_{01}(\bar{I}_2 - 3) + c_{11}(\bar{I}_1 - 3)(\bar{I}_2 - 3) + (J - 1)^2/d \quad (4.11)$$

where c_{10}, c_{01}, c_{11} are material constants, $\bar{I}_1, \bar{I}_2$ are principal invariants of the Cauchy Green tensor, J is ratio of the deformed elastic volume over the reference (undeformed) volume of materials, d is material incompressibility parameter, and $K = 2/d$ is the initial bulk modulus. The model parameters were determined by using a material curve fitting algorithm available within ANSYS 11.0, from empirical data kindly supplied by Dr. van Looke of the Centre for Bioengineering, Trinity College Dublin [35]. The evaluated values for c_{10}, c_{01}, c_{11} are 13.1 kPa, -9.61 kPa and 8.86 kPa respectively.

The empirical data were numerically recreated to check the performance of the curve fitting algorithm. Comparison of the numerical and experimental results is shown in Figure 4.3. Under 18% engineering strains (the ratio of total deformation to the initial dimension of the material body in which the forces are being applied), a good agreement was obtained, and the difference in Cauchy stress between the numerical and experimental results was less than 10 Pa (0.075 mmHg) for a given strain. The root mean square difference between the results for all the experimental data points (up to 30% strain) was 94.54 Pa (0.71 mmHg).

Because the calculated boundary displacements indicated a small reduction in calf volume, a value for the bulk modulus must be specified to reflect the compressibility of the soft tissues in the calf. Although skeletal muscles are very close to incompressible, the presence of blood capillaries and interstitial fluids in the lumped soft tissues as well as their displacement under compression must be accounted for. In this study, for each subject, the relationship between the effective bulk modulus and simulated area reduction of the deep veins was examined first. By fitting the measured area reduction into this relationship, the corresponding bulk modulus for each subject was then obtained. This subject-specific bulk modulus was employed in the subsequent FE model for the prediction of deep vein deformation.

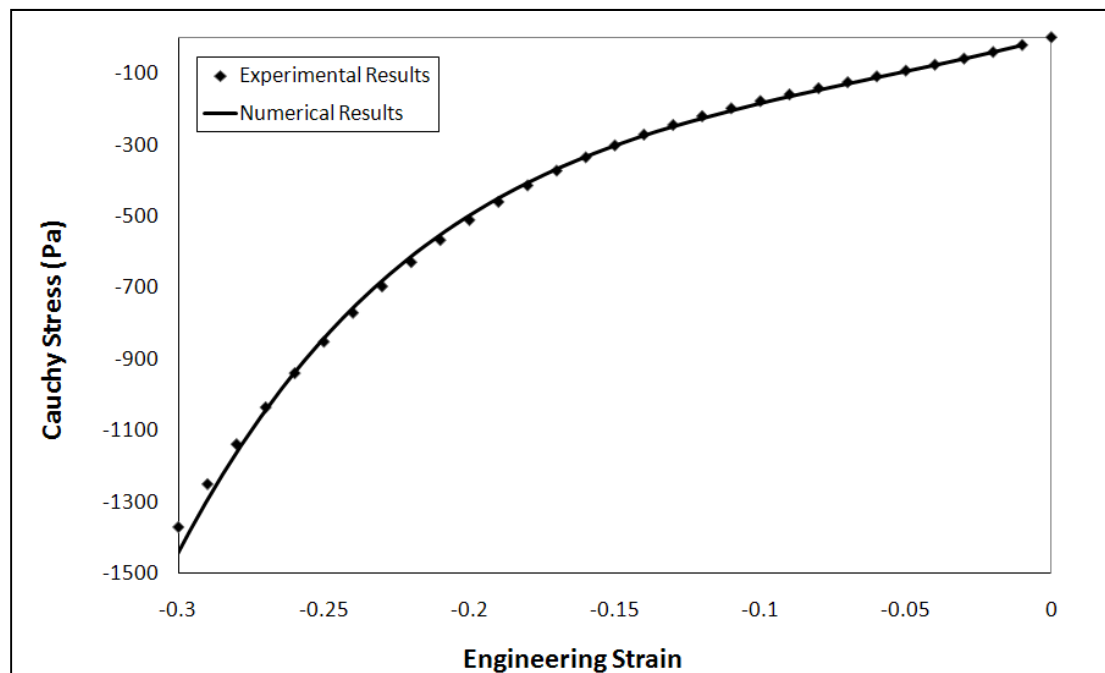


Figure 4.3 Comparison of experimental and numerical results for uniaxial compression of porcine skeletal muscle at the cross-fibre direction.

4.4 Results

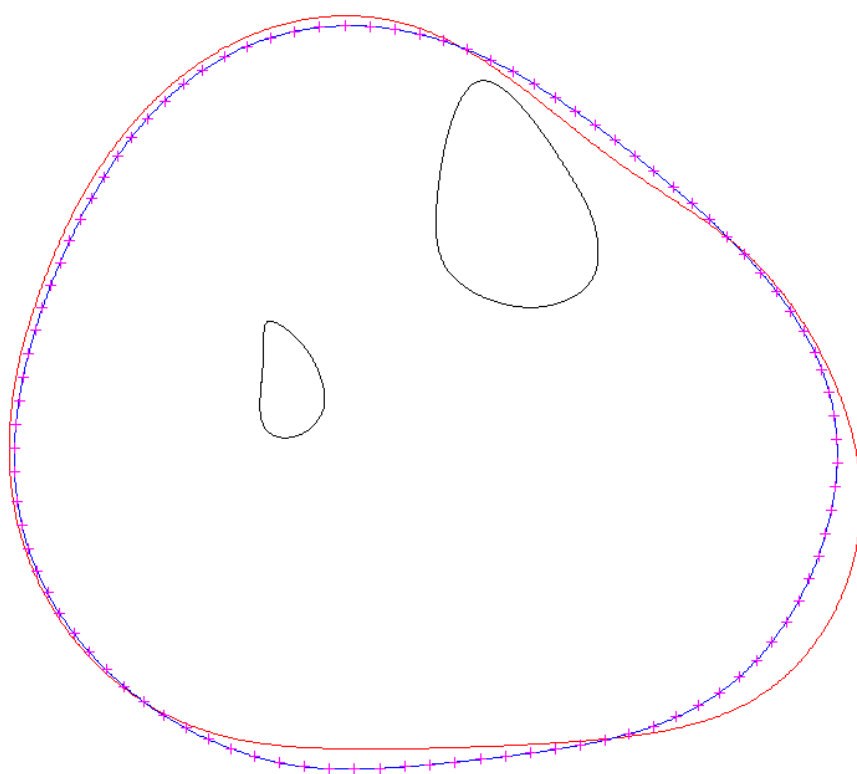
4.4.1 Analysis of the Non-rigid Registration Method

In order to assess the ability of the non-rigid registration method to recreate the deformations observed from MRI images, measured and simulated boundary deformations were compared at one randomly selected section for each subject (Figure 4.4). The results show that the simulated and measured geometries appear to coincide closely for all four subjects. In quantitative terms (Table 4.1), the discrepancies between the measured and simulated compressed area (CA) (normalised by the measured uncompressed area) at the selected sections, are less than 0.53%. For all the subjects examined, the measured compressed area is slightly larger than the simulated one. Considering that the measured geometry boundary is composed of 1000 points, while the simulated one consists of 400 points, it is very likely that most of the discrepancy is caused by numerical errors.

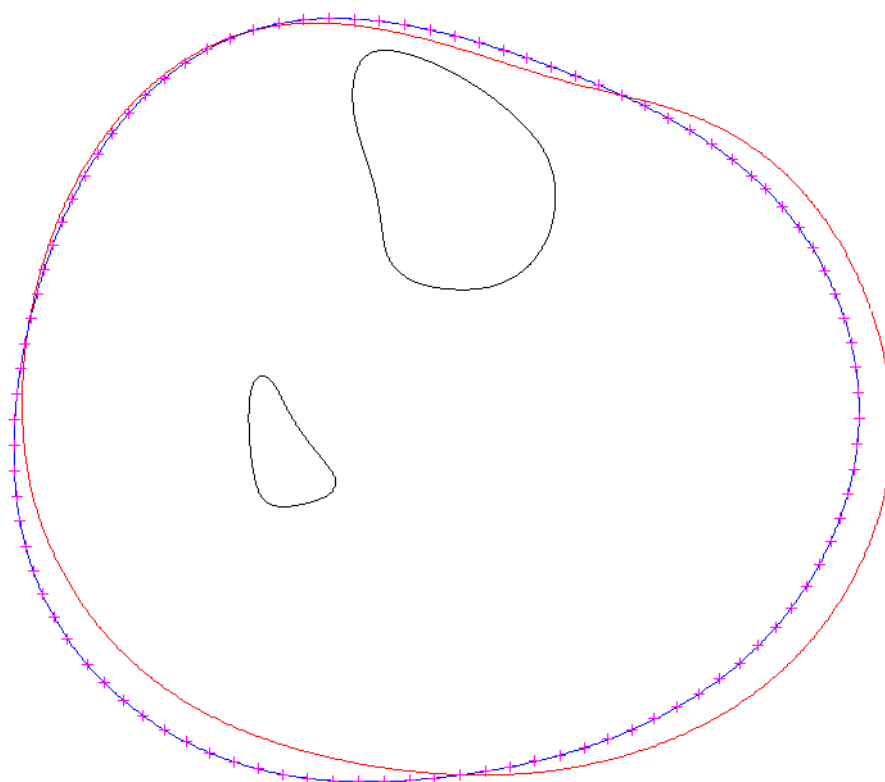
Comparison of simulated and measured deformations shows that the non-rigid registration method employed in this study is capable of generating displacement boundary conditions that are in good agreement with those measured from MRI. The displacements calculated by this method are employed as reliable boundary conditions in this study.

Table 4.1 Comparison of simulated and measured cross-sectional area (CA) of the selected sections in the lower leg. Both areas are normalized by the corresponding undeformed cross-sectional area.

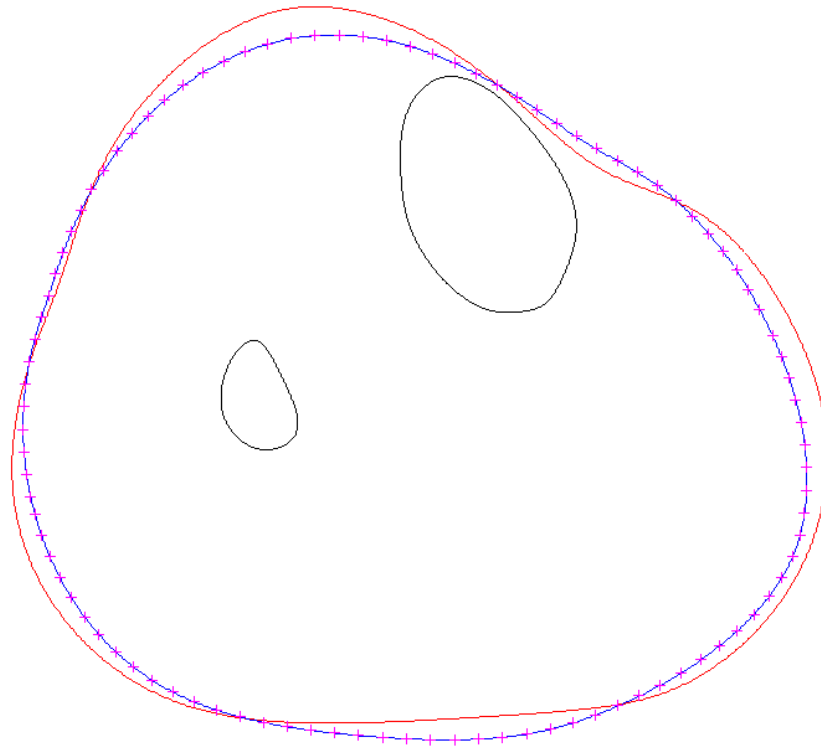
	Subject 1	Subject 2	Subject 3	Subject 4
Simulated CA	0.9752	0.9780	0.9587	0.9741
Measured CA	0.9802	0.9830	0.9636	0.9793
Discrepancy	0.00509	0.00512	0.00509	0.00529



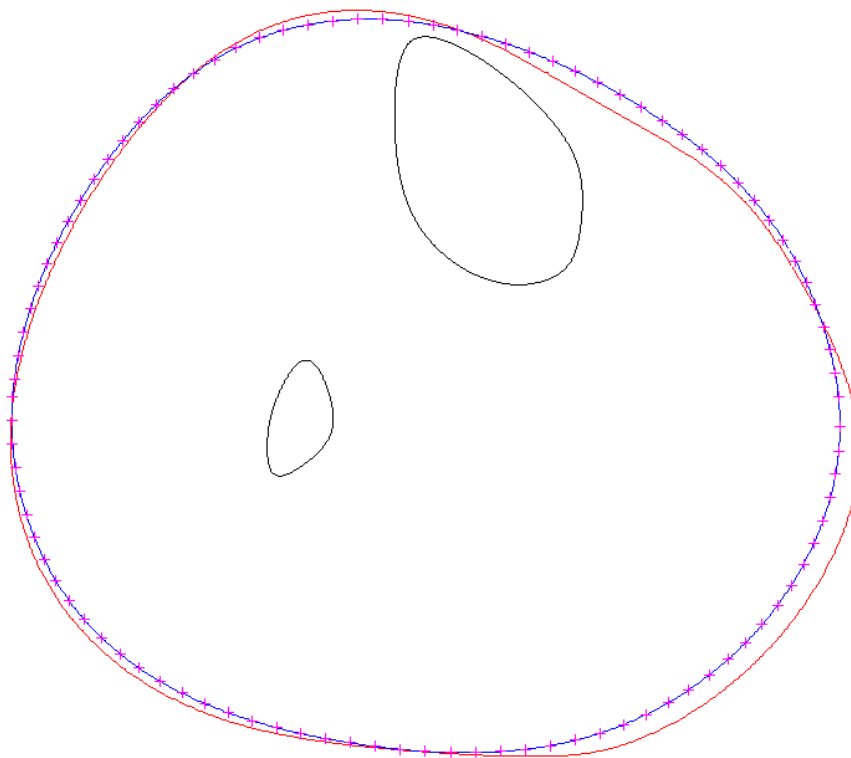
Subject 1



Subject 2



Subject 3



Subject 4

Figure 4.4 Comparison of simulated and measured deformations. Undeformed geometry is shown in red line, and MR measured deformed geometry is shown in blue line. Simulated deformed geometry is shown in magenta crosses. The bones, fibula and tibia, are shown in black.

4.4.2 Evaluation of Bulk Modulus

For each subject, a transverse section with good visibility of deep veins having distinct boundaries was selected. Employing the non-rigid registration method, the boundary displacements were generated and applied to the FE model as a boundary condition. The effect of bulk modulus on area reduction of deep veins was studied. An example of the simulated displacement distribution is shown in Figure 4.5. The calculated relationship between the bulk modulus and vessel deformation (Figure 4.6) suggested that an increase in the effective bulk modulus led to larger area reduction of the vein, implying that the vessels are more sensitive to the deformation of surrounding tissues with lower compressibility.

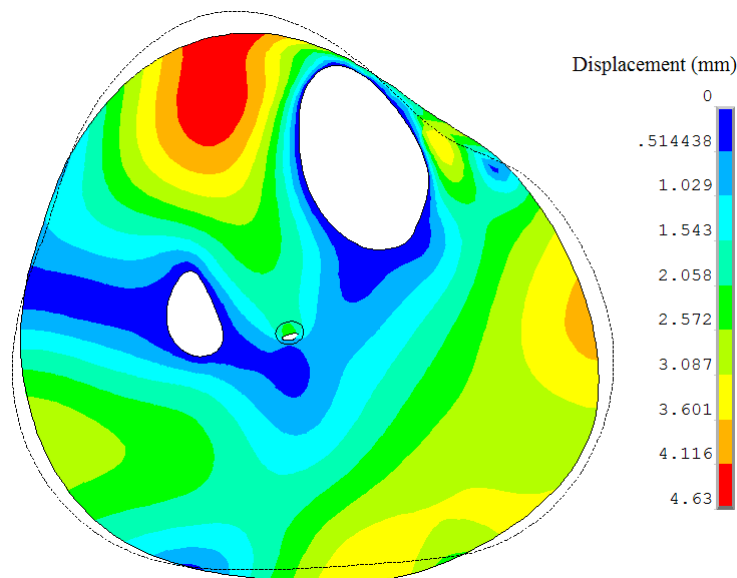
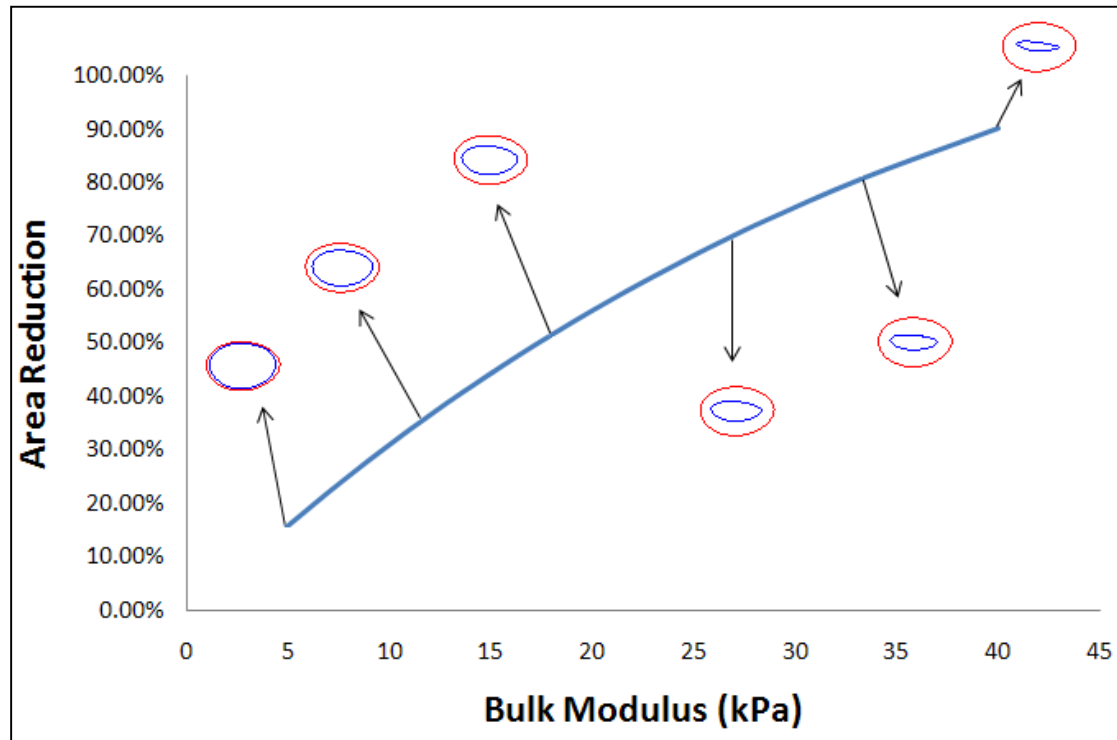


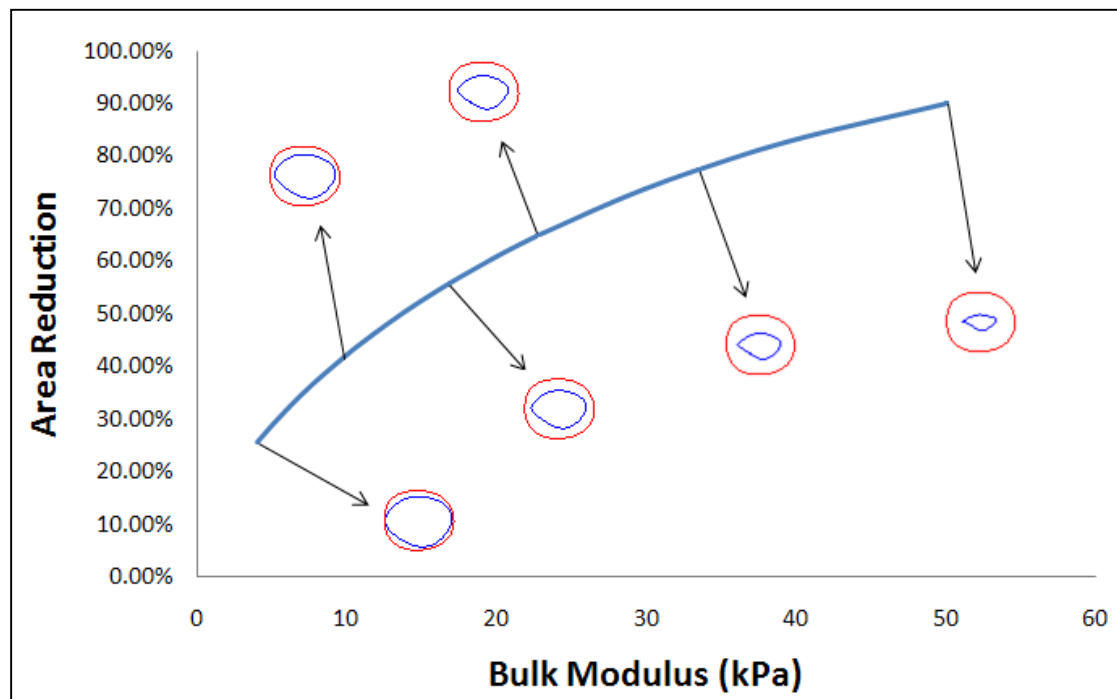
Figure 4.5 Displacement distribution generated by the FE model of subject 3. The bulk modulus of calf tissue is 28 KPa. The undeformed calf outline is shown in black dashed line.

The evaluated bulk moduli show considerable variability among subjects (Table 4.2), which is largely attributed to the physical differences between the subjects. Although the subjects are within the same age group (24-28 years old), for many other reasons, such as exercise, physical build (or body mass index), and architecture of the lower leg, it is reasonable to expect that the stiffness of the muscle and lumped compressibility of the soft tissues are different. Owing to the variability of the architecture of the lower limb, it is difficult to select a transverse section at the same

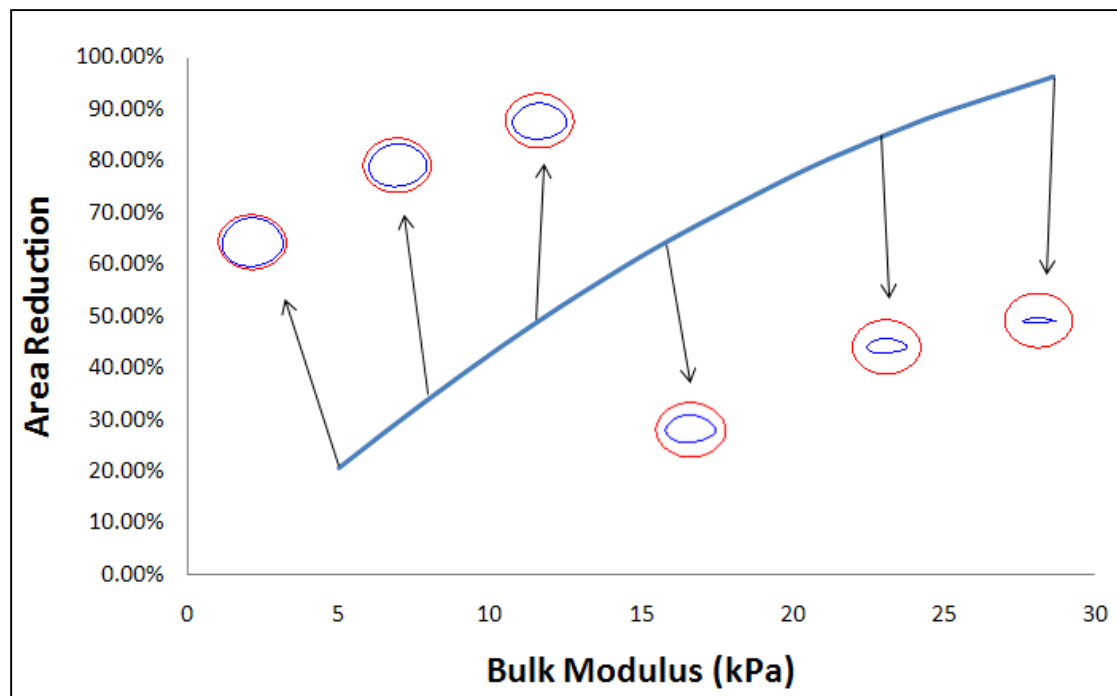
location for all four subjects, so the selection was mainly based on the visibility of the vascular system rather than location, which might also have contributed to the differences in the evaluated bulk moduli.



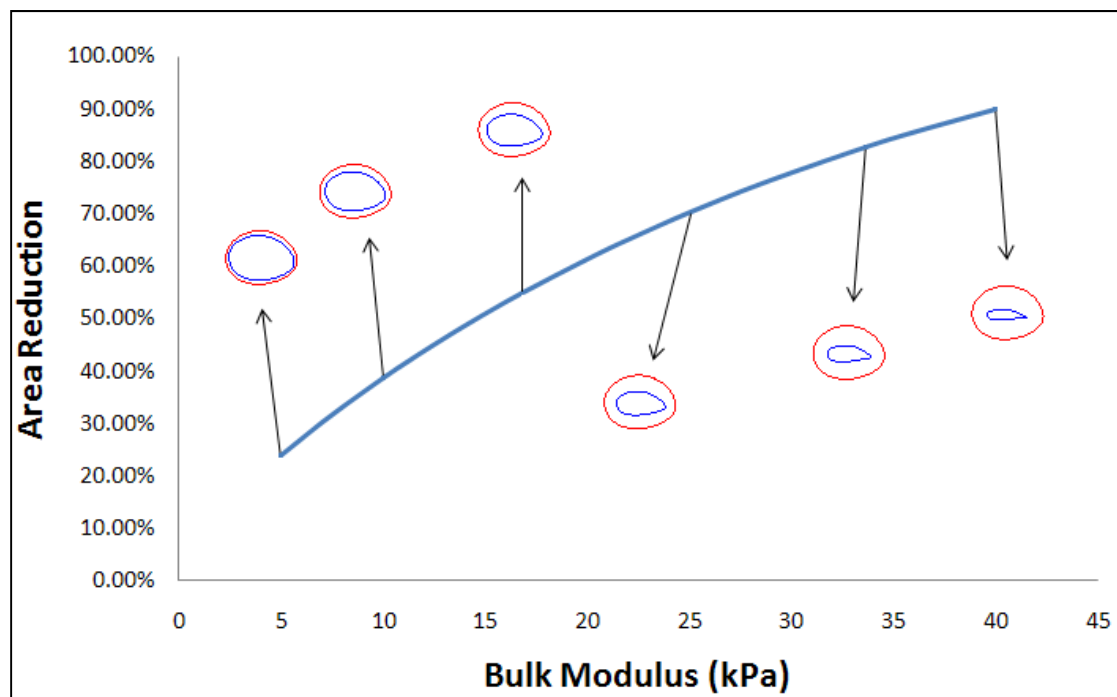
Subject 1



Subject 2



Subject 3



Subject 4

Figure 4.6 Relationship between effective bulk modulus and simulated area reduction of deep veins. The undeformed vein is shown in red, and the deformed vein is shown in blue.

Table 4.2 Evaluated bulk modulus at selection sections

	Subjects			
	1	2	3	4
Bulk Modulus (kPa)	28.45	22.69	22.93	35.41

4.4.3 Finite Element Analysis

Using the subject-specific effective bulk modulus determined, FE analyses were performed on four sections in each subject, which included the original section used to evaluate the effective bulk modulus as well as 2 mm, 6 mm and 10 mm from this section. The simulated area reductions of the 4 subjects were compared with the corresponding MR measurements as shown in Table 4.3. It can be seen that generally, a reasonable agreement was achieved between the simulation and measurement. Except for subject 1, the largest discrepancy between the simulated and measured area reductions was found at the 10 mm section. In subject 1, the simulated results were quite close to the measurements at all sections. An additional section in subject 1, which was 20 mm from the original section, was also examined. At this section, the measured area reduction was 46.4%, while the simulated result was 39.9%. Apparently, the agreement between the simulated and measured result was much poorer than at the other sections. The reason for this might be that the architecture and stiffness of the tissues are quite variable along the leg. Therefore, the bulk modulus evaluated at the original position might not be applicable at positions beyond a certain distance from the original section.

Table 4.3 Simulated (S) and measured (M) area reductions of the deep veins at different locations.

Distance from Section 1 (mm)	Subject 1		Subject 2		Subject 3		Subject 4	
	S (%)	M (%)	S (%)	M (%)	S (%)	M (%)	S (%)	M (%)
0	72.9	72.9	64.8	64.8	84.7	84.7	86.5	86.5
2	74.9	76.9	68.7	66.7	85.3	82.4	81.4	80.3
6	68.5	67.2	65.9	67.4	84.4	87.2	81.8	83.5
10	59.5	60.6	75.3	70.6	77.7	83.5	83.5	79.1

The simulated and measured deformed geometries of the veins are shown in Figure 4.7. Even though a good agreement was achieved between the simulated and measured area reduction, the deformed geometries showed notable differences. Apart from the effects of bulk modulus, the simplification of the tissues of lower leg may also contribute to the difference in the simulated deep vein deformation. The connective tissues play an important role in the structural response of deep veins to external compression. However, due to the lack of supporting data for fat and connective tissues, it is difficult to model their mechanical behaviour under compression. Therefore, the soft tissues in the lower leg were treated as a homogenous material, which undoubtedly contributed to the difference between the simulated and measured deformed geometries.

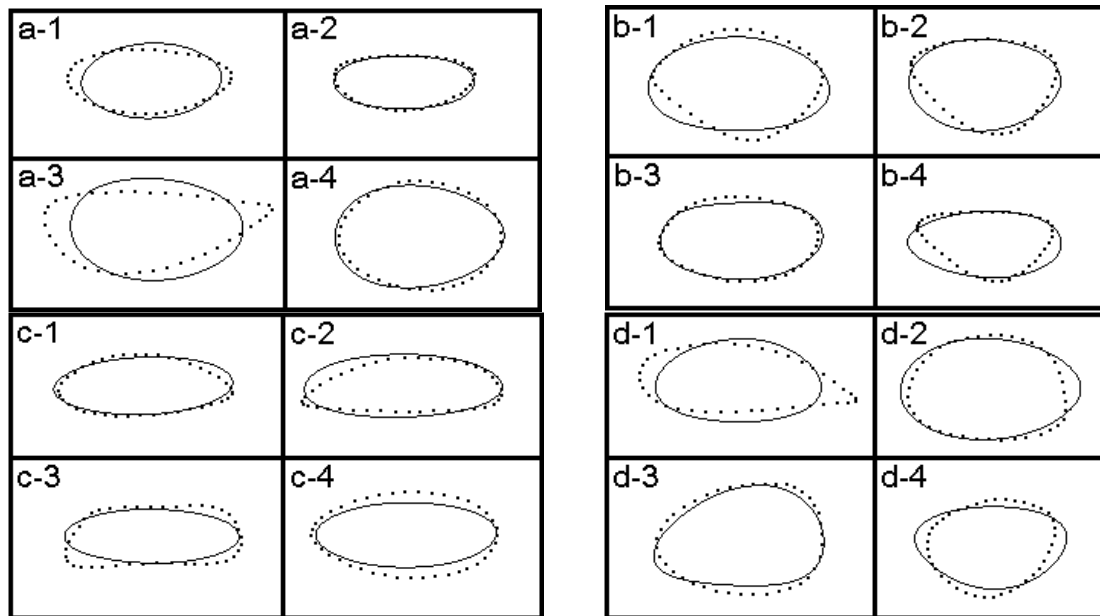


Figure 4.7 Comparison of measured (solid line) and simulated (dots) deformed geometries of veins at different distances from the original section. Here a, b, c, and d refer to subject 1, 2, 3 and 4, respectively, whereas the numbers 1-4 correspond to different sections at 0, 2, 6, and 10 mm from the original section.

The bulk modulus with which the FE model generated a perfect match with the measured results in terms of area reduction of deep veins was also evaluated at different sections (Table 4.4). Comparison of results in Table 4.3 and Table 4.4 showed a same trend at all the sections. When the simulated area reduction of deep veins was lower than the measured results, the evaluated bulk modulus at the section

was higher than that at the original section, and vice versa. This is consistent with the conclusion drawn in section 4.2 that when all the other conditions remained unchanged, the area reduction of deep veins increased with bulk modulus.

Table 4.4 Evaluated bulk moduli (KPa) at different sections

	Distance from Slice 1 (mm)			
	0	2	6	10
Subject1	28.45	29.55	27.76	28.95
Subject2	22.69	21.33	23.74	19.83
Subject3	22.93	21.74	24.40	24.33
Subject4	35.41	33.97	37.04	32.82

The discrepancy between the simulated and measured cross-sectional area of deformed veins was further evaluated using the following equation:

$$D = \frac{1}{n} \left(\sum_{i=1}^n |(a_i^s - a_i^m)/a_i^m| \right) \quad (4.12)$$

where D is the averaged discrepancy, n is the number of samples, a_i^s is the simulated deformed area of subject i , and a_i^m is the measured deformed area. This would allow a more detailed quantitative assessment of the discrepancy in addition to the information given in Table 4.3.

Average discrepancies evaluated using Eq. (4.12) were compared between different sections (Table 4.5) and subjects (Table 4.6) respectively. The results in Table 4.5 show that the averaged discrepancy between the simulated and measured cross-sectional area of deformed veins increased with the distance from the original section, so did the standard deviations. This indicates that not only is the agreement between the simulated and measured deformed vein areas better at sections closer to the original section, the ‘uncertainty’ of the results is also smaller, which is consistent with the conclusion drawn earlier that errors introduced by using the effective bulk modulus evaluated at a given section are likely to increase with the distance from this section owing to the variability of mechanical properties of lower leg along its length.

Comparison among the subjects showed that the best agreement between the simulated and measured cross-section area of deformed veins was achieved on subject 1, while subject 3 showed the worst agreement.

Table 4.5 Discrepancy between simulated and measured area reduction of veins based on distances

	Distance from Slice 1 (mm)		
	2	6	10
Max Discrepancy (%)	16.6	21.4	22.4
Min Discrepancy (%)	5.7	3.9	2.7
Averaged Discrepancy (%)	9.2	10.1	15.5
Standard Deviation (%)	4.5	7.0	8.2

Table 4.6 Discrepancy between simulated and measured area reduction of veins based on subject.

	Subject 1	Subject 2	Subject 3	Subject 4
Max Discrepancy (%)	8.4	15.9	22.4	21.1
Min Discrepancy (%)	2.7	4.6	16.6	5.7
Averaged Discrepancy (%)	3.8	6.6	15.1	9.3

4.5 Discussion

In this chapter, a 2D FE model was developed to predict the deformation of deep veins under external compression based on subject-specific data acquired non-invasively. Displacement boundary conditions generated by a non-rigid registration method were employed in the FE model. The ability of the non-rigid registration method to reproduce the calf outline deformations observed from MR images was assessed on a randomly selected transverse section for each subject. The simulated displacements of calf outline showed a good agreement with the MR measurements, demonstrating the reliability of displacement boundary conditions generated by the non-rigid registration procedure.

The relationship between cross-sectional area reduction of deep veins and the effective bulk modulus of their surrounding tissues was studied. The results showed that the effect of external compression on the deformation of deep veins was very sensitive to the compressibility of the surrounding tissues. For a given displacement of the calf outer boundary, lower compressibility of the surrounding tissues led to larger cross-sectional area reduction of deep veins. Employing this relationship, the effective bulk modulus corresponding to the measured area reduction of veins was obtained for each subject and employed by the hyperelastic FE model for further analyses.

The evaluated effective bulk modulus showed considerable variation among the subjects (23-35 kPa), owing to individual variability of the architecture and stiffness of calf muscles and different locations of the transverse section where the bulk modulus was evaluated. In a recent study [150], the calibrated material properties showed higher incompressibility of muscle with the bulk modulus ranging from 69 to 82 kPa, but no information about the location of the calf section was specified, making a direct comparison with the present study impossible. However, the factors responsible for the variability of the bulk modulus evaluated in this study was also very likely responsible for the difference between the material properties. Another factor might be responsible for this is the difference in the external pressure. In Avril et al.'s study, the observed area reduction of the transverse section was 4.5%, which was larger than that in this study ($2.3 \pm 1.2\%$) and likely caused by a higher pressure

distribution. Because the FEM was developed based on MR images with geometry information that was only available before and after compression, the larger volume reduction might lead to a higher overall incompressibility due to the non-linear mechanical behaviour of the tissues.

In Avril et al.'s study [150], hydrostatic pressure was chosen as the most appropriate stress measure since it related most closely to the transmural pressure that the vein walls would be subjected to. Compared to their results, the simulated hydrostatic pressure was lower in this study (Figure 4.8) and highly variable among subjects. This phenomenon was likely caused by several factors, including the material properties and load boundary condition. Unlike the study by Avril et al. [150], the material constants (c_{10} , c_{01} , c_{11}) of the three-parameter Mooney-Rivlin model were evaluated using experimental data obtained from porcine skeletal muscles. The lower level of stiffness of the calf tissues represented by the Mooney-Rivlin model was responsible for the smaller hydrostatic pressure in comparison to Avril et al.'s study [150].

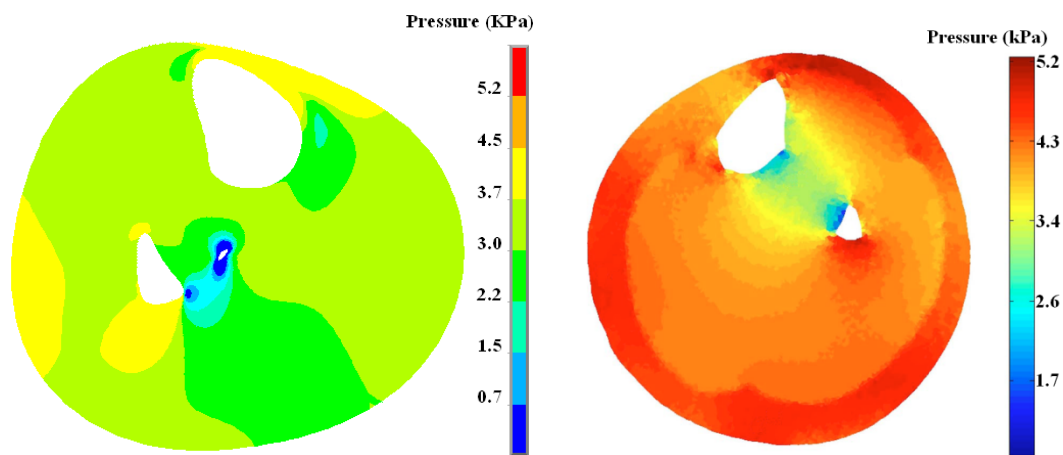


Figure 4.8 The simulated hydrostatic stress distribution: An example from subject 2 (left) was compared with the result of Avril et al.'s study [150] (right).

Due to a lack of supporting data regarding the pressure distribution generated by the compression stocking, boundary displacements were employed as the load condition instead of pressure employed by Avril et al. [150]. The application of pressure led to a hydrostatic pressure distribution with a clear trend that the region between the two bones showed low hydrostatic pressure, while the region close to the surface had high hydrostatic pressure. In this study, the boundary displacement had significant influence on the hydrostatic pressure distribution. For the purpose of optimizing the

design of compression stockings, the application of a pressure value specified by the manufacturer to the FEM would be more practical, but an independent method for the estimation of calf tissues properties is also required, which is the main purpose of this study.

FE analysis using subject-specific compressibility was performed on four transverse sections for each subject. The results showed that the model is able to predict the area reduction of deep veins with a good accuracy (Discrepancy = $8.7 \pm 6.4\%$), especially for sections close to the original location where the effective bulk modulus was evaluated. Beyond a certain distance, the discrepancies increased and became quite variable. The reason for this is that the architecture and stiffness of the calf tissues vary along the leg, making the effective bulk modulus evaluated at the original position less accurate at positions farther from the original section.

Although a good agreement was reached between the measured and simulated results in terms of deep vein area reduction after compression, the simulated and measured deformed geometries showed obvious differences in some cases. Both the manual segmentation method of the non-rigid registration procedure and high level of assumptions inherent in the model may make great contributions to the errors inherent in the model. Due to the relatively large volume fraction of muscle in the calf and lack of the mechanical properties of other tissues, a homogenous material model based on muscle was applied to represent all the soft tissues. However, some tissues, especially the connective tissues in the calf, undoubtedly play an important role in the structural response of deep veins to external compressions, and leaving out of these components would certainly cause errors. Improvement of the model is likely to benefit from better understanding of the mechanical properties of the different components of lower leg and increasing the accuracy of the segmentation. For the later, adding traceable marks to the boundaries would probably be a feasible solution.

4.6 Summary

A 2D FE model employing displacements boundary conditions generated by a non-rigid registration procedure was developed in this study. A good agreement between the simulated and measure results in terms of the calf boundary deformation was reached, which demonstrated the reliability of the non-rigid registration procedure.

Using the deformation of deep veins as a parameter, the compressibility of the calf tissues was evaluated at a transverse section. The estimated compressibility was then applied to other cross sections of the calf and the simulation results showed that the compressibility was reliable within a certain distance from the original transverse section. The variation of the calf anatomy architecture and muscle stiffness was very likely responsible for this phenomenon.

Ideally, a FE methodology using pressure profile provided by the manufacturer would be more suitable for the evaluation of design of compression devices, but the mechanical properties of calf tissues are highly variable among subjects and a method that can estimate the mechanical properties of the tissues is required. With further development in the MRI technique and better understanding of the mechanical behaviour of different calf tissues, such a model would be of great use for future design and optimisation of compression stockings.

Chapter 5

Computational Fluid Dynamics Analysis: the Effect of Compression on Blood Flow in the Deep Veins

5.1 Introduction

This chapter focuses on the effects of external compression on the deep venous flow in the calf. Under the assumption that fast flowing blood can flush away the thrombi, early design of compression devices aimed at generating high peak velocity. However, evidence to date has supported wall shear stress (WSS) as a factor that regulates blood vessel structure and influences the development of vascular pathology [10, 69, 70, 166]. DVT has a propensity to occur in areas where blood flow is slow and changes direction, such as venous valve pocket [61, 167, 168]. In these susceptible areas, the endothelial monolayer is exposed to very low WSS. Conversely, steady flow and moderate levels of WSS have been shown to be important in keeping the health of the vascular system [16, 169, 170]. The biological responses of endothelial cells to WSS suggest another aspect of the working mechanism of the compression devices.

Previous studies [7, 171-173] have been devoted to the exit velocity and volumetric flow rate in the femoral (thigh length compression) or popliteal (knee length compression) veins rather than the deep calf veins. Although analysis of downstream hemodynamic conditions can provide some useful information about the upstream, it may not capture the exact effects of calf compression stocking.

In this study, real-time blood flow data of the deep calf veins were acquired using phase contrast MR velocity mapping, together with anatomical images of the calf, with and without the presence of a compression stocking. Ten young healthy volunteers were involved and all scans were performed in a supine position.

Three-dimensional geometries of the deep veins were reconstructed from the MR images, and computational fluid dynamics (CFD) was employed to analyse blood flow in the deep vessels under subject-specific flow conditions based on MR flow measurement. To the best knowledge of the author, this is the first use of flow data directly measured within the reconstructed deep vessels in calf, in order to provide matching geometry and flow boundary conditions.

5.2 Theory

5.2.1 Computational Fluid Dynamics

5.2.1.1 Overview

Computational fluid dynamics (CFD) is a generalised term for the numerical methods and algorithms that are used to solve and analyze systems involving fluid flows. The fundamental physical principles governing the fluids behaviour can be expressed in terms of a series of partial differential equations. Using CFD, these equations can be replaced with discretized algebraic forms which can be solved at discrete points by computers. Instead of a closed-form analytical solution, CFD produces a collection of numbers as result.

The main purpose of CFD is to investigate fluids systems where physical experiments are either costly or impractical. The development of CFD is based on the rapid growth of high-speed digital computer, which makes the manipulation of thousands, even millions of numbers possible. Nowadays, the strongest force that drives the development of supercomputer is actually coming from the CFD community.

For all CFD approaches to field problems, there are three steps towards obtaining a solution:

- During pre-processing, the geometry (domain) of the problem is defined and then divided into discrete cells (the mesh). The governing equations expressing the physical model and the boundary conditions are also specified.
- The discretized forms of the governing equations are solved iteratively as a steady-state or transient at each nodal point on the mesh.
- Post-processing includes analysis and visualization of the resulting solution.

5.2.1.2 The Governing Equations

The physical aspects of any fluid flow are governed by the following three fundamental principles: (1) mass conservation; (2) momentum conservation; and (3) energy conservation. These fundamental principles can be expressed in terms of mathematical equations which are developed by considering an infinitesimally small control volume of the fluid domain. This small volume is either fixed in space or moving with flow and containing fixed mass. (Figure 5.1)

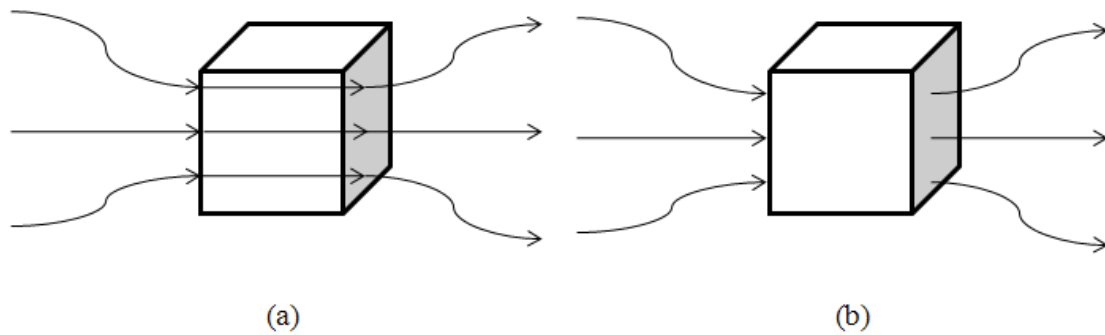


Figure 5.1 The different models of flow: (a) the control volume fixed in space; (b) the control volume of fixed mass moving with the flow.

Based on the control volume fixed in space, the governing equations can be expressed in the conservation form as follows:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{u}) = 0 \quad (5.1)$$

$$\frac{\partial (\rho u)}{\partial t} + \nabla \cdot (\rho u \mathbf{u}) = -\nabla p + \nabla \cdot (\mu \nabla \mathbf{u}) + S_m \quad (5.2)$$

$$\frac{\partial \rho T}{\partial t} + \nabla \cdot (\rho \mathbf{u} T) = \nabla \cdot \left(\frac{k}{c_p} \nabla T \right) + S_T \quad (5.3)$$

where ρ is density, $\mathbf{u}$ is the velocity vector, μ is dynamic viscosity, T is temperature, k is thermal conductivity, c_p is specific heat capacity, ∇ is the vector differential operator, and S_m and S_T are source terms.

Eq. 5.2 is the momentum equations. The derivation of the form written above is under the assumption that the fluid is Newtonian. They are known as the Navier-Stokes

equations, after the two scientists who derived them independently. Eq. 5.1 is the continuity equation, and Eq. 5.3 is the energy conservation equation. In many cases the Navier-Stokes and continuity equations are sufficient to provide a description of the system. The energy equation is only required when considering flows where there is significant variation in the density of the fluid or where heat transfer is important.

The above conservation equations can be expressed by the generic equation.

$$\frac{\partial(\rho\phi)}{\partial t} + \nabla \cdot (\rho\phi u) = \nabla \cdot (\Gamma \nabla \phi) + S_\phi \quad (5.4)$$

where ϕ is an arbitrary variable which is conserved and Γ is the corresponding diffusivity tensor.

5.2.2 Finite Volume Method

‘Discretization is the process by which a closed-form mathematical expression, such as a function or a differential or integral equation involving functions, all of which are viewed as having an infinite continuum of values throughout some domain, is approximated by analogous (but different) expressions which prescribe values at only a finite number of discrete points or volumes in the domain [174].’ Discretization is a necessary part of all the methods involved in CFD. Finite difference method, finite element method and finite volume method are the three most dominant discretization methods, and finite volume method (FVM), also named as control volume method, is the standard approach used most often in commercial software and research codes in CFD.

In finite volume method, the domain of interest is divided into many small control volumes and the governing partial differential equations are integrated in each control volume and then discretized. This guarantees the conservation of the variable ϕ within each control volume, and therefore, guarantees the conservation of ϕ in the whole domain, which is one of the advantages of FVM.

As the key step of FVM, integration of the generic equation (Eq. 5.4) over a control volume leads to:

$$\int_V \frac{\partial \rho \phi}{\partial t} dV + \int_V \nabla \cdot (\rho \phi) dV = \int_V \nabla \cdot (\Gamma \nabla \phi) dV + \int_V S_\phi dV \quad (5.5)$$

where V is the control volume.

According to Gauss's divergence theorem, for a vector $\mathbf{a}$, there is:

$$\int_V \nabla \cdot \mathbf{a} dV = \int_A \mathbf{n} \cdot \mathbf{a} dA \quad (5.6)$$

where $\mathbf{n} \cdot \mathbf{a}$ is the component of $\mathbf{a}$ in the direction of the vector $\mathbf{n}$ normal to surface element dA (Figure 5.2). By introducing Gauss's theorem to Eq.5.5, we can get:

$$\int_V \frac{\partial \rho \phi}{\partial t} dV + \int_A \mathbf{n} \cdot (\rho \phi \mathbf{u}) dA = \int_A \mathbf{n} \cdot (\Gamma \nabla \phi) dA + \int_V S_\phi dV \quad (5.7)$$

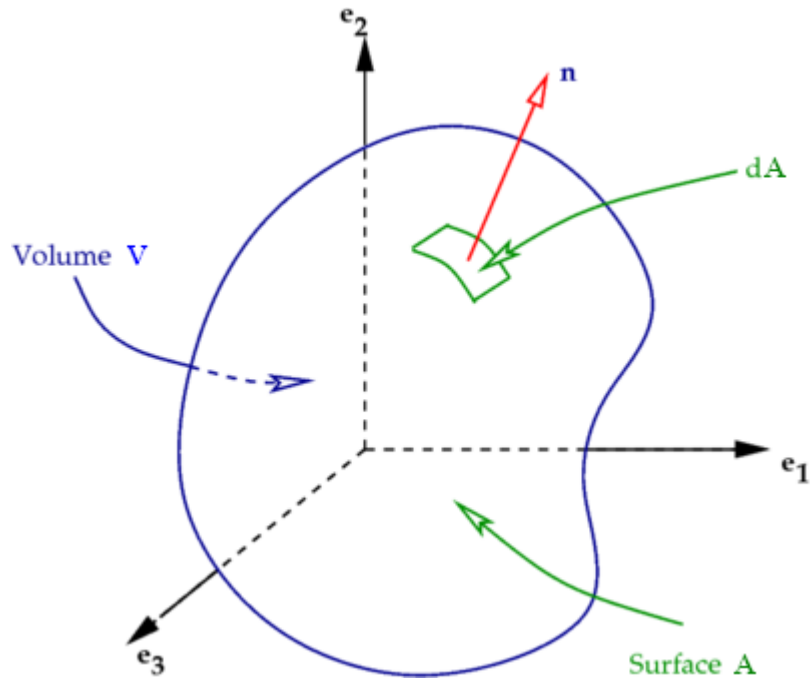


Figure 5.2 Control volume for application of the divergence theorem

In FVM, the subdomain as a result of discretization of the domain of interest is called grid, which is composed of four elements: node, control volume, face and grad line (Figure 5.3). A nodal point is defined at the centre of each cell, at which all of the independent variables are defined. Values at locations between the nodes are

calculated by linearized interpolation functions from the nodal values. Eq. 5.7, applied to the discretised global control volume, gives:

$$\sum_{n=1}^m \int_{V^{(n)}} \frac{\partial \rho \phi}{\partial t} dV^{(n)} + \sum_{n=1}^m \int_{A^{(n)}} \mathbf{n} \cdot (\rho \phi \mathbf{u}) dA^{(n)} = \sum_{n=1}^m \int_{A^{(1)}, \dots, A^{(n)}} \mathbf{n} \cdot (\rho \phi \mathbf{u}) dA^{(n)} + \sum_{n=1}^m \int_{V^{(n)}} S_{\phi} dV^{(n)} \quad (5.8)$$

where m is the number of cells in the assembly and q the number of faces for cell n .

Correct formulation of these interpolation functions is of paramount importance to the stability and accuracy of the method. The fundamental properties which must be reflected in their formulation are: conservativeness, boundedness and transportiveness.

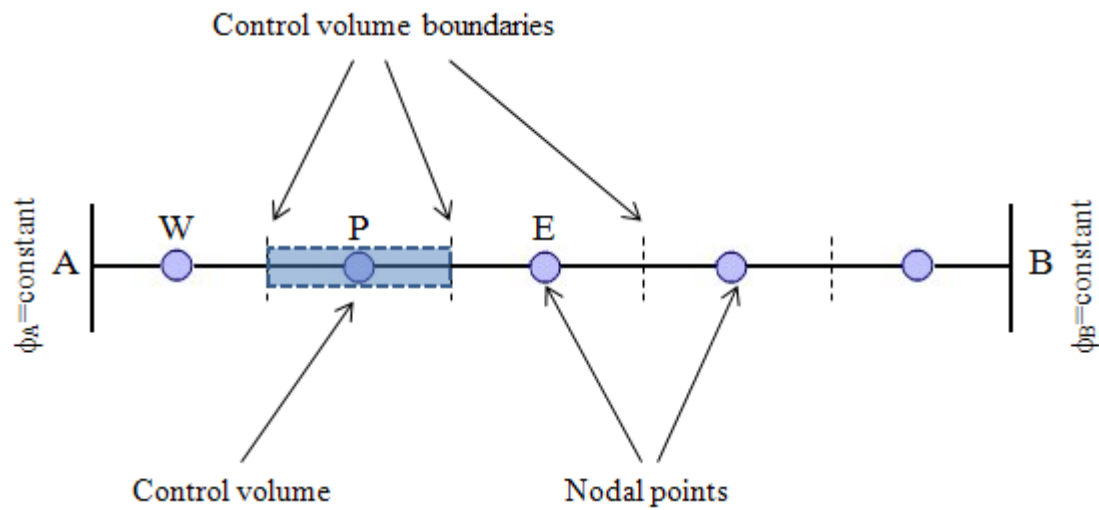


Figure 5.3 One dimensional finite volume grids [175].

5.3 Materials and Methods

5.3.1 MRI Imaging Protocol

In this study, ten healthy volunteers (24–35 years old) without any history of venous disease were included. The study was approved by the local research ethics committee, and informed consent was obtained from all participants. Scans were performed at the CMR Unit at the Royal Brompton Hospital. All scans were performed with the subject in the supine position. A cushion was used to support the subjects' ankles which were lifted by about 10 cm to avoid compressing the calf muscles against the table (Figure 5.4).



Figure 5.4 Scan position of the subject.

None of the subjects was on any medication. The compression devices employed in this study were knee-length grade 1 static compression stockings (T.E.D.[™] Covidien Inc.). According to the manufacturer's instructions, the length and circumference of each subject's calf were measured (Figure 5.5) and the stocking of appropriate size was selected for each subject. The following MRI scan procedure was adopted:

1. The subject lay on the patient table in a supine position without wearing any compression stockings. Short localiser scans (~15 seconds each) were performed to determine the location for the full MR examination.
2. A 19 cm section of the calf was scanned using a 3D balanced steady state free precession (bSSFP) sequence. The echo time (TE), repetition time (TR) and full acquisition time (TA) were 1.86 ms, 4.29 ms and 3 min 51 s, respectively. Fat suppression pulses were applied during interruptions of the bSSFP every 172 ms. The field of view (FOV) covered an area of $200 \times 200 \text{ mm}^2$ and the spatial resolution was

$0.625 \times 0.625 \times 2$ mm. A total of 96 images were acquired along the calf length for each subject.

3. The subject was given 2-3 minutes to become accustomed to the metronome-guided respiration [26], before real-time phase contrast velocity mapping was performed and blood flow data were recorded over a period of approximately 38 s to ensure at least 5 complete respiratory cycles were captured. MRI sequence parameters, TE/TR/TA=5.2 ms/ 39.8 ms/ 954.7 ms, were employed. The FOV was 150×150 mm² with 320 primary phase encoding steps and readout samples, which led to spatial resolution of 0.5×0.5 mm.

4. The compression stocking was put onto the subject's right leg, while the subject remained in a relaxed supine position.

5. A period of approximately 5 minutes was allowed to elapse before any subsequent images were acquired. Then a further set of images and velocity data were acquired following the same procedure as described above.

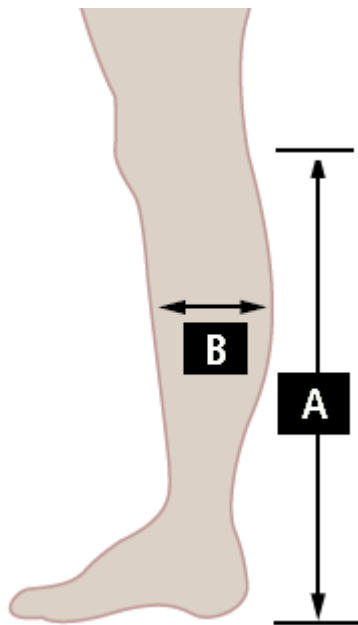


Figure 5.5 Parameters of stocking size selection. A: Length from bend of knee to bottom of heel, B: Calf circumference.

The real-time phase contrast velocity mapping sequence used in this study was specially optimised for use in the lower leg. Details of the imaging sequence have been reported elsewhere [176] at lower spatial resolution, hence only a brief summary will be given here. It utilised a spiral k-space trajectory, split into 12 interleaves, each repeated for ‘symmetric’ velocity encoding achieving a final velocity range (VENC) of ± 5 cm/s. A parallel saturation band was used to suppress signal from the arterial blood entering the image slice, and slice-selective water excitation (using a spatial-spectral (1, 1) binomial RF pulse series) was used in order to reduce ‘off-resonance blurring’ artefact due to fat signal. The slice thickness was 5mm and acquired in-plane resolution was 0.5 by 0.5mm reconstructed to 0.3 x 0.3 mm.

Velocity measurements were taken from the images using CMR Tools (Cardiovascular Imaging Solutions Ltd, London, UK). Regions of interest (ROI) were drawn around the peroneal veins on the real-time anatomical images that showed greatest in-flow enhancement of the veins (and compared with an ROI drawn on the corresponding slice from the 3D sequence). This ROI was then transferred to all the velocity maps of that series, keeping the ROI static throughout. Spatial mean velocities were recorded, multiplied by the ROI area for calculations of the volume flow. An ROI was placed within the muscle mass, also assumed to be stationary throughout the image series, to obtain background offset error corrections for the velocity images.

The real-time data were reconstructed using an in-house Matlab (Mathworks Inc.) programme with a sliding data window to achieve a final (interpolated) temporal resolution of 79.6 ms.

5.3.2 Venous Flow data

The main deep vessels include peroneal veins, posterior tibial veins and anterior tibial veins, also known as the axial veins (Figure 5.6). To some extent the architecture of the deep venous system is a mirror of the local arterial network, with vessels running alongside their corresponding arterial branches. In many cases, including the vessels mentioned above, the artery is accompanied by two or more veins.

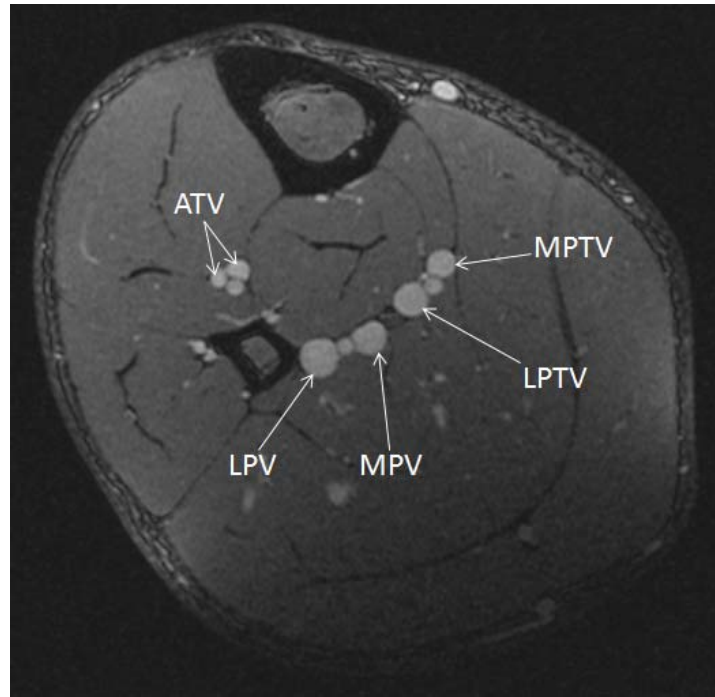
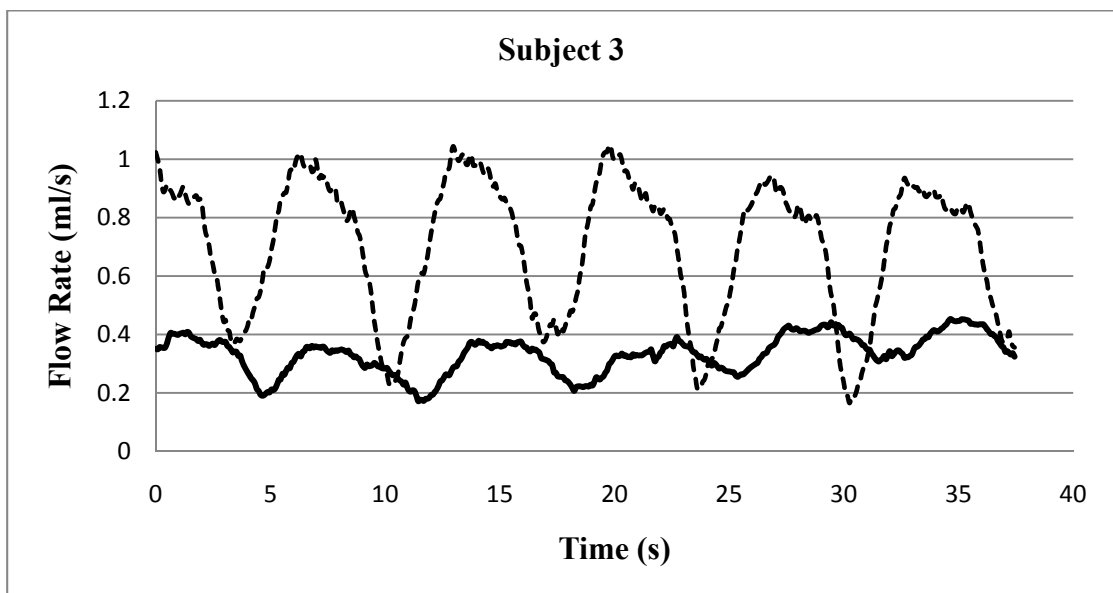
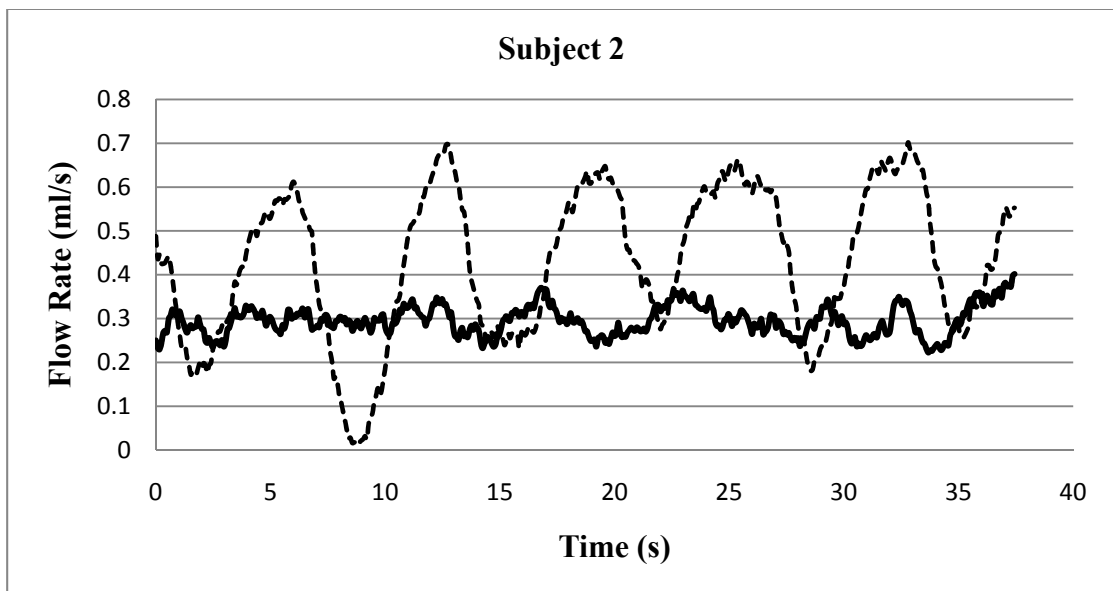
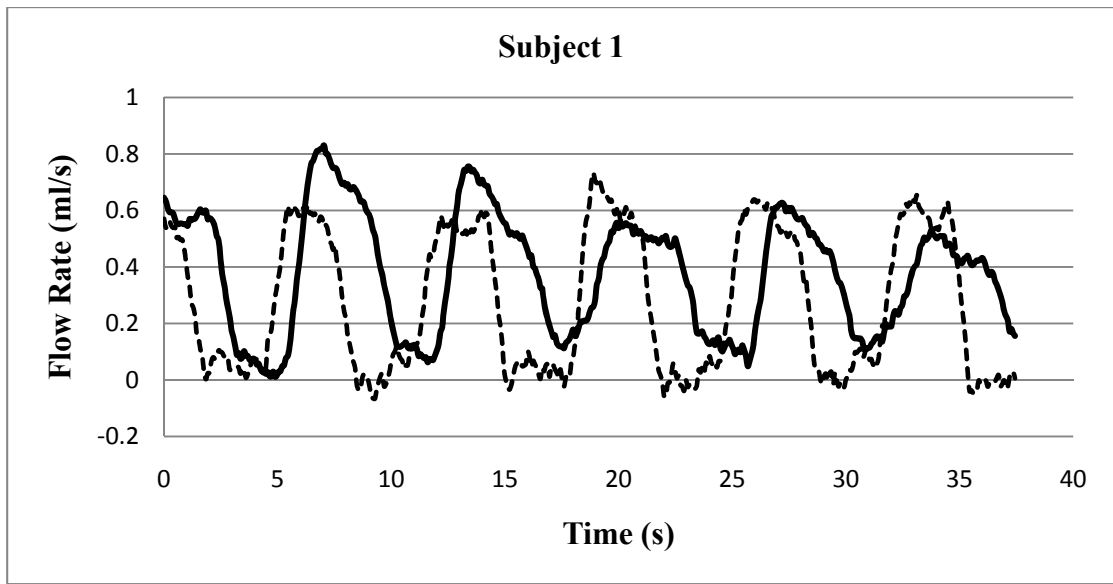
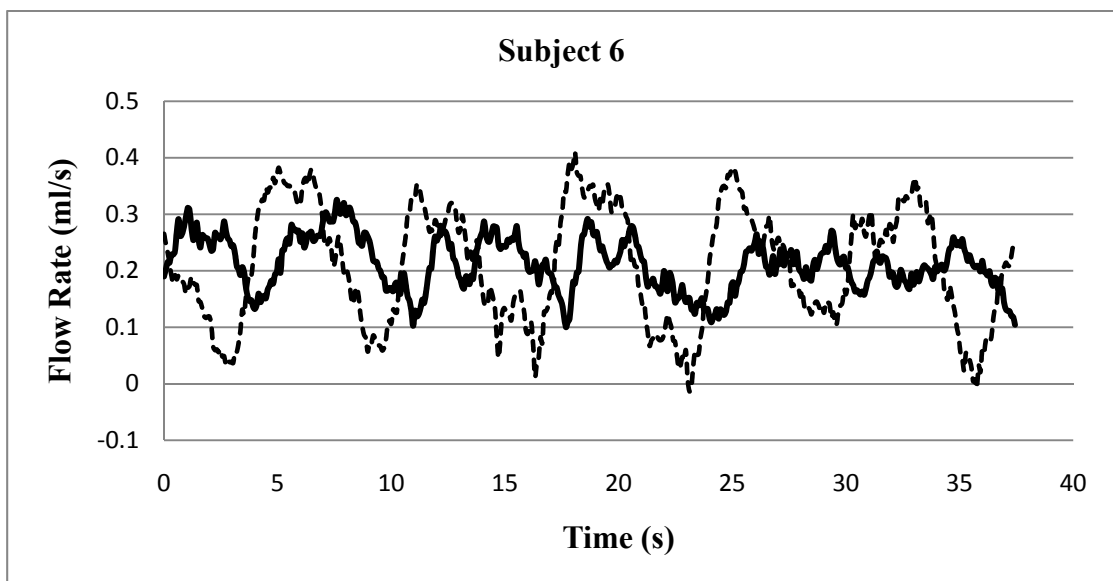
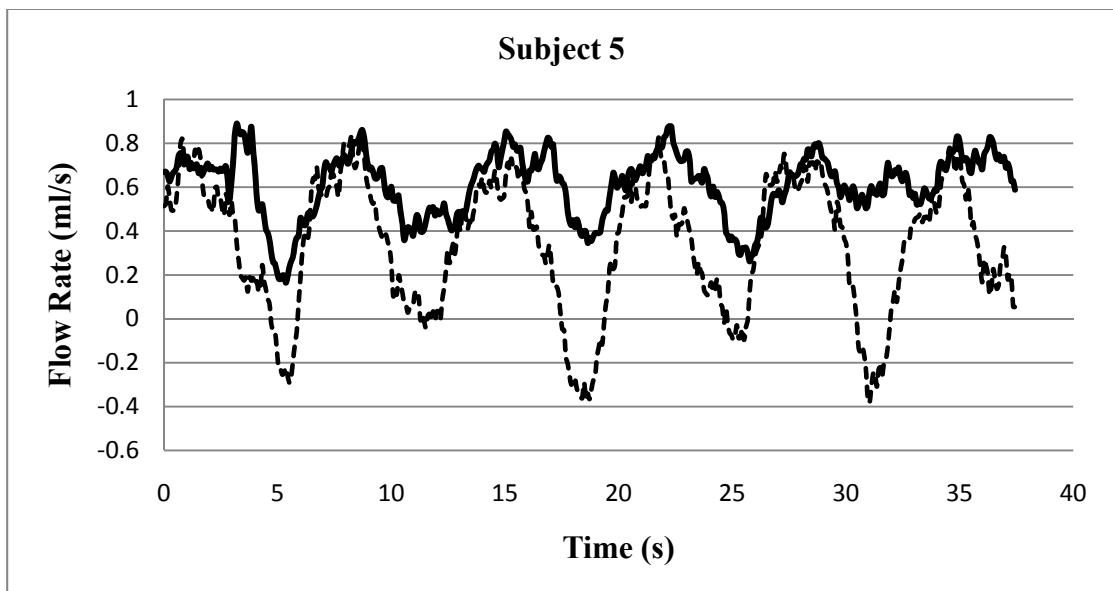
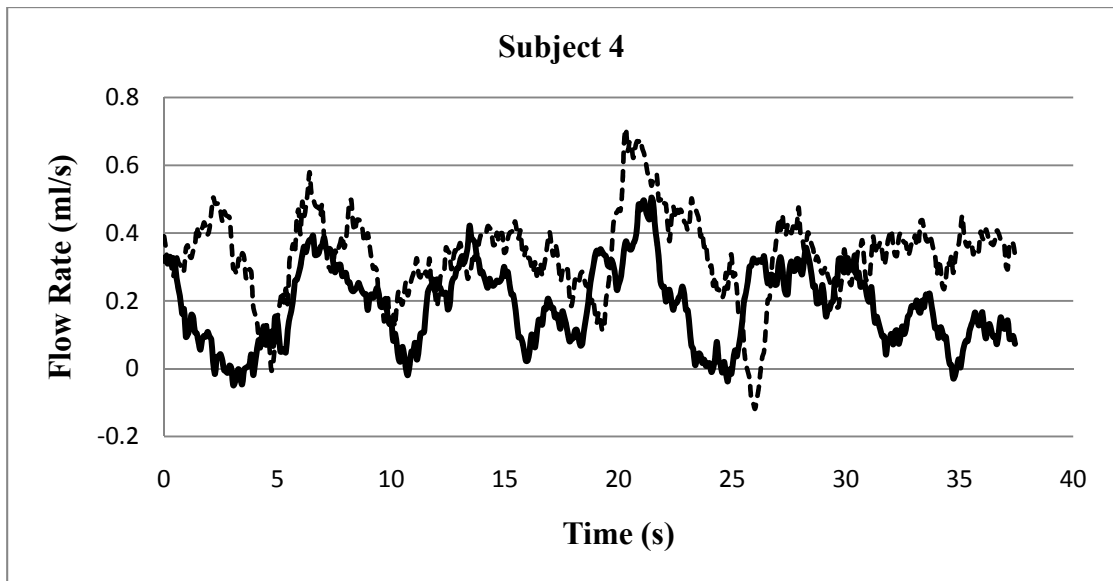
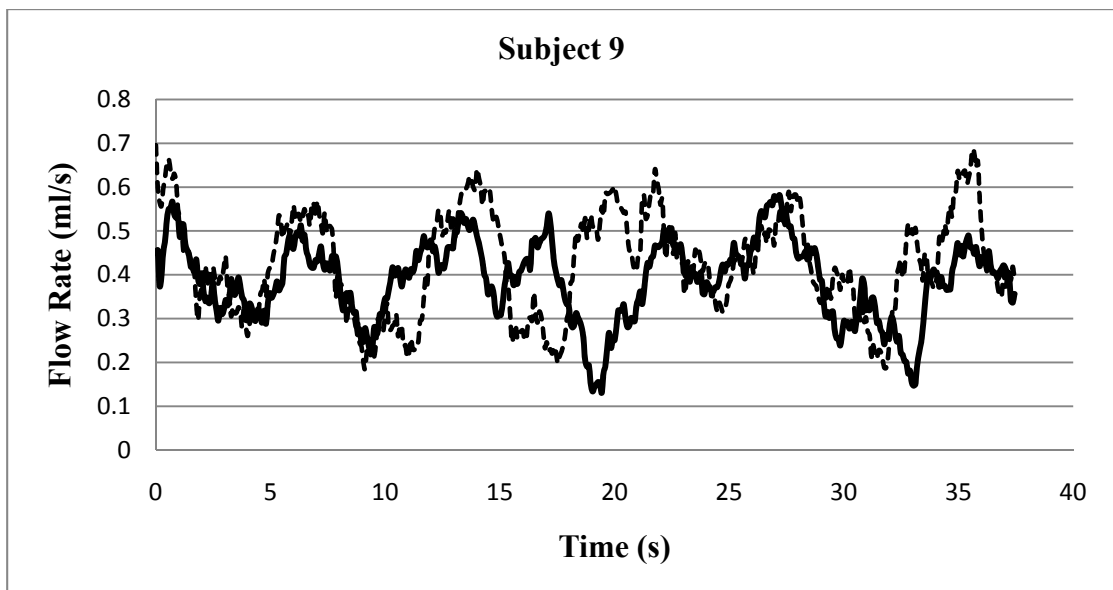
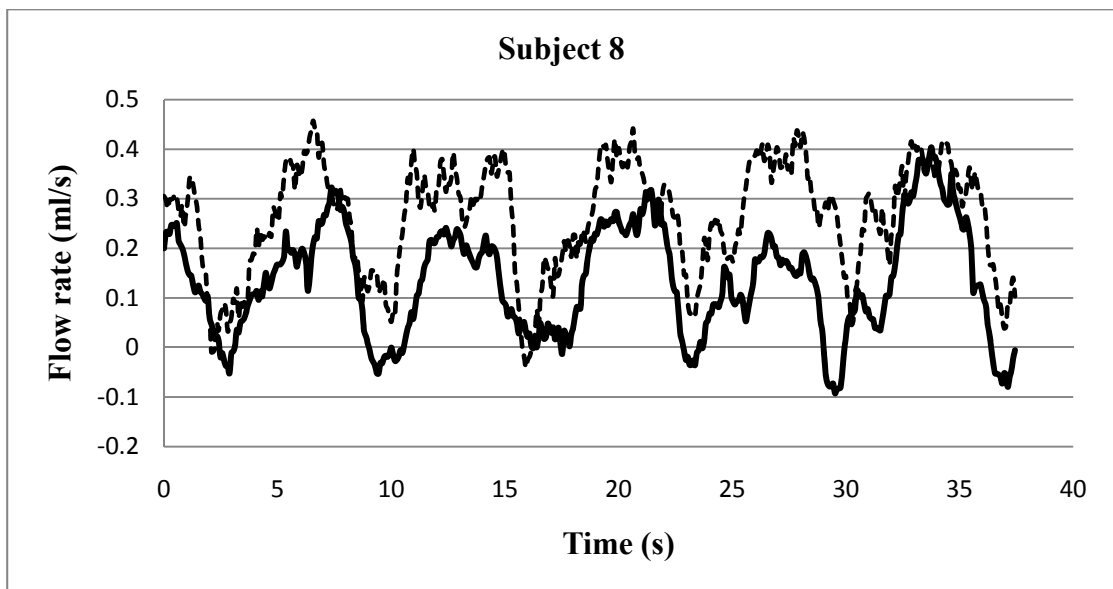
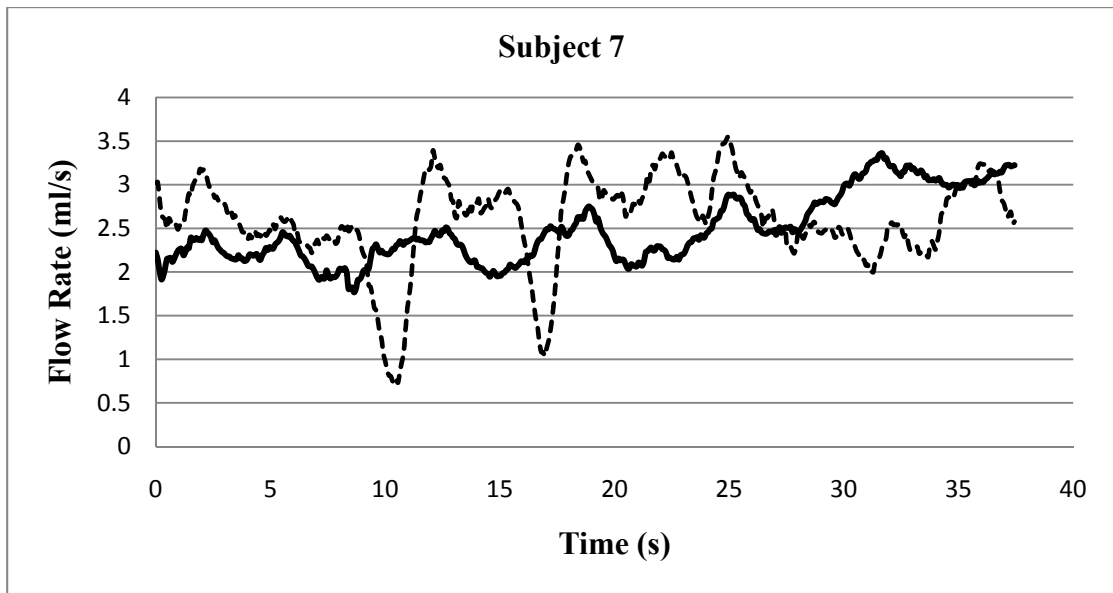


Figure 5.6 MR image of an uncompressed calf. ATV-anterior tibial vein, LPV/MPV - lateral/medial peroneal veins, LPTV/MPTV - lateral/medial posterior tibial veins.

Compared with the peroneal veins and the posterior tibial veins, the anterior tibial veins are much smaller in diameter. The spatial resolution of whole-body MRI scanners is insufficient for an accurate flow measurement in such small vessels, unless acquired over a longer timescale. On the other hand, the peroneal veins involve fewer bifurcations than the posterior tibial veins. For these reasons, in this study, blood flow rates in the peroneal veins were measured. Although flow data in both the lateral peroneal vein (LPV) and medial peroneal vein (MPV) was acquired, the LPV is very close to the fibula, which can affect the LPV deformation significantly. The deformation of the MPV is believed to be less subject-dependent compared with the LPV; hence the MPV was selected for the CFD analysis. For all the subjects, flow velocity was measured at about 5 cm below the popliteal vein bifurcation. The measured flow rates in the MPV of all subjects before and after compression are shown in Figure 5.7.







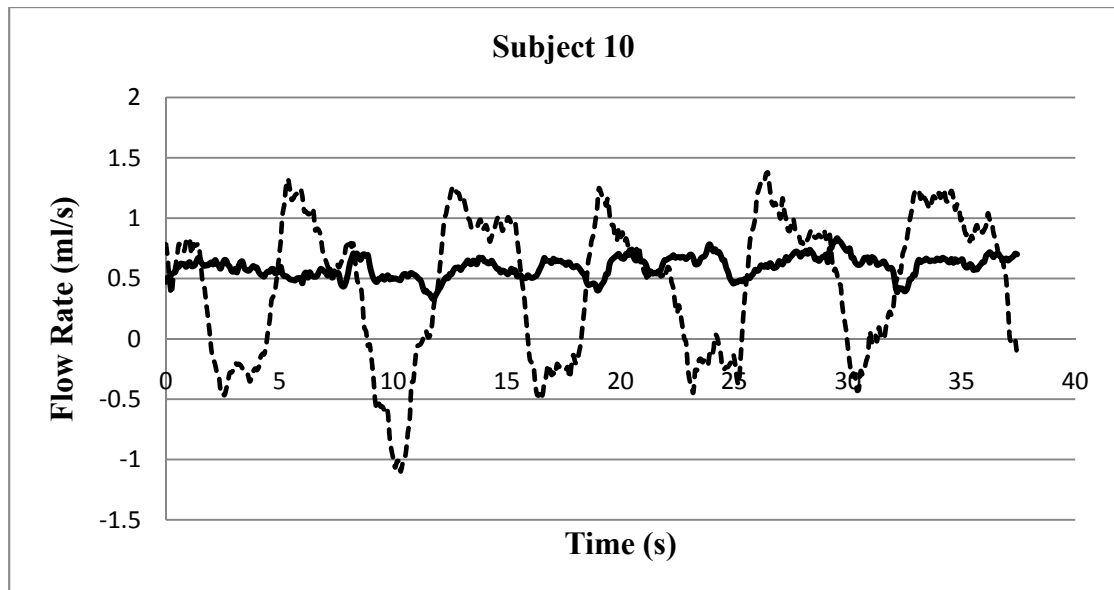


Figure 5.7 Volumetric flow rate waveforms derived from MR flow mapping before (dashed lines) and after (continuous lines) compression.

For each subject, a representative flow waveform was calculated by taking an ensemble average of 5 cycles from the actual flow data acquired (Figure 5.8). This subject-specific representative flow rate waveform was applied as an inlet boundary condition in CFD simulations.

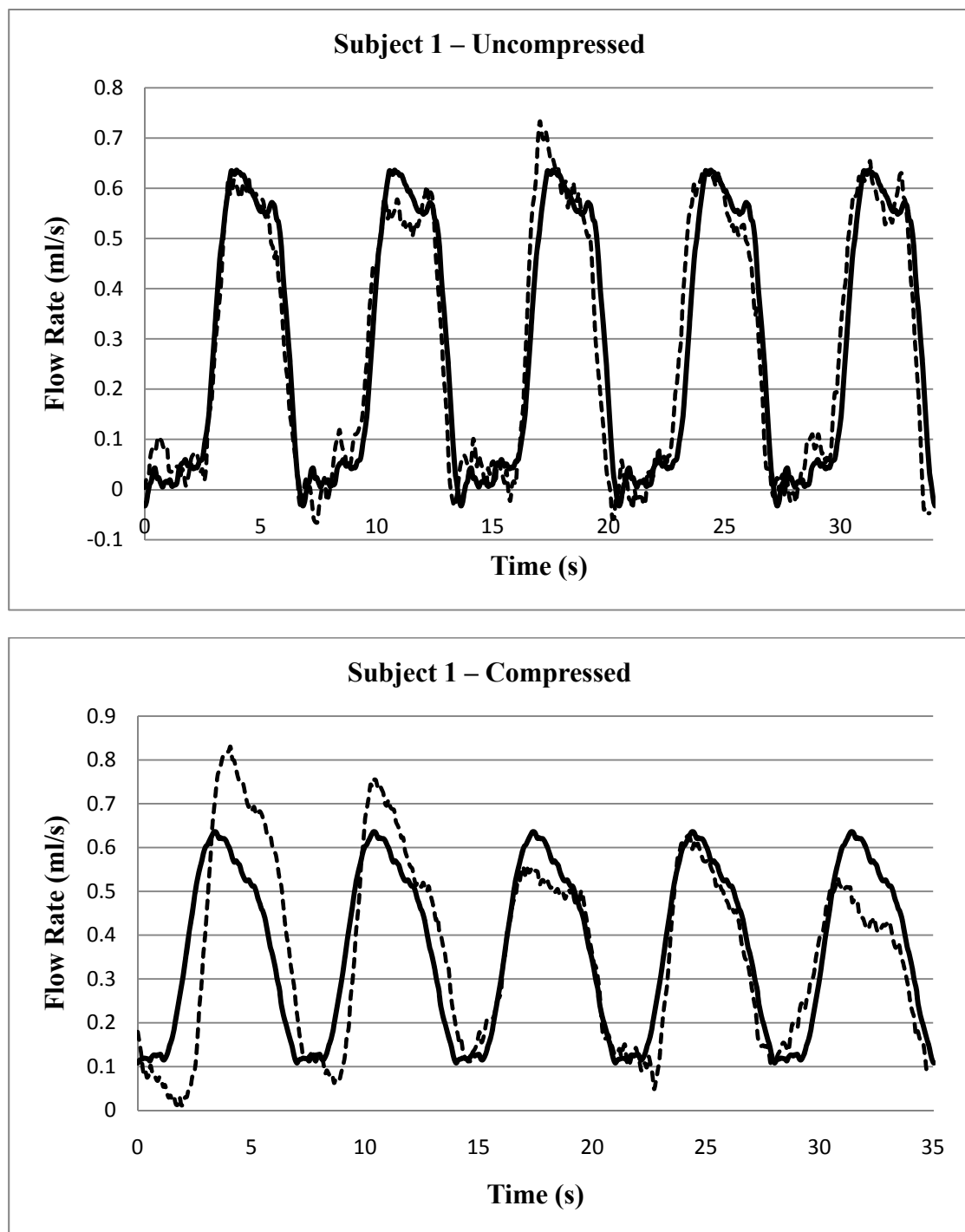


Figure 5.8 Comparison of sample representative waveforms (continuous lines) and the MRI flow data (dashed lines). Data are taken from the medial peroneal vein in subject 1, before (top) and after (bottom) compression induced by the static stocking.

5.3.3 CFD Modeling

The geometry of MPV was reconstructed using Mimics 13.0 (Materialise Group, Belgium). The inlet of the reconstructed MPV corresponded to the section where the MR flow rate was acquired, but in order to avoid the inclusion of bifurcations, the position of the inlet was varied slightly ($\pm 6mm$) depending on the architecture of the MPV. Because at any given time, blood flow rate should remain approximately constant within a section of vessel without any bifurcation, it is reasonable to assume that the slight variation in inlet position will have little effect on the subsequent flow analysis.

ICEM CFD (Ansys Inc., USA) was employed to generate the computational mesh for each reconstructed geometry (physical domain). The physical domain was divided into hexahedral structured grids, with an example shown in Figure 5.9. Increasing the nodes number from 310,000 to 2,480,000 resulted in a difference of less than 1% in terms of the spatial mean time averaged wall shear stress. A mesh size of 310,000 nodes was therefore selected. Spatial discretisation of the governing equations was performed via a hybrid 1st/2nd order scheme while temporal discretisation was performed via a fully implicit second order backward Euler scheme. The algebraic multigrid method was used to solve the resulting discretised equations.

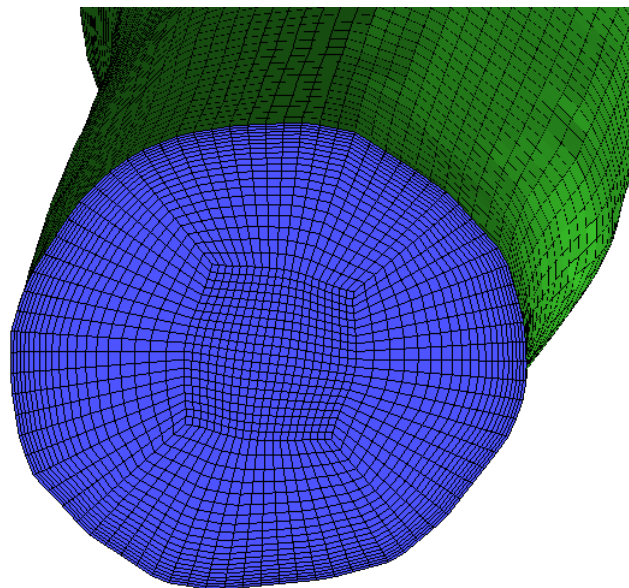


Figure 5.9 Structured hexahedral mesh generated with ICEM CFD

The vessel wall was assumed to be rigid with a no-slip condition. The subject-specific representative venous flow rate waveform was applied at the model inlet which was extended upstream by 6 times the inlet diameter, and zero relative static pressure was specified at the outlet. Blood was treated as a Newtonian fluid with density 1060 kg/m^3 and viscosity $3.5 \text{ mPa}\cdot\text{s}$. For the subjects included in this study, the peak Reynolds numbers at the inlet ranged from 30 to 162 and therefore, laminar flow assumption was made.

5.4 Results

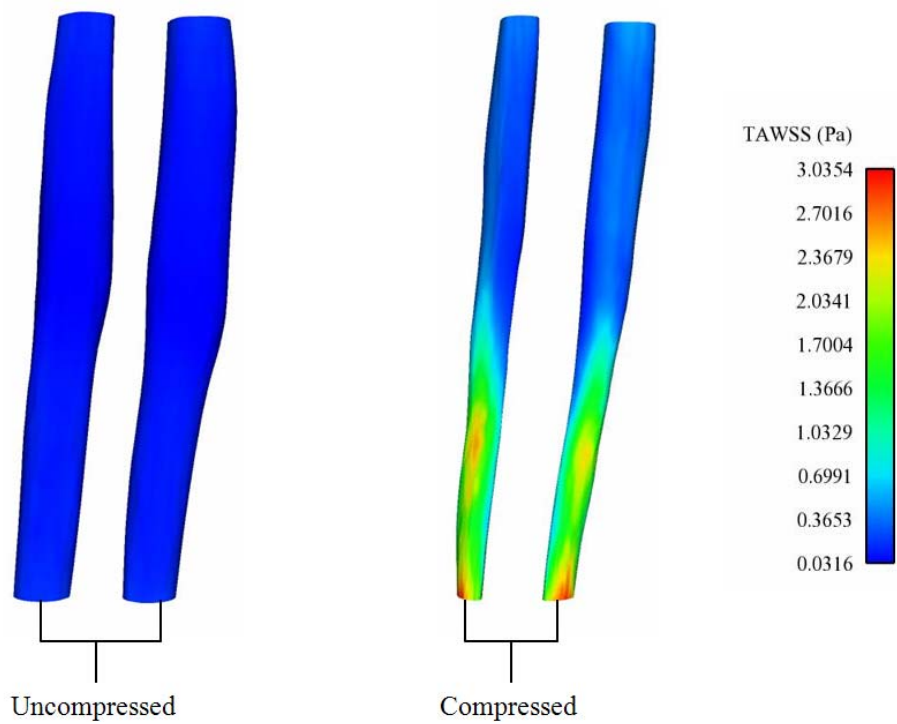
Results for time-averaged wall shear stress (TAWSS) obtained from the CFD simulations are shown in Table 5.1. In terms of the spatial mean TAWSS, 9 out of 10 subjects showed increase after compression. Only Subject 2 showed lower TAWSS with compression stocking than that without compression stocking. The overall result showed an average increase $((TAWSS_c - TAWSS_u)/TAWSS_u)$ of 398%, but individual results varied from -17% to 1934% (median 98%). Among the 9 subjects showing higher TAWSS after compression, subject 9 showed no significant difference between the uncompressed and compressed results, while subject 5 showed the largest increase.

Table 5.1 Time-averaged wall shear stress for all subjects before and after compression.

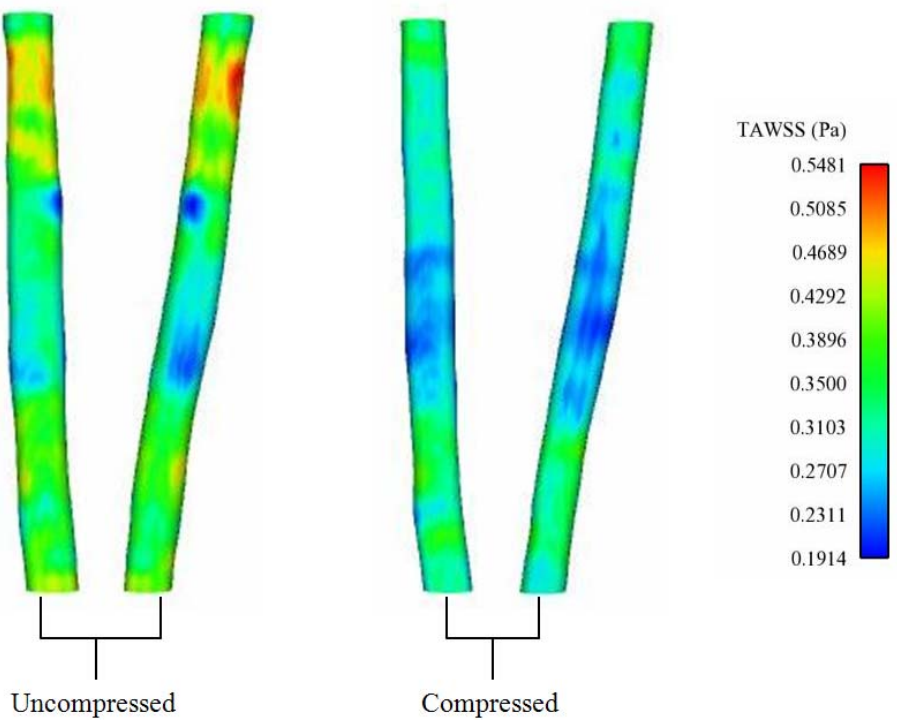
Subject	Uncompressed (Pa)			Compressed (Pa)		
	Min	Max	Spatial Mean	Min	Max	Spatial Mean
1	0.032	0.219	0.098	0.110	3.035	0.740
2	0.191	0.548	0.358	0.206	0.402	0.295
3	0.297	1.106	0.634	0.528	1.650	1.035
4	0.024	0.103	0.055	0.037	0.200	0.094
5	0.010	0.052	0.029	0.073	2.596	0.590
6	0.024	0.136	0.081	0.071	0.203	0.136
7	0.072	0.786	0.284	0.461	1.954	0.956
8	0.033	0.158	0.077	0.080	0.276	0.173
9	0.085	0.331	0.190	0.127	0.330	0.204
10	0.009	0.118	0.039	0.084	0.867	0.363
Mean	0.078	0.356	0.185	0.178	1.151	0.459
Median	0.033	0.189	0.090	0.097	0.635	0.329

The spatial distributions of TAWSS also varied significantly among subjects (Figure 5.10), although in general uncompressed MPV had more uniform TWASS than the compressed vessels. The deformation patterns of MPV under external compression were found to be highly variable among subjects, which was mainly responsible for the large variation in wall shear stress distribution. Although the analysed segments of MPV were matched for anatomical location, a number of other factors could influence the deformation of the vessel. These include the shape and location of the bones, the architecture and mechanical properties of the muscles and other soft tissues, the

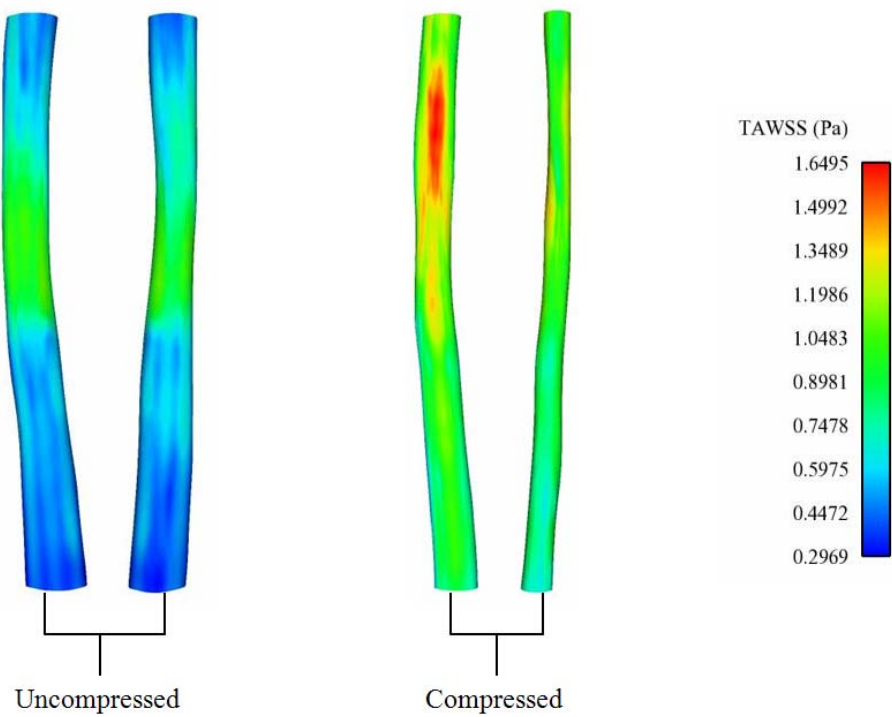
position and shape of the MPV, all of which differed to certain extent among the subjects.



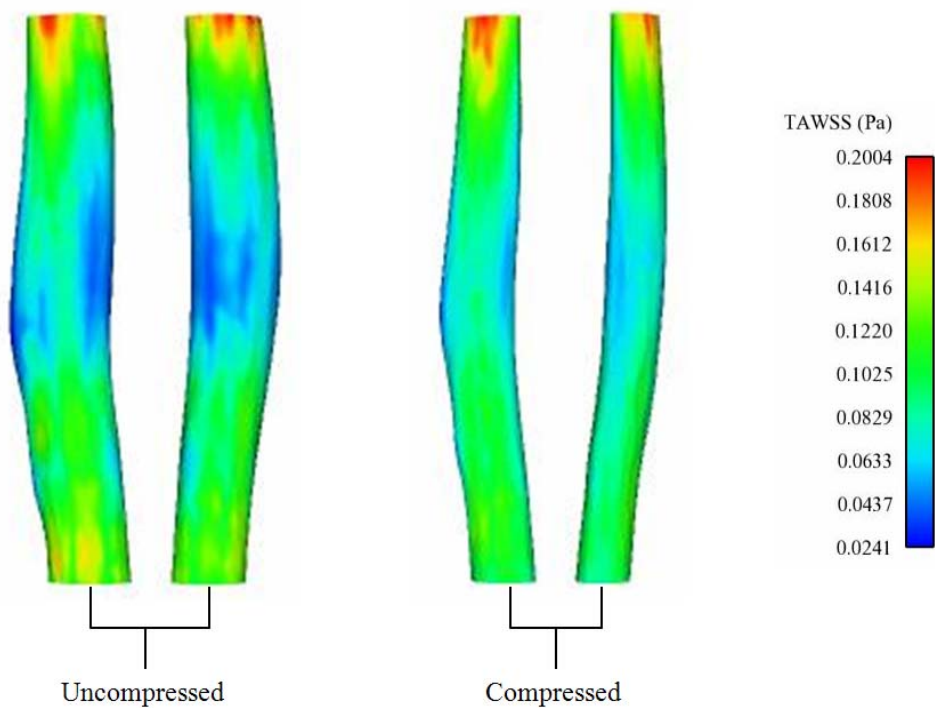
Subject 1



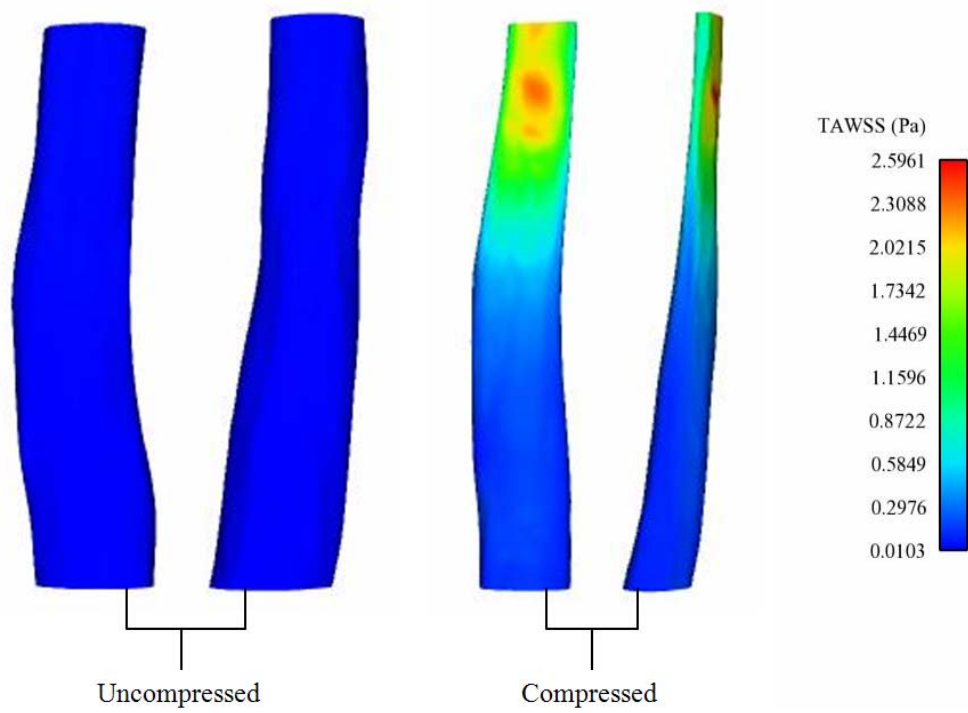
Subject 2



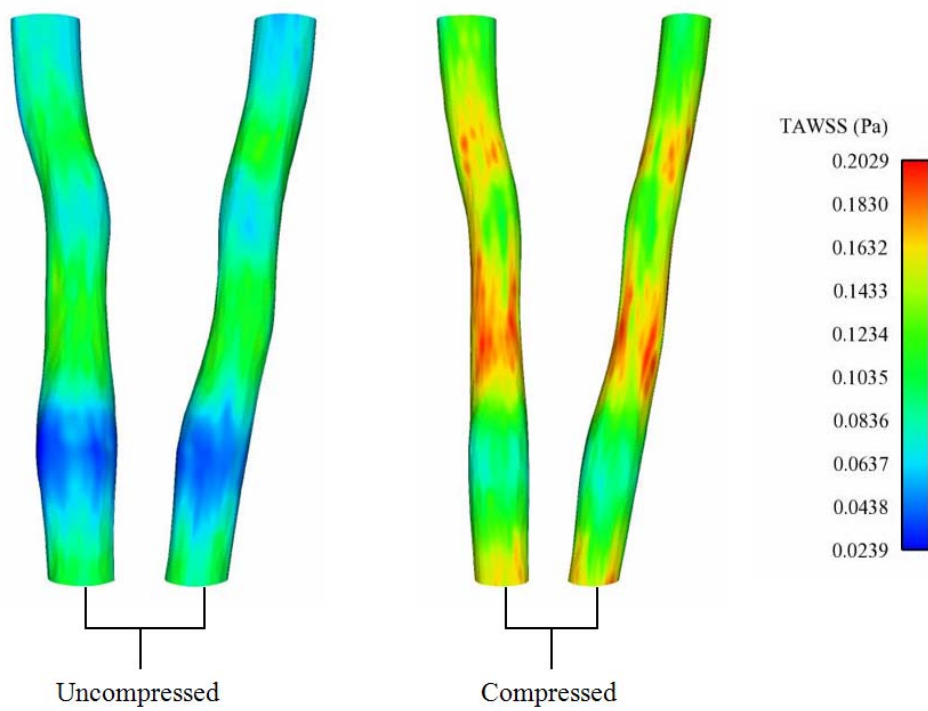
Subject 3



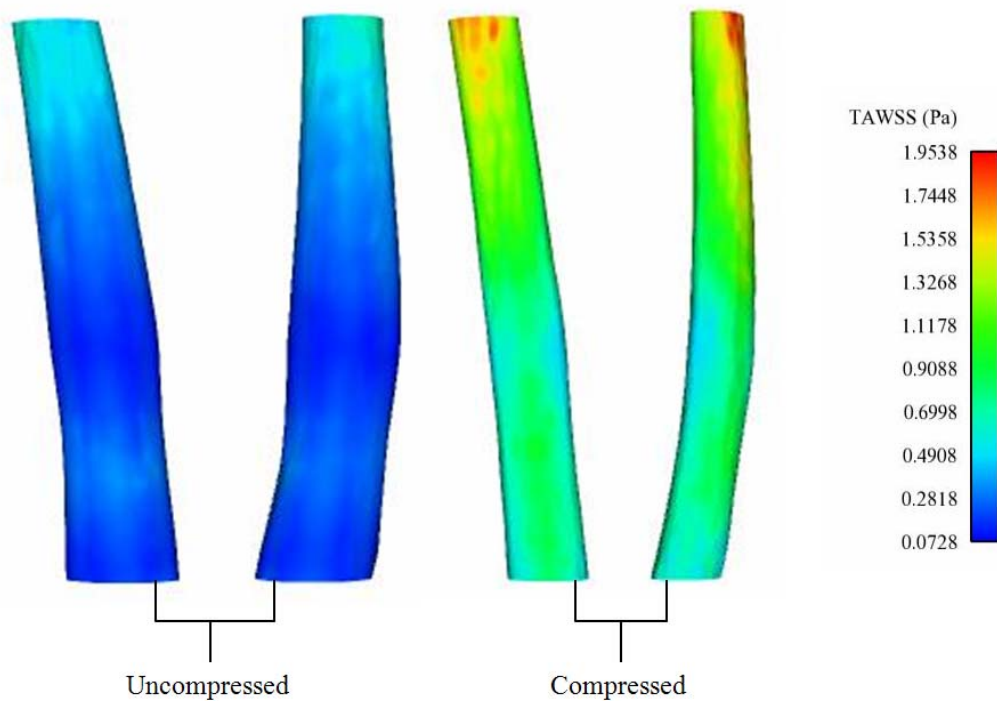
Subject 4



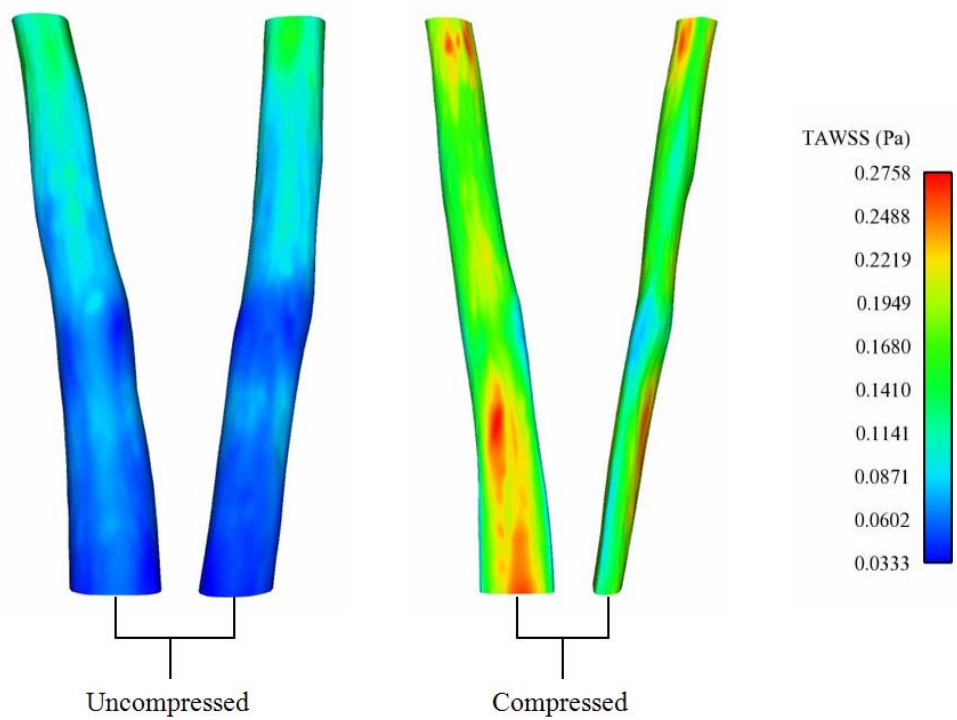
Subject 5



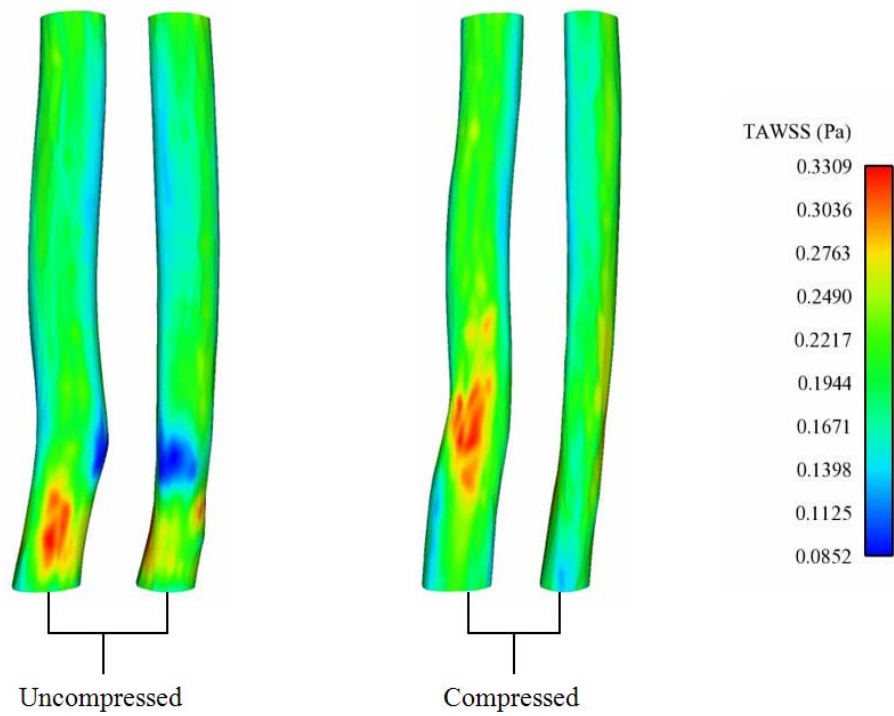
Subject 6



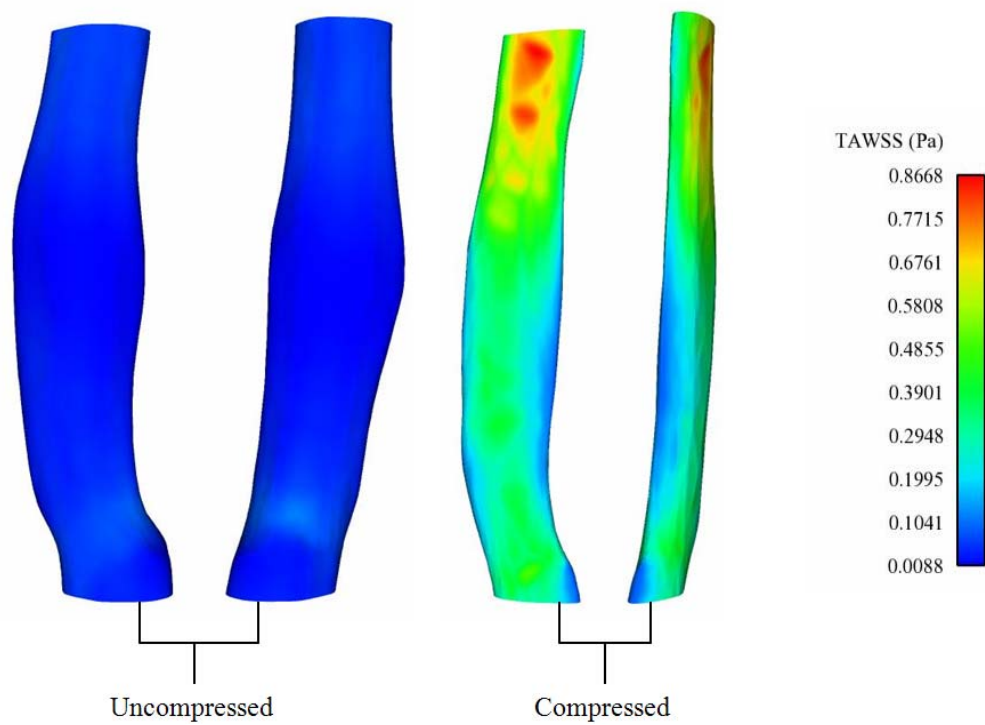
Subject 7



Subject 8



Subject 9



Subject 10

Figure 5.10 Time-averaged wall shear stress distributions in the MPV before and after compression.

Nevertheless, the results from the ten subjects had some features in common. As shown in Figure 5.10, higher TAWSS always occurs at locations with smaller diameter owing to local flow acceleration as a result of area reduction. This is consistent with the findings of previous study [177]. Since the magnitude of wall shear stress depends on vessel geometry (shape and size) and flow rate, it would be useful to compare measured flow rates in the MPV before and after compression. Previous studies [178, 179] have shown that external compression can reduce flow rate in femoral veins, but no direct measurement data is available about the effect of compression on flow in the deep veins in the calf. Table 5.2 shows the comparison of time-averaged volumetric flow rates in the MPV before and after external compression. These data were obtained from the MR flow measurements presented earlier. Our results showed a small reduction (mean 7%; median 7%) in mean MPV flow rate after compression, with 6 out of 10 subjects experiencing a reduced flow rate and 4 subjects experiencing an increased flow rate. The MPV flow rate in subject 7 was significantly higher than in the other subjects (2.60 ml/s vs. 0.60 ml/s before compression and 2.48 ml/s vs. 0.56 ml/s after compression).

Table 5.2 Time-averaged volume flow rate in the MPV before and after compression.

Subject	Uncompressed (ml/s)	Compressed (ml/s)
1	0.2756	0.3814
2	0.4291	0.2949
3	0.7021	0.3332
4	0.3342	0.1868
5	0.3428	0.6109
6	0.2090	0.2120
7	2.6011	2.4787
8	0.2618	0.1354
9	0.4272	0.3871
10	0.4479	0.5956
Mean	0.6031	0.5616
Median	0.3850	0.3573

Although external compression reduced (albeit slightly) the volumetric flow rate in the deep vein on average, it also caused the deep veins to collapse which could negate the influence of flow reduction and lead to a higher blood velocity. The volumes,

before and after compression, of the 4 cm sections of MPV examined are shown in Table 5.3. An average volume reduction of 51% was found after compression.

Table 5.3 Volume of the segmented section of MPV before and after compression.

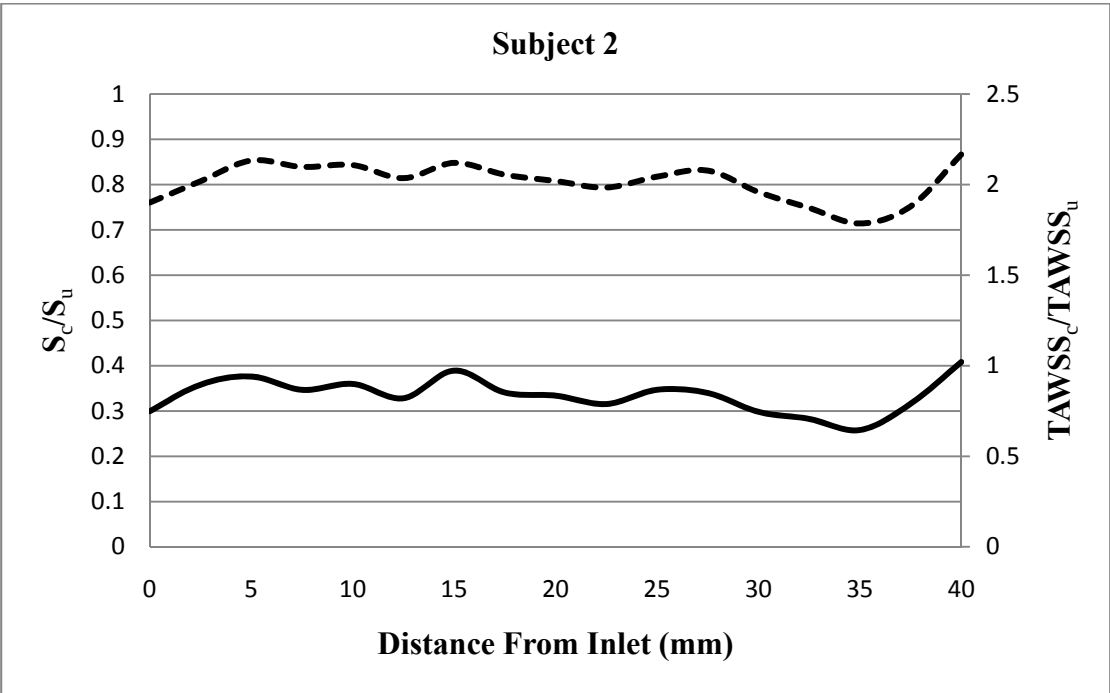
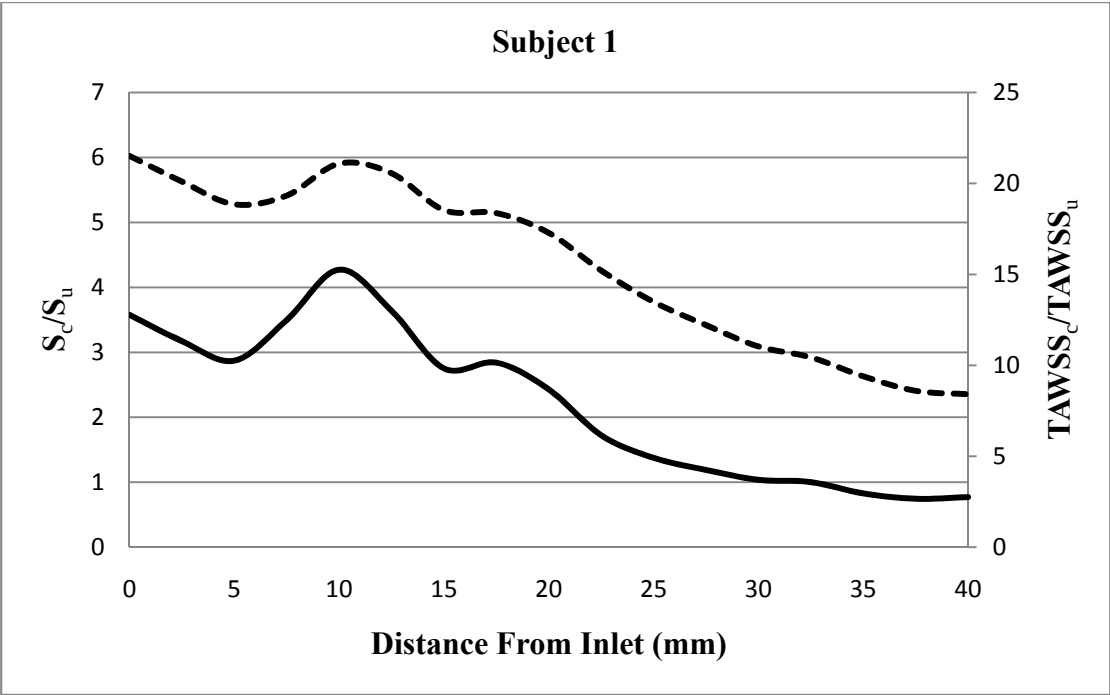
Subject	Uncompressed (mm ³)	Compressed (mm ³)	Volume reduction
1	714	255	64%
2	401	342	15%
3	387	170	56%
4	1182	572	52%
5	2037	601	71%
6	684	446	35%
7	1805	753	58%
8	835	331	60%
9	651	508	22%
10	2228	591	73%
Mean	1092	457	51%

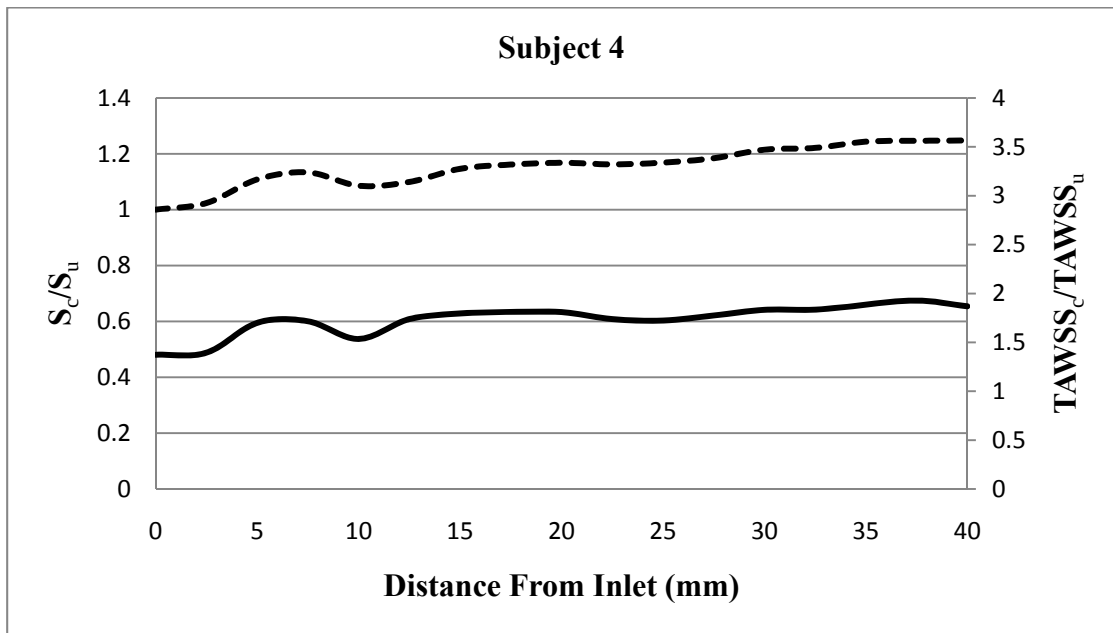
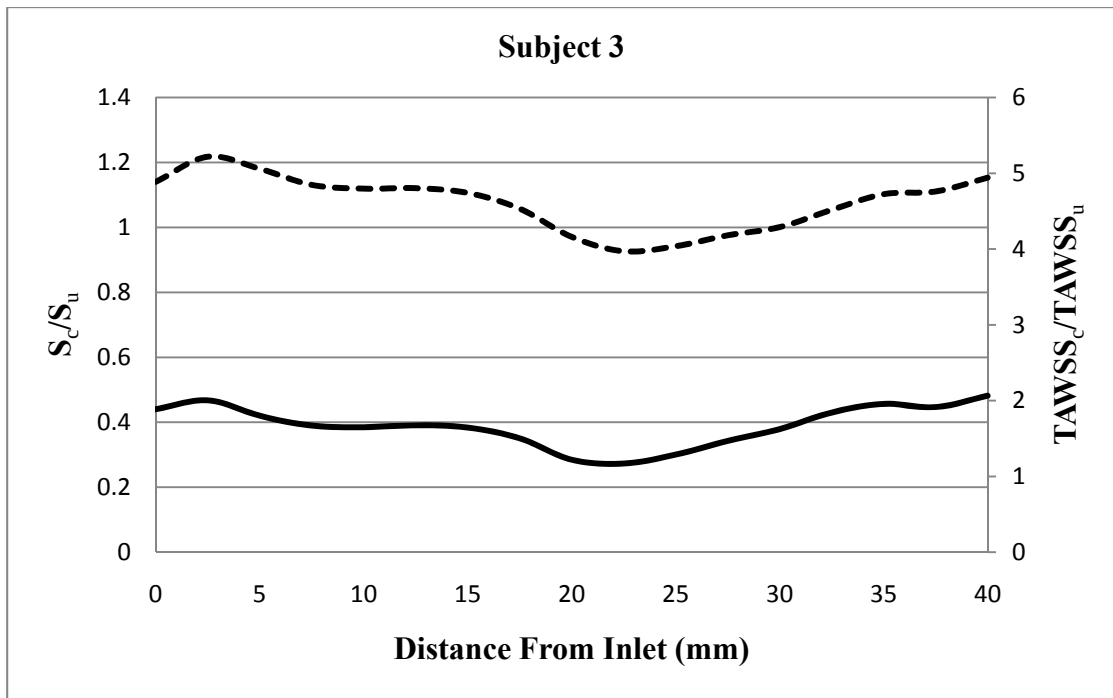
The effect of flow rate and cross-sectional area on wall shear stress in the deep vein was further investigated by examining the axial variation of the cross-sectional mean velocity which is defined as:

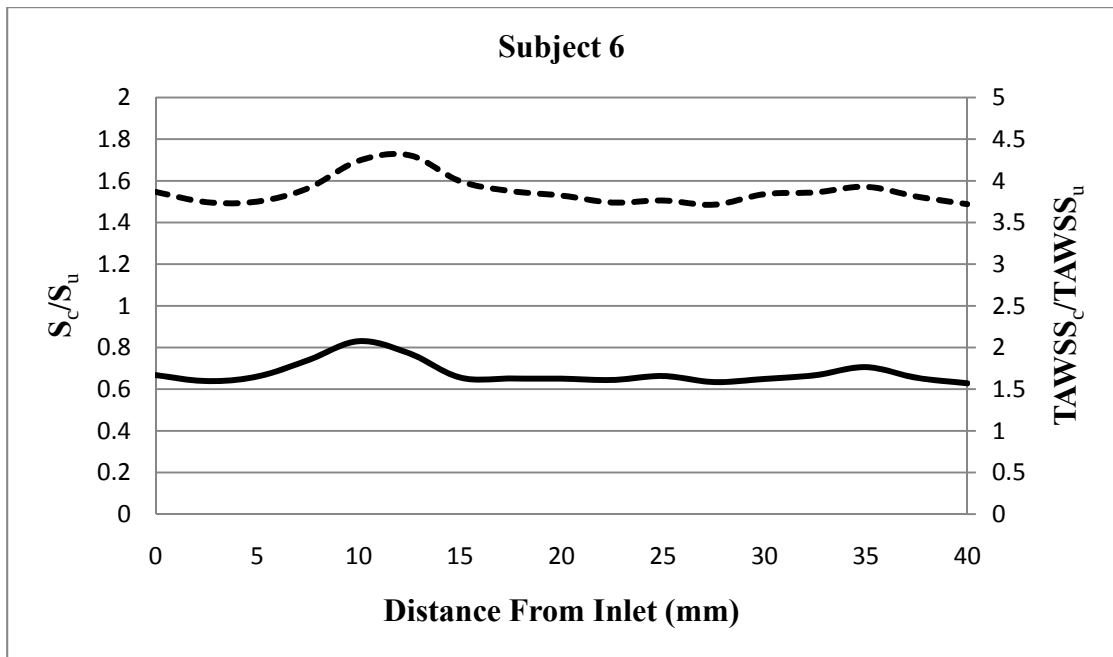
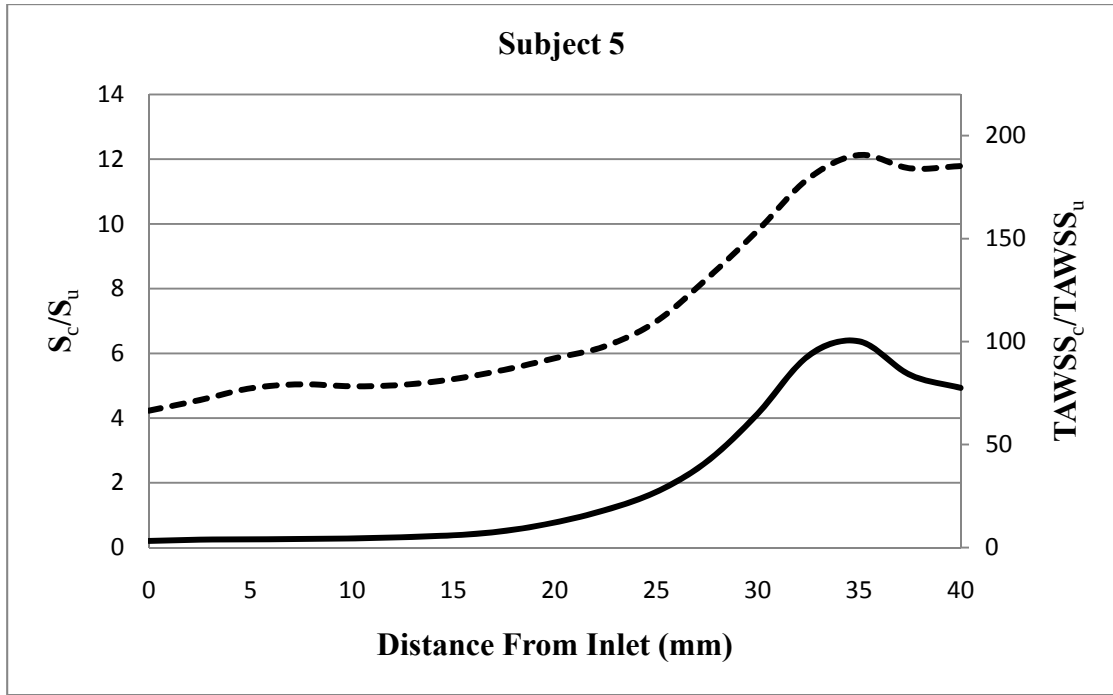
$$\frac{S_c}{S_u} = \left(\frac{V_c}{A_c} \right) / \left(\frac{V_u}{A_u} \right) \quad (5.9)$$

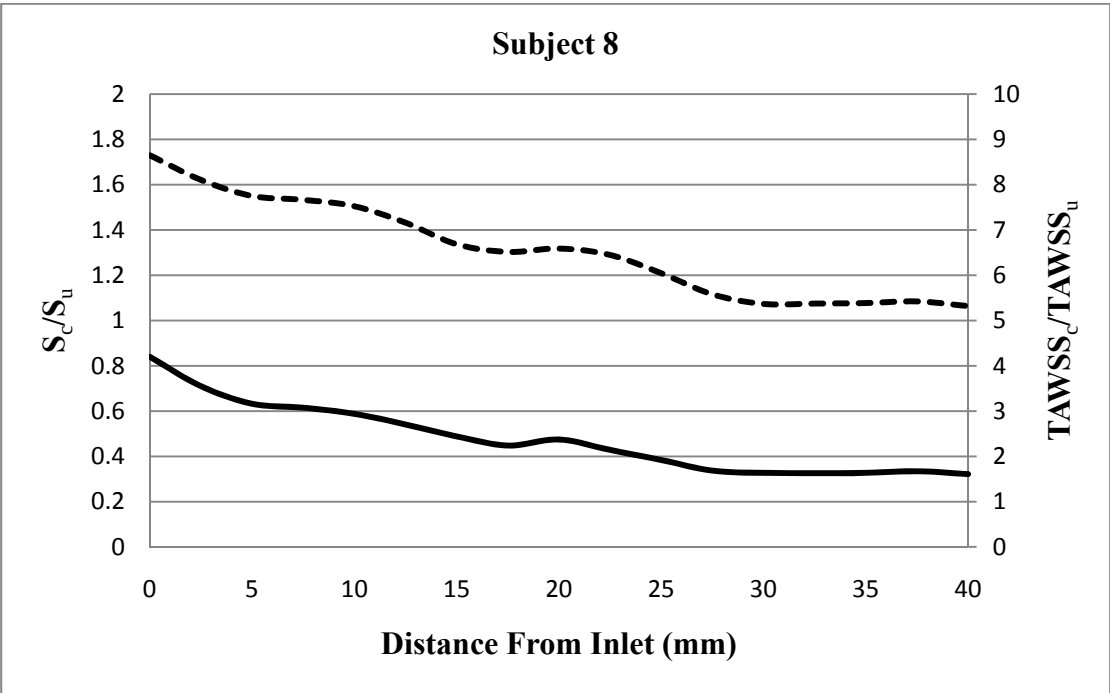
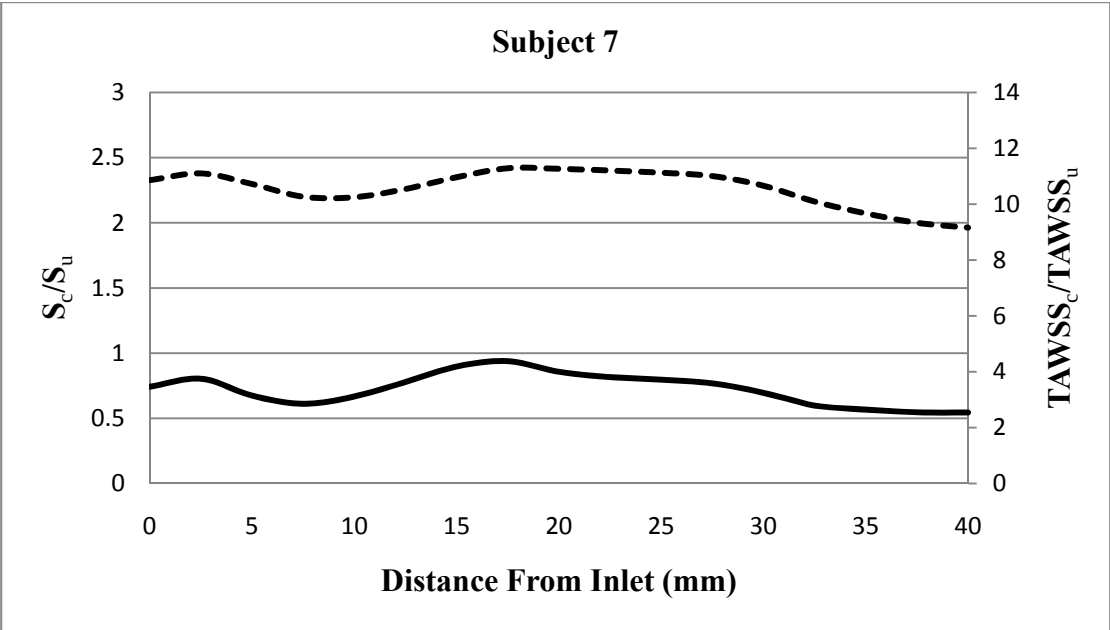
where V_u and V_c are the volumetric flow rates, and A_u and A_c are the cross-sectional areas, before and after compression respectively.

The cross-sectional mean velocity ratio after and before compression, as well as the corresponding ratio of TAWSS are shown in Figure 5.11. Obviously, the axial variation of the TAWSS ratio followed a very similar trend to that of the mean velocity ratio, suggesting that the correlation between circumferentially averaged TAWSS and mean velocity in MPV is approximately linear. However, the quantitative relationship between mean velocity and TAWSS is subject dependent, since cross-sectional geometry of the MPV, which is highly variable among the subjects, plays an important role in determining WSS distribution.









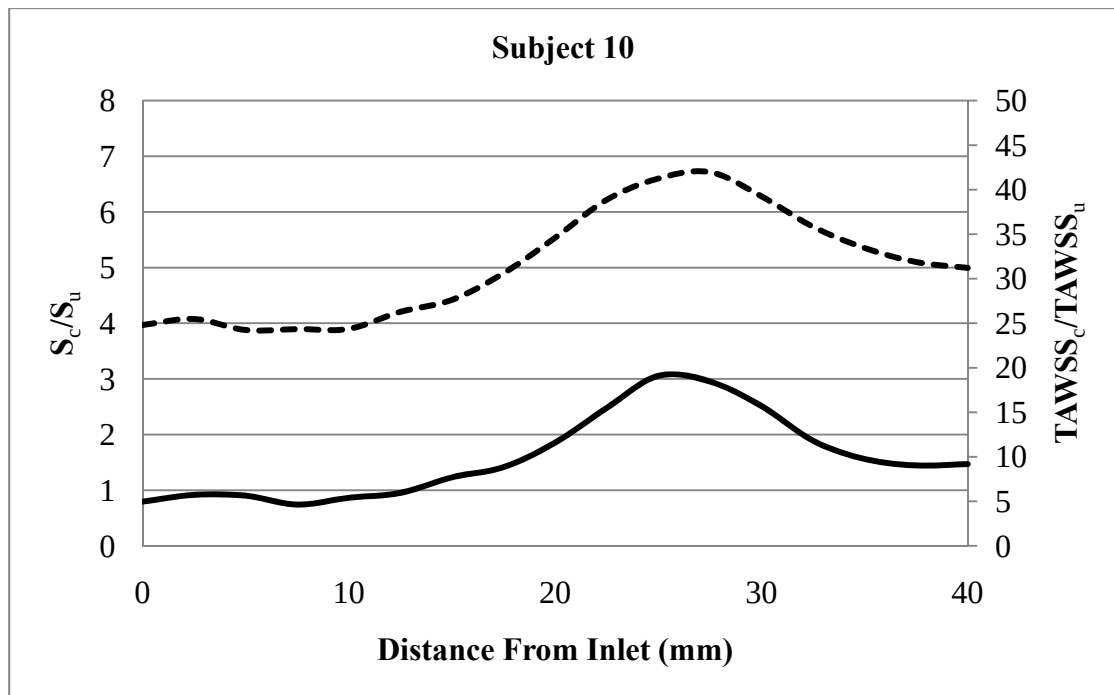
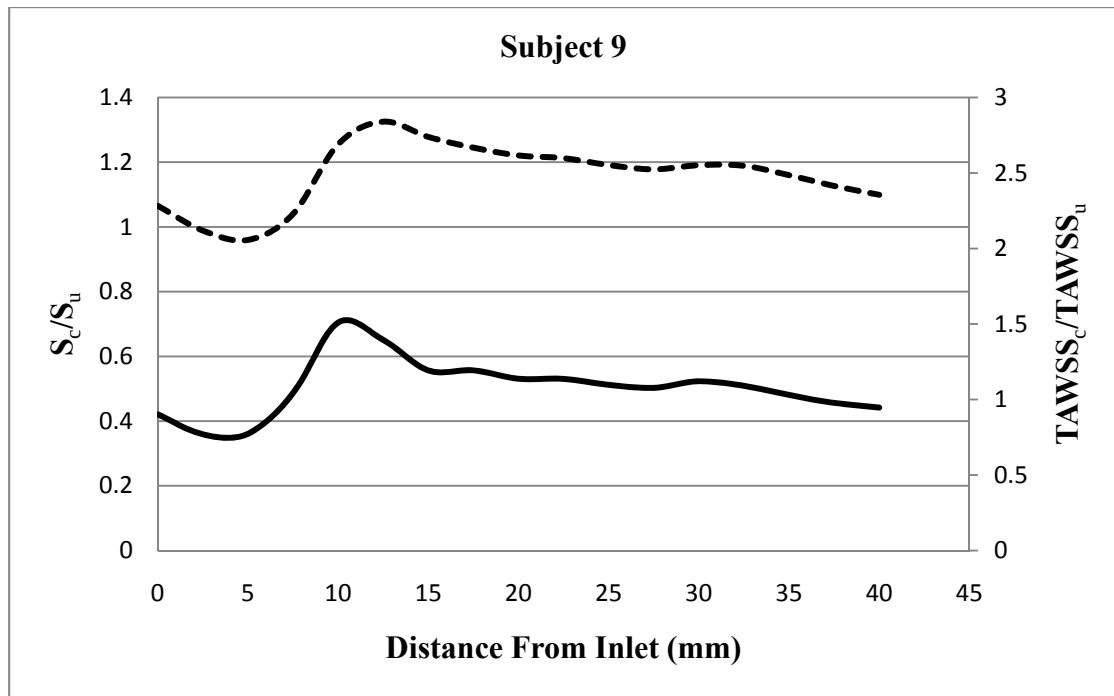


Figure 5.11 Axial variation of the ratio of cross-sectional mean velocity after and before compression (dashed lines), compared with the axial variation of the ratio of circumferentially averaged TAWSS after and before compression (continuous lines).

Variations of circumferentially averaged WSS and cross-sectional mean velocity with time also exhibited high level of linear correlation, as demonstrated by an example shown in Figure 5.12.

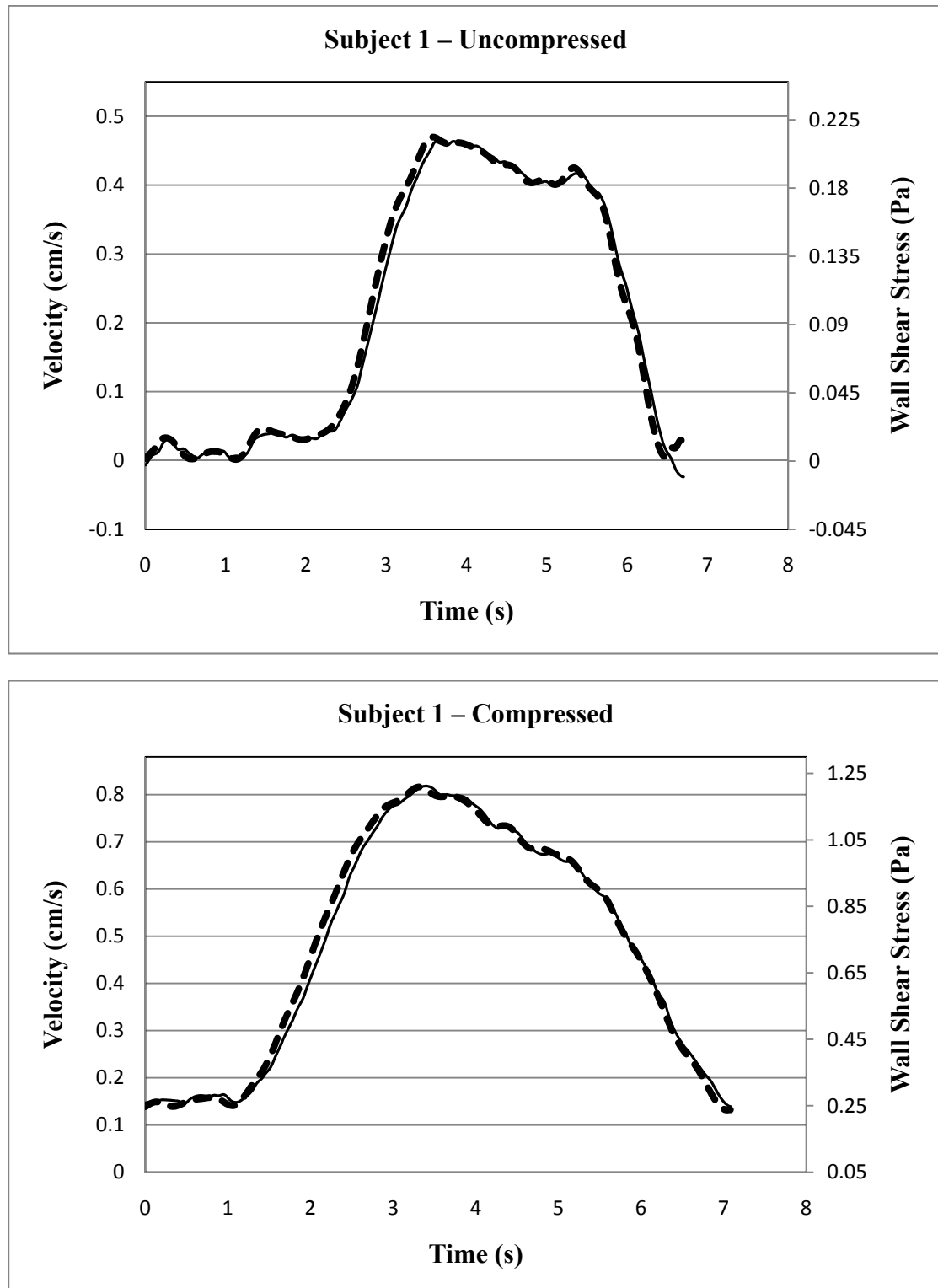


Figure 5.12 Variation of cross-sectional mean velocity (solid line) with time before (top) and after compression (bottom), compared with the corresponding WSS variation (dash line).

5.5 Discussion

In this study, grade 1 compression stockings were employed to investigate the effect of static external compression on flow in the deep veins in the calf. MRI images and flow data were acquired from 10 healthy subjects before and after the application of the stockings. Real-time flow measurement in the deep veins was performed using a newly developed MR phase contrast velocity mapping sequence. The architecture of the deep venous system in the calf is highly variable among subjects. In order to have a common ground for comparison, all the flow data were measured at approximately 5 cm below the popliteal vein bifurcation, but only the medial peroneal vein (MPV) which is larger than the other deep veins at the same location, was chosen for detailed flow and wall shear stress analysis. Because observations from the acquired real-time phase-contrast images suggested that there was hardly any change in the shape and size of the veins during a respiratory cycle especially when the compression stocking was on (an example is shown in Figure 5.13&5.14), a CFD model with rigid wall was employed for the flow analysis. A similar study was performed by Downie et al [113], but the corresponding venous flow data were estimated from Doppler ultrasound measurement made in the popliteal and great saphenous veins above the level of the stocking, which was the main limitation of the study as stated by the authors. The present study is an improvement over the previous study in that real-time flow measurements in the reconstructed deep vessels within the calf were made and used in the subject-specific analyses of flow and wall shear stress.

A reduction in femoral vein flow rates as a result of static external compression was observed in previous studies [178, 179]. In this study, compression stocking reduced the flow rate in MPV in 6 out of 10 subjects, with the mean (and median) MPV flow rate being reduced by 7%. The effect of compression on flow rate in other veins in the calf was not evaluated since accuracy of flow measurement could not be guaranteed for veins that are non-perpendicular to the imaging slice and for small veins due to insufficient spatial resolution. Although it is expected that the total flow rate in the calf veins would remain unchanged after compression, the effect of compression on the deep and superficial systems could be different. For cases where compression reduced the flow rate in the deep veins, it is possible that more venous flow was

carried by the superficial system. In a previous study where the effect of elastic compression on vessel deformation was evaluated for both the superficial and deep veins, it was found that the mean cross-sectional area reduction was greater in the deep veins (64%) than in the superficial veins (39%) after the application of a flight stocking [18].

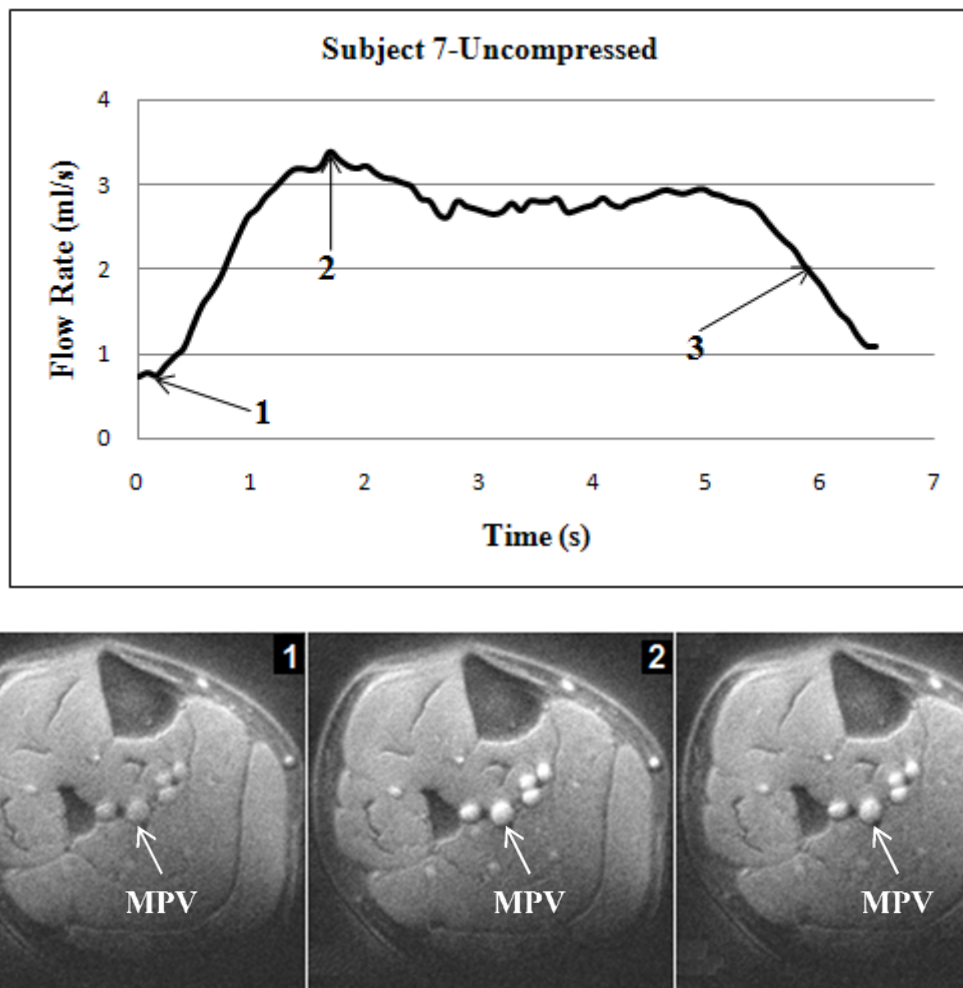


Figure 5.13. Anatomical MR images at different time points of the diaphragmatic controlled breathing cycle generated by using the real-time phase contrast velocity mapping sequence without compression stocking. MPV: Medial peroneal vein.

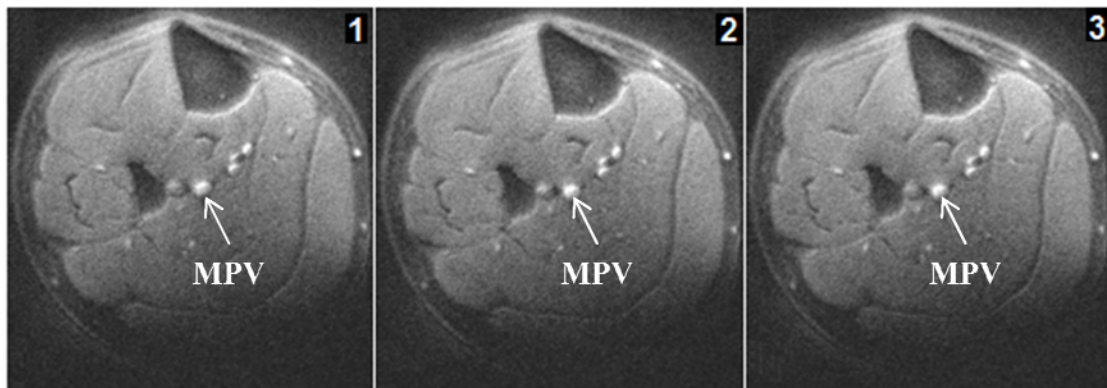
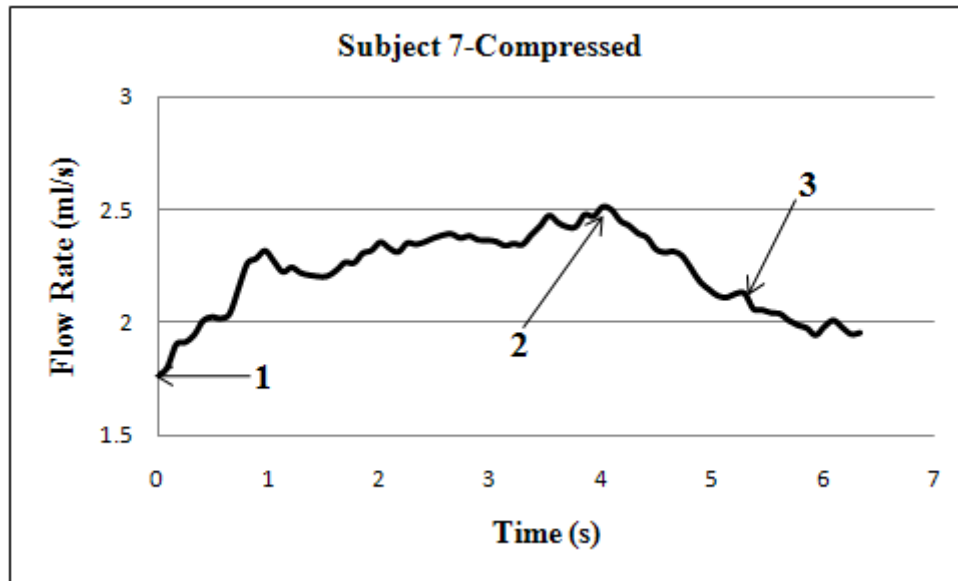


Figure 5.14. Anatomical MR images at different time points of the diaphragmatic controlled breathing cycle generated by using the real-time phase contrast velocity mapping sequence with compression stocking. MPV: Medial peroneal vein.

The measured waveforms of subjects 5 and 10 suggested the presence of significant reverse flow in the deep vein before compression. It is interesting that subjects 5 and 10 also showed the largest volume reduction among the 10 subjects. The collapse of the deep vein induced by the application of the stocking ceased when a balance between the external and internal pressure was resumed. Increase in the local blood pressure caused by external compression has been found in human calf arteries [180, 181] and femoral veins of dog [178, 179]. The implication of the information is not quite straightforward, but it is possible that under the same external pressure profile, the internal pressure of the deep veins should rise to a similar magnitude after compression, suggesting that the vessels experiencing larger deformation might have

lower internal pressure before compression. Although dysfunction of the venous valve at the measurement location could be a reason, considering the age and the medication history of the subjects, and the elimination of the reverse flow after the application of the compression stocking, this would be highly unlikely. Perforator veins can induce disturbances to the flow, but none of them was observed at the velocity measurement location. However, the observed architecture of the deep venous system was highly variable. At a short distance from the location where velocity measurement was taken, overlapping of small veins with the MPV was recorded. It is possible that these small branches, either leaving or joining the MPV, provided an alternative path for the venous flow, which might have led to the observed retrograde flow at the measurement section.

Since the cross-sectional area reduction of the deep veins, in response to the application of the stocking, outweighed by far the reduction in venous flow rate, the overall effect of compression was to increase blood velocity in the deep veins. In a previous study of four subjects, it was found that the application of the compression stocking reduced the level of pulsatility in the velocity waveform and increased the time averaged blood velocity in the popliteal veins [113]. In the present study, results for the MPV of ten subjects showed that mean velocity was increased in nine subjects and the pulsatility of the waveform was reduced in only six subjects (two examples are shown in Figure 5.15). The influence of external compression on increasing the deep venous blood velocity was consistent with the previous findings, but its effect on the pulsatility was not as significant as indicated before.

It has been demonstrated that DVT mostly arises in calf veins where most of the venous valves are located and is usually initiated from a venous valve pocket. In these susceptible areas, the venous flow is slow and eddies are present. Previous studies have shown that a steady and high level of wall shear stress is important for the health of the vascular system [16, 17, 169, 170]. In this study, the application of the static compression stocking increased the wall shear stress (WSS) in MPV in nine out of ten subjects and by an average of 398% (median 98%). The general trend is consistent with the previous study [113], although the latter overestimated the increase in WSS by assuming there was no change in flow rate before and after compression owing to the lack of direct measurement of flow rate in the deep veins.

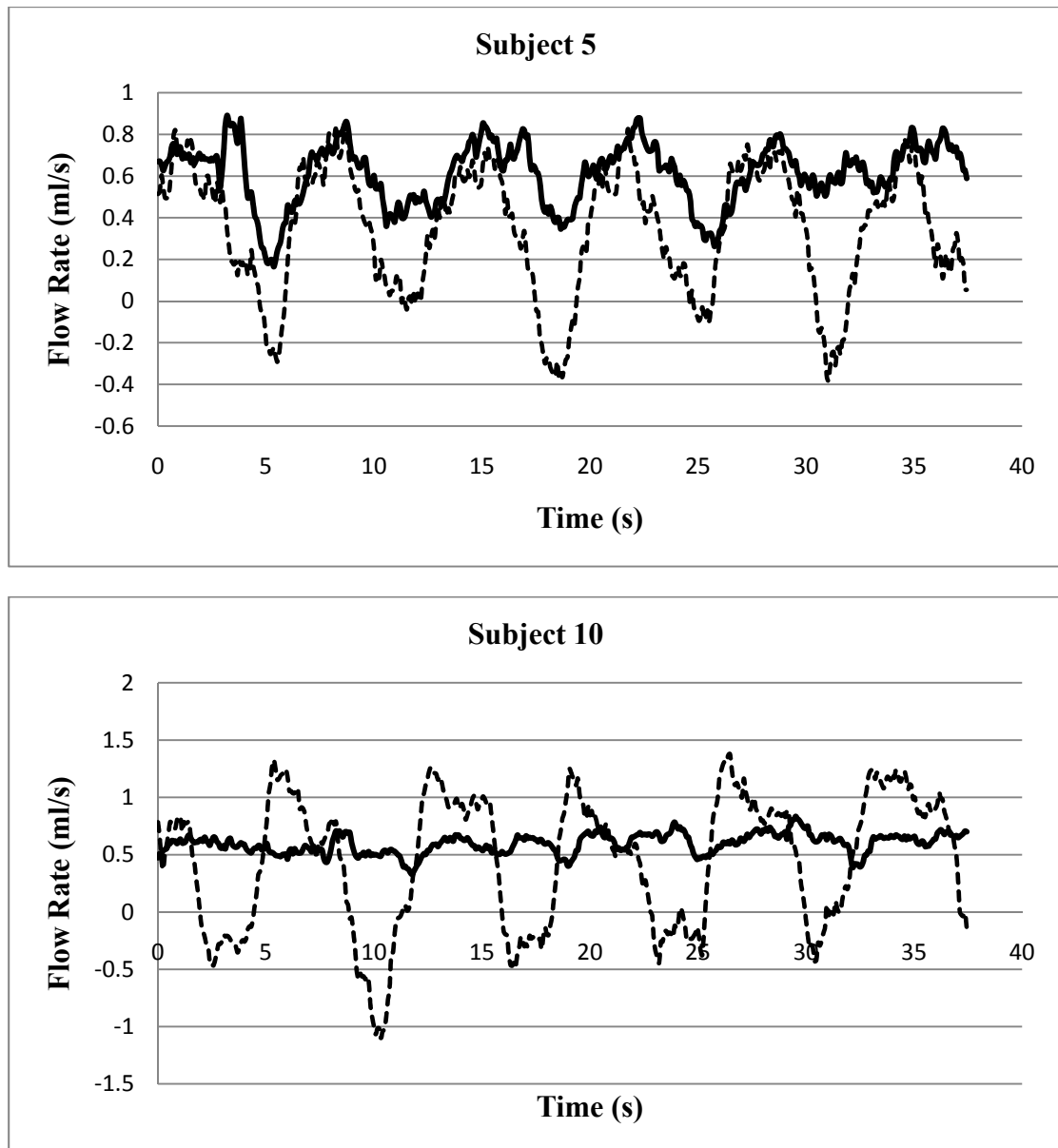


Figure 5.15 Measured blood flow waveforms of 2 subjects before (dashed lines) and after (continuous lines) compression. In both cases, an increase in the time averaged velocity and a reduction in the waveform pulsatility were induced by the external compression.

While the overall results showed that the application of the stocking led to positive influences on the venous flow, the magnitude of the effect was highly variable among subjects. Disregarding the subject on whom the stocking generated a negative effect, the increase in time-averaged WSS ranged from 7% to 1934%. The reconstructed geometry of the MPV before and after compression showed that the deformation of the MPV as a result of the static external compression was also very subject-

dependent. Although the selection of the location of the reconstructed segment was based on the same anatomic landmark, other factors such as the shape and location of the bones, the architecture and mechanical properties of the muscles and other soft tissues, are highly variable and can significantly affect the deformation of the deep veins, which will in turn affect the flow rate in the deep veins. All these factors act together to influence the level of WSS experienced in the deep vessels.

Although the time-averaged WSS distribution is highly variable among subjects, our flow analysis showed that variations of circumferentially averaged WSS followed those of the cross-sectional mean velocity almost linearly. This was because the Reynolds number of the flow was low (<200) and the Womersley parameter was also low ($1\sim 2$), so that blood flow in the MPV under the conditions examined was quasi-steady, and behaved like fully developed laminar flow although the effect of local geometrical features (such as non-circular cross-section and curvature) was still present.

5.6 Summary

In this study, ten subjects were involved in the investigation of the effect of grade 1 compression stocking on deep venous flow. All the subjects were scanned in supine position, and performed diaphragmatic breathing during the MR flow measurement. Our combined MR imaging and computational fluid dynamics analysis showed that the application of the stocking resulted in an average of almost 4-fold increase in wall shear stress in the medial peroneal veins. Although the magnitude of the effect was highly variable among subjects, the results demonstrated the positive influence of the stocking on deep venous flow in the calf.

Our results also indicated that reduction of the deep vein volume was an important consequence of the application of static external compression, which led to a higher blood velocity even though flow rate in the medial peroneal veins reduced by an average of 7%. Given the significant individual variability found in this study, it would be desirable to refine the procedure used to select a suitable compression stocking for a given individual and increase the sizes and ranges of stockings available in order to optimise their therapeutic effects.

Chapter 6

Fluid-Structure Interaction Analysis: the Effect of Compression on Blood Flow in the Deep Vein and its Deformation

6.1 Introduction

In this chapter, a three-dimensional fluid-structure interaction model is developed to analyze the responses of the soft tissues and deep venous system to external compression. The two-dimensional structure analysis described in chapters 3 and 4 has demonstrated the potential of using finite element analysis (FEA) to predict the mechanical responses of calf tissues to static compression, but there are still uncertainties about the validity and accuracy of two-dimensional FEA of objects which actually have a three-dimensional structure.

In chapter 5, the CFD analysis based on MR images has provided detailed information about the hemodynamic conditions in the deep veins before and after static compression. This methodology can be employed as a useful tool in evaluating designs of compression stockings. However, there is still a disconnection between the biomechanical parameters which are directly implicated in the biological pathways of venous thrombosis, such as hemodynamic wall shear stress, and the mechanical parameters of the compression devices. A methodology capable of coupling the FEA and CFD analysis is expected to provide a useful tool for the investigation of dynamic interactions between the compression devices and deep venous system.

In this chapter, a preliminary investigation of the potential of fluid-structure interaction model to predict the influences of external compression on deep venous system is presented. The material properties evaluated using different two-dimensional finite element methods (FEM) were employed to describe the mechanical behaviour of the three-dimensional solid domain. In a previous study, Avrial et al. [150] used a numerical approach based on image processing to determine the elastic

properties of calf tissues. The estimated material function was compared with the hyperelastic model developed in chapter 4. This analysis aimed at investigating the role of solid material properties in the FSI simulation and evaluating the capability of material properties estimated using 2D FEM to represent a three-dimensional structure.

The geometry employed in the model was reconstructed based on MRI images. Due to the high complexity of the architecture of the deep vessels, the deep vein in the model was generalized. The solid domain representing the calf tissues was discretized using a finite element method, while the blood flow was assumed to be Newtonian and governed by the Navier-Stokes equations. An Arbitrary Lagrangian Eulerian method was used to capture the interaction between the structure and fluid.

Because the external compression was applied within a much shorter period of time compared to the breathing cycle, instead of pulsatile waveforms, a time-averaged volume flow rate was applied to the vessel inlet. Although variable pressure distributions around leg were observed even when using a uniform compression [15], due to the lack of the measured information, a uniform pressure profile was employed as the external load.

A properly validated model of this type would offer a potential methodology for investigating the prototype of compression devices, including both compression stockings and intermittent compression device. Furthermore, revelation of responses of venous system to compression without knowing the deformed venous cross-sectional geometry as a prior condition can significantly reduce the reliance on MRI.

6.2 Theory

In computational fluid dynamics (CFD) analysis, the fluid domain is usually discretized using a finite difference, finite element or finite volume method in an Eulerian frame where the mesh point is fixed in space (Figure 6.1). This approach is efficient for solving flow problems with fixed boundaries, but difficulties arise when moving or deformable interfaces are involved, such as flow in collapsible tubes, and flow around heart or venous valves. In order to simulate moving interfaces, in particular the interface between a fluid and elastic solid, a number of techniques have been developed.

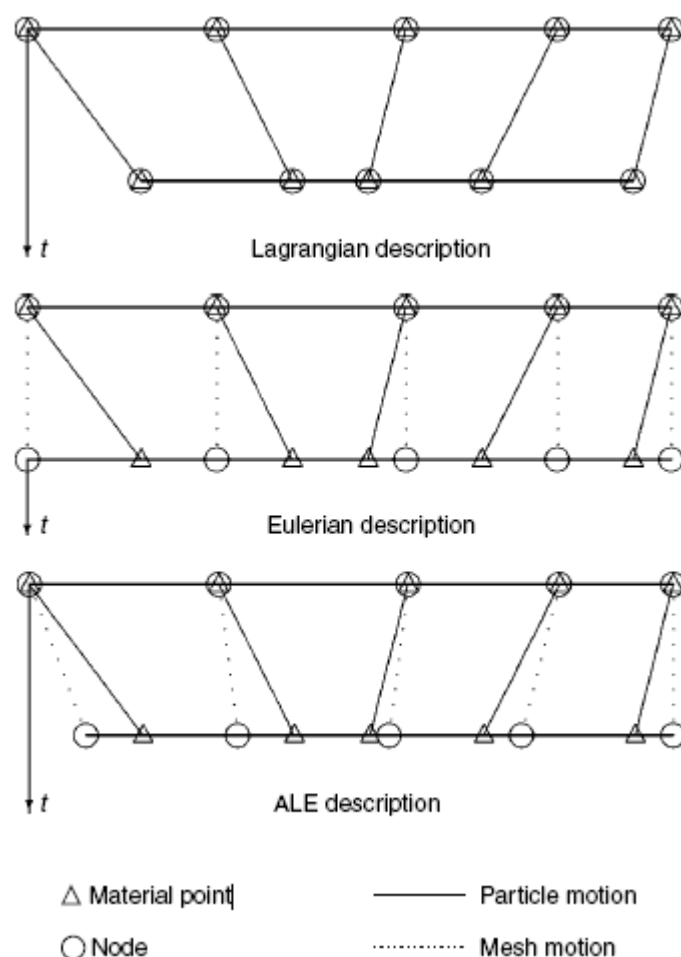


Figure 6.1 One-dimensional example of Lagrangian, Eulerian and ALE mesh and particle motion [182].

As one of the most widely used methods for fluid-structure interactions (FSI), the Arbitrary Lagrangian Eulerian (ALE) method [143, 144] allows arbitrary motion of

the mesh points inside the domain to optimize the shapes of elements (Figure 6.1). When applying ALE method to a multi-material system, the mesh points on the boundaries or interfaces can move along with material domain to track the boundaries or interfaces. In FSI problems, the solid domain and the fluid mesh point at the fluid-solid interface are moved following a Lagrangian algorithm (Figure 6.1). Due to its easy implementation, low computational cost and high accuracy, the ALE method is recommended whenever possible. Although the degree of freedom for mesh movement provided by the method allows distortions of the continuum, when translations and rotations of the solid are very large or the mesh points display inhomogeneous movements, elements of the fluid domain may become ill-shaped, which can lead to a reduction in the solution accuracy or cause problems in convergence. Remeshing is a common method of dealing with such conditions, but it is a very complicated and time consuming process. In addition, the mapping of solution from the degenerated mesh to the new mesh may introduce artificial diffusion, causing loss of accuracy.

Unlike the ALE method which accurately captures the FSI interface, the immersed boundary method [145, 183] first evolved from the field of finite difference generates solutions without changing material continuum boundaries. In this method, the boundary of solid domain is expressed as a set of non-conforming points immersed in the fluid and mutually interconnected by an elastic law. The FSI interactions are represented by imposing a body force from the solid boundary points to the fluid and the velocity at each solid point is coupled to the fluid velocity at the same position. Actually, the introduction of body force has become the basic idea behind several non-boundary-fitting FSI methods.

Another method that is very similar to the immersed boundary method is the fictitious domain method [147, 184], which was first developed within a finite element framework. A (distributed) Lagrange multiplier is used to establish constraint of the fluid and solid domain at their interface, which is extended to the inner body. The application of the multipliers in the weak form, representing the body forces, leads to a distributed manner using an integral formulation in which the forces are imposed. Although having the capability to simulate large solid deformations, non-boundary-

fitting methods as immersed boundary and fictitious domain method have a reduced accuracy for the solution near the fluid–solid interface due to interpolation errors.

6.3 Details of the FSI Model

The three-dimensional geometry was reconstructed by using MR images. According to the clarity of the images, a section of calf with a length of 12 cm was rebuilt. The geometries of tibia, fibula and soft tissues were segmented from MR images acquired without the compression stocking using the protocol described in chapter 5. Due to the complexity of the deep veins architecture, it was not considered possible to attempt an accurate reconstruction of deep vein geometry. An idealised vessel with a circular cross-section was placed in the model to represent the deep vein.

Owing to the irregular nature of the solid domain, an unstructured mesh of tetrahedral elements (Ansys element ref: solid185) was generated, which was refined near the vein, as shown in Figure 6.2. The fluid domain was divided into hexahedral structured grids. All the mesh was generated using ICEM CFD (ANSYS Inc.). Refining the mesh from 150, 061 nodes to 311,786 nodes produced a difference of 0.0015% in term of stress intensity. According to the results, it was decided that a mesh density corresponding to the 150, 061 nodes mesh was sufficient. Spatial discretization of the Navier-Stokes equations was performed via a hybrid 1st/2nd order scheme. The solid part was moved in a Lagrangian manner, while the fluid domain followed an arbitrary Lagrangian Eulerian algorithm except the points at the fluid-solid interface, which followed a Lagrangian algorithm. A two-way implicit fluid-structure interaction (FSI) coupling was employed.

Since previous investigations presented in chapters 3 & 4 have demonstrated the advantage of hyperelastic model over linear elastic model in reproducing the structure behaviour of calf tissues, two different hyperelastic models were employed to describe the elastic properties of calf muscles in the FSI model. These include the three-parameter Mooney-Rivlin, hyperelastic material model adopted in chapter 4, and a Neo-Hookean strain energy function adopted by Avril et al. [147], which is expressed as follows:

$$W = C_{10}(I_1 - 3) + K_v[(J_2 - 1)/2 - \ln(J)] \quad (6.1)$$

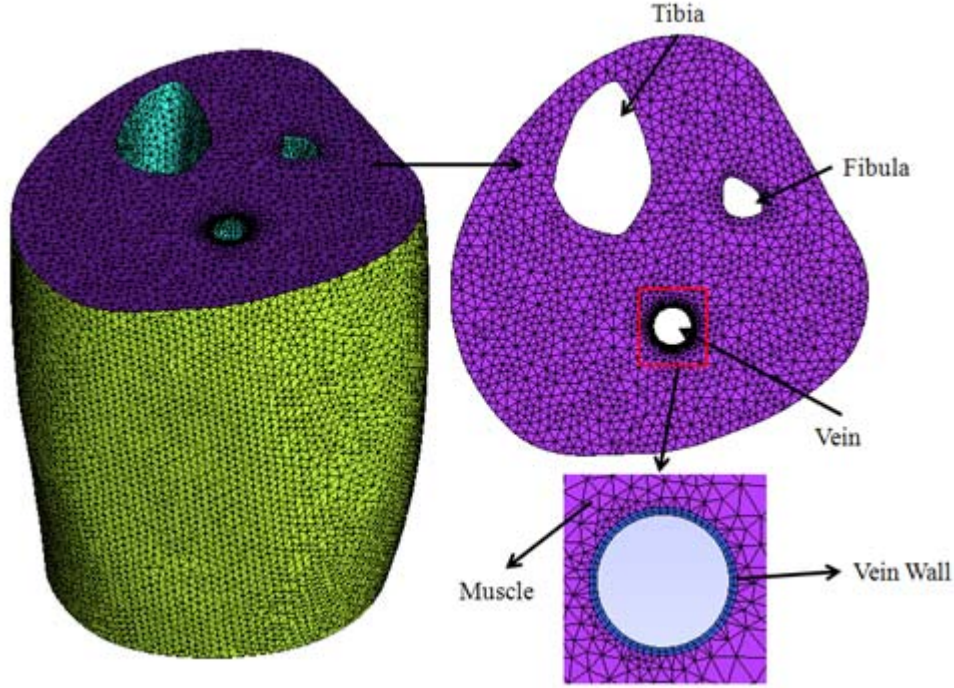


Figure 6.2 Solid mesh generated by ICEM CFD.

where $J = \det(F)$ and $I_1 = J - 2\text{Tr}({}^t F.F)/3$ with F being the deformation gradient and Tr the trace of a matrix. $2C_{10}$ is the initial shear modulus and K_v is the initial bulk modulus. Avril et al. [150] obtained values for C_{10} and K_v by minimizing the distances between selected landmarks shown in the MR images and simulated results, and found these to be 89.6 KPa and 69.5 KPa, respectively.

The deep vein wall was governed by a linear elastic model. A Young's modulus of 0.133 MPa was applied to the vein wall, which was assumed to be nearly incompressible with a Poisson's ratio of 0.49 [14]. Because no accurate data for deep venous wall thickness was available, a wall thickness of 1 mm within the reported range of saphenous vein wall thickness in the leg ($1.05 \pm 0.2 \text{ mm}$) [185] was employed, giving a wall/lumen diameter ratio of 0.09. The tibia and fibula were treated as rigid and incompressible and therefore, the elements attached to the bone were fixed in the space.

With regard to the pressure load, according to the manufacturer's instruction (T.E.D.TM Covidien Inc.), an 18 mmHg external pressure should be generated at the

knee. In a recent study [15], the measured pressure distributions produced by different types of intermittent compression devices demonstrated that although the bladder were designed to generate a uniform compression, the pressure distribution could be affected by the limb geometry. The measurements showed that the pressure increased with the calf diameter and the highest pressure was found at the middle of the calf where external pressure could be 5~36% higher than that at the knee [15].

Because the reconstructed section corresponds to the middle part of the calf and the responses of deep venous system to large deformations of surrounding tissues was one of the objectives of this study, the uppermost reported pressure increase was employed. Therefore, a 25 mmHg pressure was applied to the outer surface of the calf as the external load. The initial geometry was reconstructed from the MR images without the presentence of compression stocking, and the external pressure was applied gradually from 0 to 25 mmHg within 1 sec.

Blood was modelled as an incompressible Newtonian fluid with density 1060 kgm^{-3} and viscosity $3.5 \text{ mPa}\cdot\text{s}$. Reynolds number was in the laminar flow regime (<200) for all simulations so the assumption of laminar flow was adequate. Because the period of load application (1 sec) was much shorter than the diaphragm-dominated respiration cycle (6 sec), a constant volumetric flow rate scaled according to the cross-sectional area ($A_{\text{FSI}} : A_{\text{MRI}} = 1.12 : 1$) was applied to the inlet. A pressure of 10 mmHg within the reported range (2-15 mmHg) [186] was applied to the outlet and a no-slip condition was applied to the fluid at the FSI interface. A uniform time-step of 0.01 sec was specified for the FSI simulation.

6.4 Results and Discussion

6.4.1 Analysis of Stress and Displacement

In the FSI model, two different hyperelastic models, Mooney-Rivlin model (M) and Neo-Hookean model (N), were employed to describe the elastic behaviour of calf tissues. The parameters of the Mooney-Rivlin model were identified using the finite element method based on a non-rigid registration procedure developed in chapter 4. The parameter values of the Neo-Hookean model were extracted from the literature [150].

The simulated displacement distributions of the solid domain are shown in Figure 6.3. The FSI model with Mooney-Rivlin function representing the solid domain (FSI with M) generated larger deformation than the FSI model with the Neo-Hookean function describing the solid domain (FSI with N). Under the same level of external load, the deformation of the solid domain was dependent on the material properties. Compared to the Neo-Hookean model, the lower stiffness of the Mooney-Rivlin model led to a larger deformation.

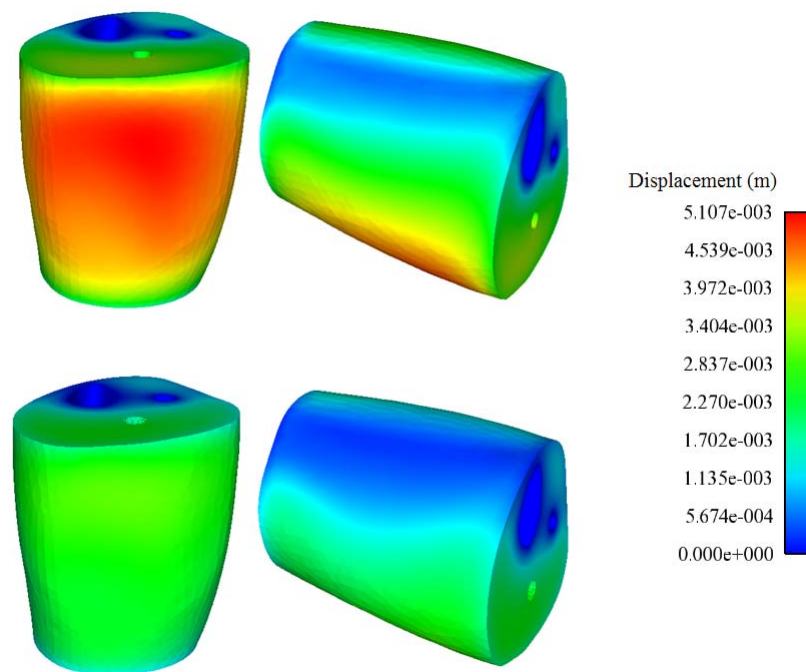


Figure 6.3 Displacement distributions of solid with hyperelastic properties under external compression: FSI with M (upper) & FSI with N (lower).

The high level of rigidity of the bones obviously imposed a certain level of restriction on the deformation of their surrounding tissues. Similar to the measured results of the two-dimensional transverse section, the region between the tibia and fibula underwent smaller deformations than the other part of the calf. The back of the calf, whose boundary was the farthest from the bones showed the largest displacements. In addition, the influence of external compression declined as it was transmitted deep into the tissue.

The simulated displacement distributions of the deep vein wall are shown in Figure 6.4. The spatial-average hydrostatic pressures on the vein wall predicted by the FSI models were 5.83 KPa (FSI with M) and 3.39 KPa (FSI with N), respectively. Consequently, the deep vein volume reduction generated by the FSI with M (25%) was 35% larger than that generated by the FSI with N (19%). However, the volume reductions predicted by both models were much smaller than that derived from the MR images (58% for MPV). A previous investigation of the muscle mechanical properties [40] showed that the stiffness of skeletal muscle was higher in the cross-sectional direction than the axial direction. Therefore, using 2D FEA based on a transverse section of the calf might have overestimated the stiffness of calf tissues in three dimensions.

Unlike the observations from the MR images, which showed significant collapse of the deep vein, in the FSI simulation, the vein wall generally maintained its shape while its cross-sectional area was reduced (Figure 6.5). The idealized circular shape of the deep vein might be one of the reasons for this phenomenon. According to the ‘tube law’, an elastic tube is more capable of maintaining its shape when it’s circular. The difference in the initial geometry of the deep vein might cause different levels of resistance to the external pressure. The difference between the simulated and measured results in terms of hydrostatic pressure distribution on the vein wall might also be responsible, but due to the lack of experimental data, the influence of this factor remained unclear.

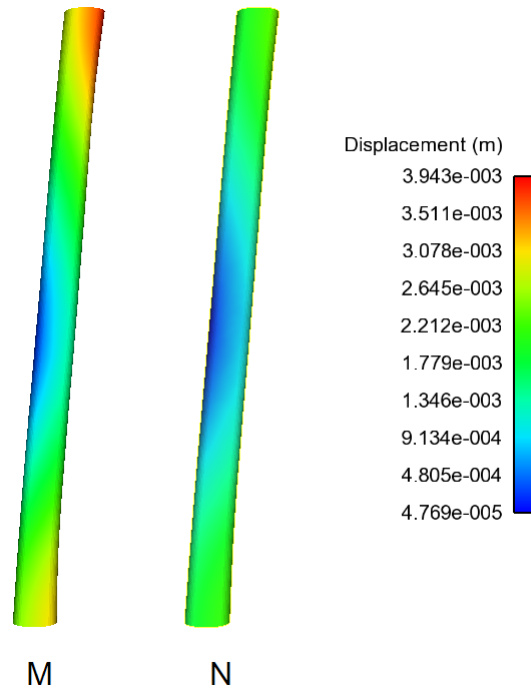


Figure 6.4 Displacement distributions of deep vein wall after compression simulated by FSI model: M-FSI with M, N-FSI with N.

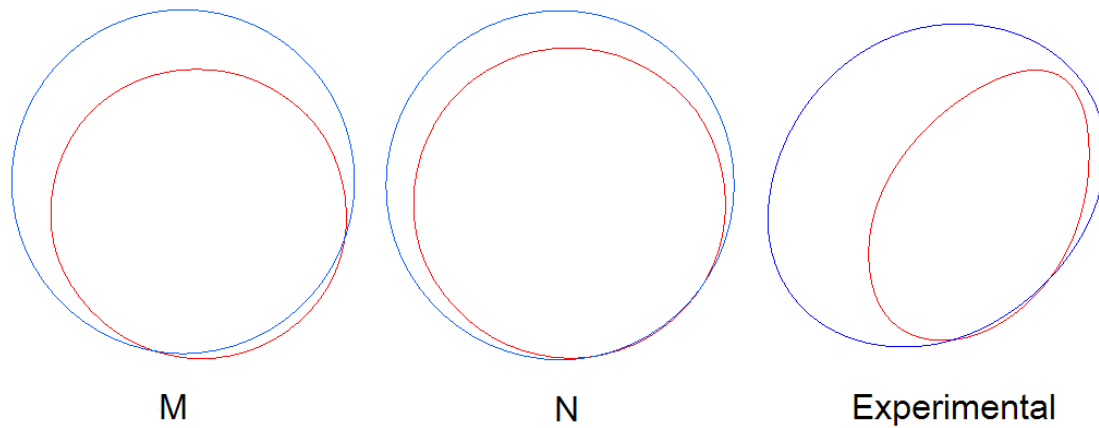


Figure 6.5 Geometries of deep vein cross section boundaries before (blue) and after (red) compression: M - FSI with M, N - FSI with N, Experimental – segmentation contours from MR images.

6.4.2 Flow Analysis

The calculated transient variation of spatial-average wall shear stress (SAWSS) is shown in Figure 6.6. As the external pressure rose from 0 to 25 mmHg, the simulated SAWSS also increased. Since the volumetric flow rate applied to the FSI model was

constant, the reason for the increase in wall shear stress was due to the reduction in deep vein cross-sectional area as a result of compression. The deformation of the deep vein is strongly influenced by the difference between its external and internal pressure (i.e. transmural pressure). Apparently, the higher level of hydrostatic pressure generated by the FSI with M led to a larger cross-sectional area reduction, hence slightly higher wall shear stress than the FSI with N model. The SAWSS showed a non-linear relationship with the external compression. Considering that under small deformations of calf tissues, the hydrostatic pressure generated on the vein wall was almost linearly related to the external pressure according the FEA, the change of the internal blood pressure and tension of the vessel wall might be the reasons for this.

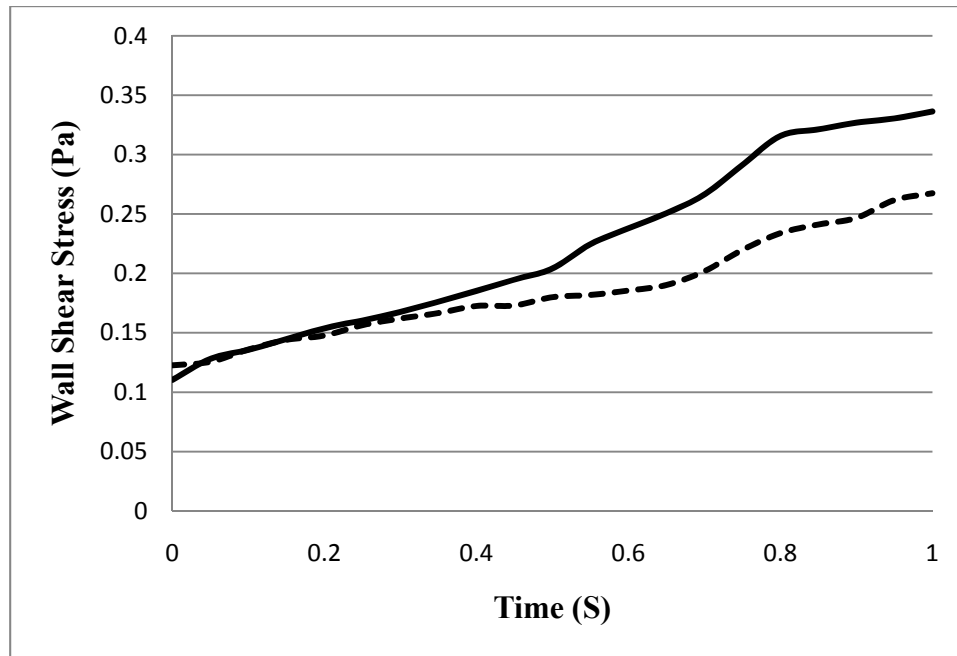


Figure 6.6 Variation of spatial-averaged wall shear stress with time: FSI with M (solid line), FSI with N (dashed line).

In correspondence to the area reduction, the FSI with M produced an increase rate $((SAWSS_c - SAWSS_u) / SAWSS_u)$ of 205% in terms of SAWSS, while the FSI model using the Neo-Hookean constitutive relation produced an increase of 145%, both of which were lower than the corresponding CFD analysis (337%) presented in chapter 5.

Despite the magnitude, the WSS distributions generated by the two models (Figure 6.7) are quite similar. The regions with high level of WSS corresponded to the calf region that had relatively large deformations. The lower part of the vessel, surrounded

by less calf tissues than the upper part, showed lower magnitude of WSS. It has been suggested that at the ankle where bones had a relatively large volume compared to the other tissues, and as a result, a higher magnitude of pressure was required for the collapse of the veins [187]. In the calf, the load transmission of external compression was achieved through the muscles and could be retarded due to the presence of the bones.

Comparison of the FSI simulation results showed that the WSS distribution generated by the FSI with N was less variable than that generated by the FSI with M. This is very likely caused by the difference in the stiffness calculated by the hyperelastic models. The soft tissues properties described by the Neo-Hookean model showed higher stiffness, which reduced the deformation of the vessel.

Compared to the simulation results of the FSI models, the WSS distributions from the CFD analysis showed higher level of variation (Figure 6.8). The reason for this is that in the CFD analysis, a pulsatile flow was applied, but in the FSI simulation, the time averaged volume flow rate was employed. Furthermore, the vessel generally maintained its regular circular shape during the deformation simulated by the FSI model, while the CFD analysis showed significant collapse of the vein, which enhanced the variation of WSS distribution [177].

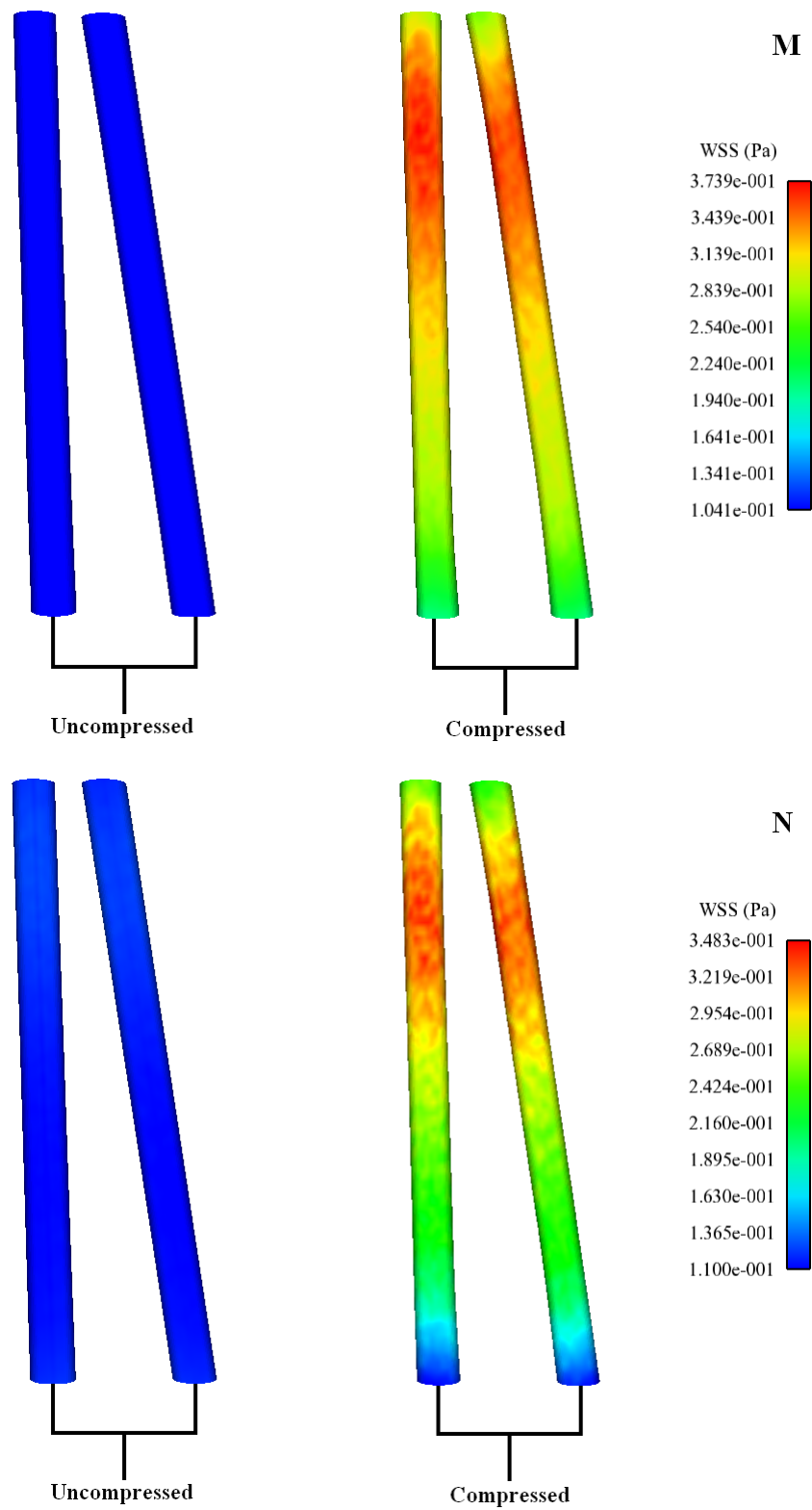


Figure 6.7 The simulated wall shear stress distributions. M-FSI with M, N-FSI with N.

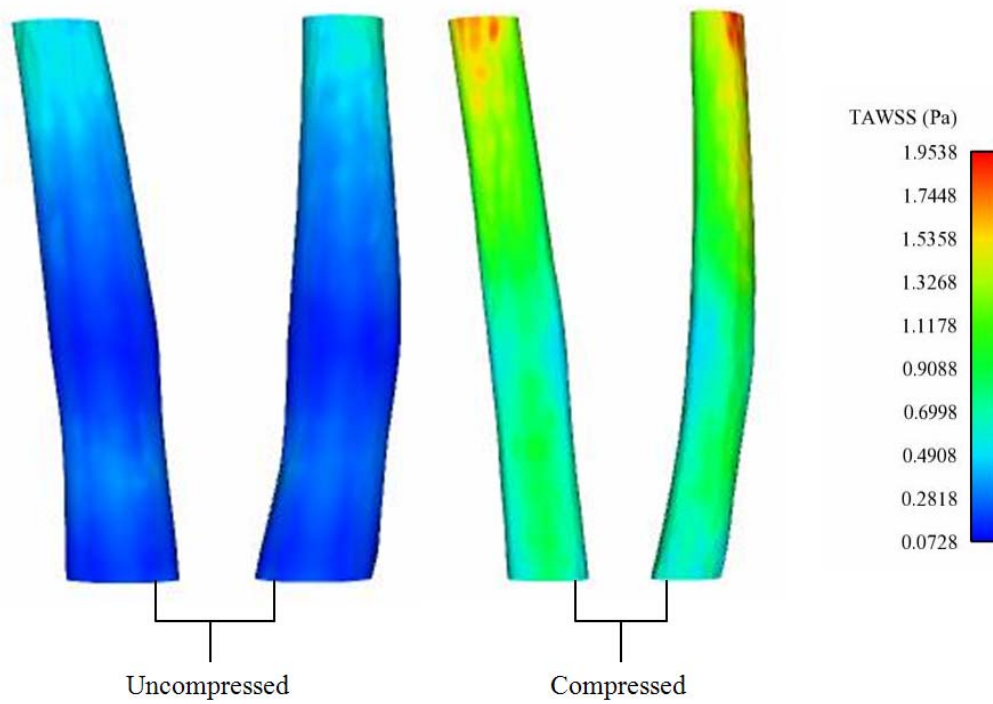


Figure 6.8 Wall shear stress distributions generated by the CFD analysis with rigid walls.

6.5 Summary

FSI simulations incorporating two different hyperelastic models for the calf tissues were performed. Compared to the Neo-Hookean model, the Mooney-Rivlin model with lower level of stiffness produced a higher hydrostatic pressure around the deep vein, which led to larger deep vein collapse. However, in comparison with the measured results from the MR images, both FSI models underestimated the deformation of the deep vessel. This could be due to a number of reasons, including simplification of the calf tissues as a homogeneous material, overestimation of the stiffness of the calf tissues using two-dimensional FE methods, and representation of the deep vein as a straight circular tube.

Compared to the FSI model with N, the FSI with M model produced a higher increase in SAWSS, which is in better agreement with the results of CFD analysis based on realistic geometry and flow data. The haemodynamic changes within the deep vein were strongly influenced by the deformation of the vein wall. When the volumetric flow rate was kept the same, the increase in wall shear stress was dependent on the volume reduction of the deep vein.

The purpose of the study presented in this chapter is to demonstrate the potential of FSI model to simulate the responses of soft tissues and deep venous system of calf to the external compression. A validated FSI methodology which is capable of mimicking the dynamic interactions between the external compression and deep venous system, and predicting the influence of compression devices without MR data after compression will have great advantages over the CFD analysis alone in the design optimization of compression devices.

Chapter 7

Conclusions and Recommendations for Future Work

7.1 Conclusion

Deep vein thrombosis (DVT) is a common post-operative complication, and a serious threat to the patient's general recovery. In recent years, there has been an increasing awareness of the risk of DVT in healthy individuals after prolonged immobility. Mechanical methods of DVT prophylaxis, such as elastic compression stockings, have gained widespread acceptance. Although it is generally understood that compression stockings function by causing the deep veins to partially collapse, thereby increasing venous blood velocity, there is a lack of detailed knowledge about the quantitative effects of external compression and how these may vary among individuals. Therefore, the aim of this study was to explore the use of computational modelling based on *in vivo* images to quantify the effect of compression on the deformation of and flow in the deep veins in the calf. For this purpose, magnetic resonance imaging (MRI) was used to provide *in vivo* anatomical and flow data, while both finite element structural mechanics and finite volume-based computational fluid dynamics were employed to perform subject-specific computational analysis.

This work has made unique contributions to the understanding of the effect of elastic compression in the following aspects:

- Evaluation of calf deformations induced by external compression using finite element models with different strain-stress boundary conditions and material functions representing the calf tissues.
- Quantitative analysis of the haemodynamic conditions within the deep venous system before and after compression using computational fluid dynamics (CFD) methods based on MR images and real-time flow information.

- A preliminary investigation of the transient response of deep veins to external compressions using a fluid-structure interaction (FSI) method.

Detailed conclusions drawn in each of the above aspects are summarised below.

7.1.2 Effect of Compression on Deep Vein Deformation

Observations from the MR images showed that the deformations of calf muscles induced by external compression were not uniformly distributed. Among the four muscle components (deep posterior compartment (DPC), anterior compartment (AC), lateral compartment (LC), and superficial posterior compartment (SPC)) of calf, the boundary of DPC had smaller displacements than the other three muscle compartments. Hence, finite element models (FEM) with different strain-stress boundary conditions were built to simulate the mechanical behaviour of the muscles. It was found that by using the plane strain boundary condition on DPC, which restricted its out-of-plane deformation, a better agreement between the simulated and measured results in terms of the displacement and area reduction of deep veins was achieved, as compared to the homogenous plane stress boundary condition. Nevertheless, the area reductions of the two-dimensional transverse section predicted by the FEM were much larger than those recorded by MRI, indicating that the plane stress boundary condition might have overestimated the ‘compressibility’ of the soft tissues caused by displacement of blood and interstitial fluids, and out-of-plane deformation of the muscles. A two-dimensional FEM with plane strain conditions for all muscle groups produced a better agreement with the observed results in terms of area reduction of the calf cross section, but the simulated deep vessel deformation was much smaller than the simulation results with the plane stress condition and MRI measurements. Apparently, compared to the linear elastic model used by the FEM, the *in vivo* mechanical behaviour of the soft tissue showed much higher efficiency in load transmission.

In an attempt to improve the two-dimensional FEM, a hyperelastic material model with adjustable compressibility was investigated. Due to the lack of experimental data on the external pressure distribution, displacements along the model boundary generated by a MRI-based non-rigid registration method were applied to the FEM as a

boundary condition. The simulated relationship between the deformations of veins and bulk modulus of their surrounding tissues showed that the collapse of the deep veins was very sensitive to the compressibility of the calf tissues. For a given displacement along the model boundary, lower compressibility of the tissues resulted in higher area reduction of the deep veins.

By fitting the simulated results to the observed area reduction of deep veins recorded by MR images, the bulk modulus of the calf tissues was derived. Due to large variation in calf structure and muscle stiffness, the evaluated compressibility was quite different among the subjects. The established hyperelastic model was then applied to other cross sections at different positions and a good agreement between the simulated and measured results was produced within a certain distance from the original section. Although the introduction of hyperelastic property improved the predictability of the FEM, there was a significant discrepancy in the deformed vessel geometry. An important drawback of the model was the exclusion of the muscular fascia between which the deep veins are located. The observed result showed that the deep veins always collapsed along the membrane and muscles slid on the membrane. This indicates that the muscular fascia plays an important role in the structural response of the calf to compression. However, due to the lack of understanding of its mechanical behaviour, it was not possible to model it explicitly in the current FEM.

7.1.3 Effect of Compression on Venous Blood Flow

The unique feature of the hemodynamic analysis of deep venous flow was the use of a novel MR phase contrast velocity mapping sequence, which provided real-time flow measurements in the deep veins. This allowed the real effect of external compression on deep venous flow to be incorporated. The results showed that the compression stocking slightly reduced the flow rate in the medial peroneal veins. However, due to the large reduction in deep vein cross-sectional area, the overall effect of compression was to increase blood velocity in the deep veins. Another observed consequence of the application of external pressure was that the venous flow became less pulsatile, but the results varied considerably among the subjects.

Based on the MRI data, CFD analysis of the deep venous flow showed a significant increase in the wall shear stress (WSS). The hemodynamic condition is dependent on the flow rate and vessel geometry, both of which were highly subject-dependent in this study. Although the flow measurement and reconstruction of the geometry were based on the same anatomic landmark, other factors such as the anatomic structure of the calf, the mechanical properties of the muscles and other soft tissues, were highly variable and could significantly affect the deformation of the deep vein, which might in turn affect the flow rate in the deep vessels. Therefore, although the overall results showed that the application of the stocking led to positive effects on the venous flow, the magnitude of the influence was highly variable among subjects.

Analysis of the pulsatile flow simulation results revealed a nearly linear relationship between the circumferentially averaged wall shear stress and the cross-sectional mean velocity. The explanation for this phenomenon was that both the Reynolds number and Womersley parameter of the venous flow were very low, resulting in a quasi-steady flow which behaved like fully developed laminar flow. There was still small magnitude of irregularity, which was possibly introduced by the non-circular cross-section and curvature along the vessel.

7.1.4 First Experience with FSI Modelling of the Calf under External Compression

The combination of MRI technique and CFD modelling provided a useful methodology of investigating the influence of static external compression on the deep venous system. But it is unable to provide insight into the dynamic response of venous flow to intermittent compressions and the reliance of the process on MRI might lead to high cost. A validated fluid-structure interactions (FSI) model has the potential to simulate the dynamic effect of compression devices without relying on MRI scanning of subjects after compression and can be adapted to evaluate all types of compression devices.

The hyperelastic material models derived from the two-dimensional FEM were employed to describe the mechanical behaviour of the solid domain in the FSI model. In consistence with the two-dimensional finite element analysis, the deformation of

the solid domain was strongly dependent on the material stiffness. Under the same external pressure distribution, the calf tissues with lower compressibility showed smaller deformation. However, tissue deformations predicted by the FSI model was smaller than those measured from the MR images. A previous investigation of the muscle mechanical properties showed that the stiffness of muscle was higher in the cross-sectional direction than in the axial direction [40], which provided an explanation for the overestimation of the tissues stiffness evaluated using the two-dimensional method when applied to a three-dimensional structure.

The deformation of the tissues led to changes in hemodynamic WSS in the deep venous system. Due to the smaller reduction in deep vein area, the resultant increase rate of WSS was lower than that calculated from the CFD analysis based on *in vivo* data acquired after compression. A number of simplifications employed in the model may have contributed to the discrepancy between the FSI and CFD analysis. These include the generalization of the vessel geometry and employment of constant volume flow rate instead of measured pulsatile flow waveforms.

The CFD analysis indicated that the influence of compression stocking on the deep venous system was highly variable among different subjects. Therefore, compression devices with a wider range or subject-specific design are expected to be more effective. The modelling framework which coupled the structure analysis of soft tissues and CFD modelling of the venous system has a potential to provide an efficient tool for the optimisation of designs of compression devices. However, it will be necessary to represent the structure and mechanical properties of calf tissues and architecture of the venous system in much greater and more accurate details.

7.2 Recommendations for Future Work

The purpose of this study was to investigate the potential of numerical modelling to investigate the influence of external compression on deep venous system. The development of computational modelling tools is expected to provide an efficient methodology for the optimization of the design of thrombo-prophylactic compression devices. To fulfil this ultimate goal, a number of improvements will be required.

First, from the FE modelling point of view, a 3D representation of the calf would be required in order to reveal more realistic information on the mechanical responses of calf tissues to external compressions. For the development of such a model, a better understanding of the tissue mechanical properties is necessary. Due to the fibre-oriented structure of muscles, the method used to evaluate or calibrate the material properties from MR images should be extended to three dimensions. Improvements of the image segmentation procedure need to be done to achieve this goal. Distinguishing the boundaries of the tissues would be very important and considering the complex anatomic structure of the lower limb, 3D surface reconstruction would require images with very high spatial resolution.

Although skeletal muscles occupy most of the calf volume, the presence of other tissues such as interosseous membrane, fascial sheath and adipose tissue, is also important in the load transmission from the external boundary to deep veins. Understanding the mechanical properties of these tissues would help to establish suitable models for their mechanical behaviour. A comprehensive, multi-component model, including all tissue types and with appropriate connectivity between discrete structures, would be capable of predicting the internal force distribution generated by compression devices and the induced deformation of the deep vascular system.

More accurate methods of measuring the deformation of different groups of calf tissues would be useful in revealing their mechanical behaviour in detail. Within the leg, there are several muscle groups, whose interactions might have important influences on the load transmission from external boundary to the deep vein. A finite element based non-rigid registration approach would be capable of providing highly detailed data concerning not only the external forces, exerted by the stocking on the

skin, but also the resulting internal force distributions. However, this would require tracking of the muscle group boundaries. In order to achieve this goal, one possible approach would be the use of MR-tagging, which is a technique to track the motion of moving tissues. The basic MR tagging sequence consists of using RF pulses to produce regular dark bands of selective saturation, followed by a conventional imaging sequence. The motion of the material can then be tracked quite readily, as the movement of the material is reflected by the deformation of saturation bands.

For the evaluation of different compression designs, an approach to measure the pressure distribution generated by compression devices would be necessary. Although the pressure profile is usually specified in the manufacturer's instruction, due to the irregular geometry of the limb, a certain level of discrepancy is inevitable. Given the high level of sensitivity of deep veins to the boundary displacement, the employment of accurate pressure distribution as the load boundary condition for the finite element model would be necessary even if the difference in the induced deformation is small compared to the size of the leg.

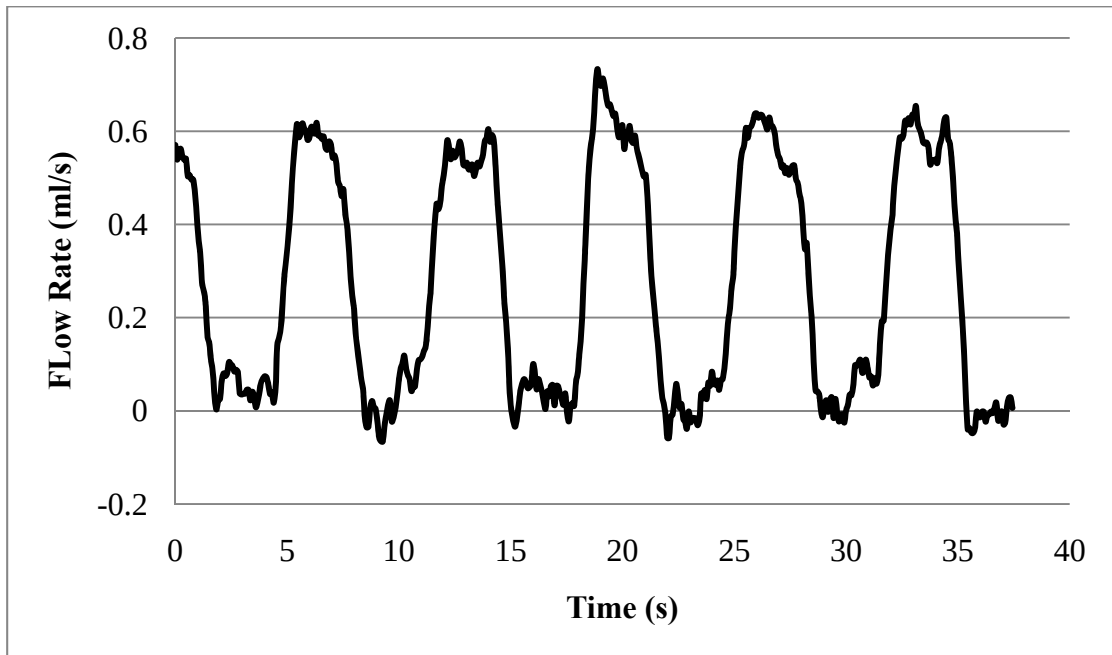
The fluid-structure interaction methodology has the potential to simulate the transient response of the deep venous system to external compression, but further improvement would be required for practical applications. These include: first, considering the highly variable architecture of the deep venous system, the reconstruction of vessel geometry would require very high spatial resolution imaging technique; second, a powerful structural mechanics solver that is able to handle highly non-linear elastic behaviours (such as large deformation) would be needed; and third, a one-way coupling method with small time steps might be more suitable for FSI simulation involving large deformations than the two-way implicit iteration method.

Given that DVT mostly originate from the venous valve pocket (VVP), FSI modelling of venous valve would provide more insight into the pathology of DVT. The development of the model would require material properties of vein valve leaflets and geometry information about VVP. B-flow mode supplemented by B-mode and pulsed-wave Doppler scanning has been shown to be able to provide transient data on venous valves [188], but further development of the technology is still required to

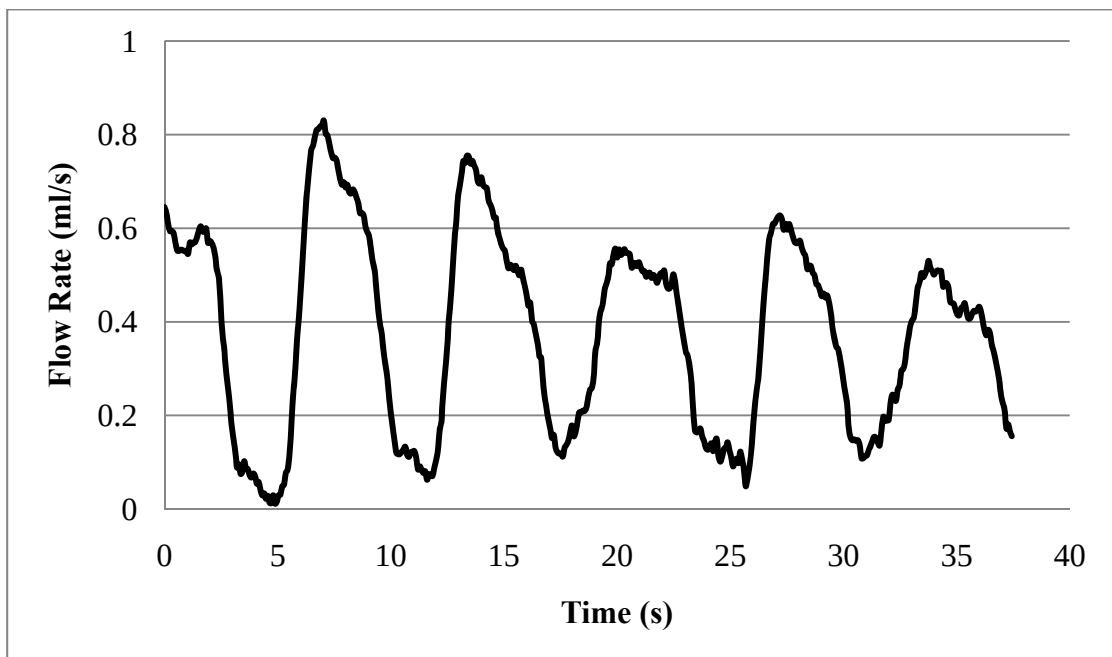
record the flow information and valve movement simultaneously, which would be important for the establishment and validation of the FSI model.

Appendix A

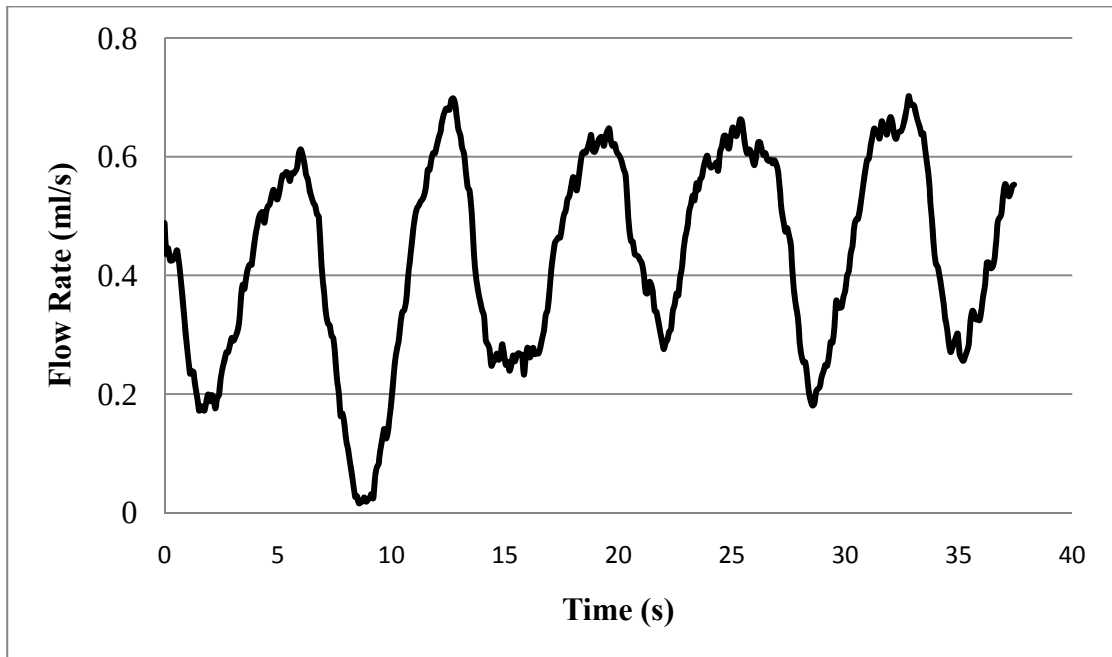
**MRI data: Volume flow rate
waveforms generated by real-time
phase contrast velocity mapping
sequence**



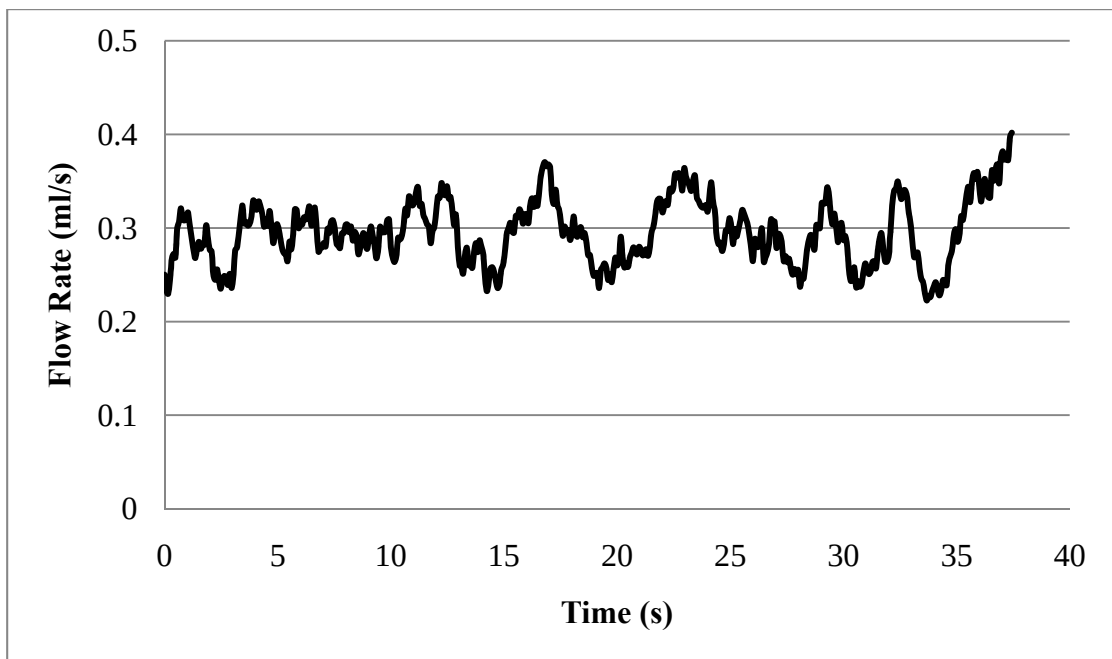
(1) subject 1 - medial peroneal vein flow without stocking



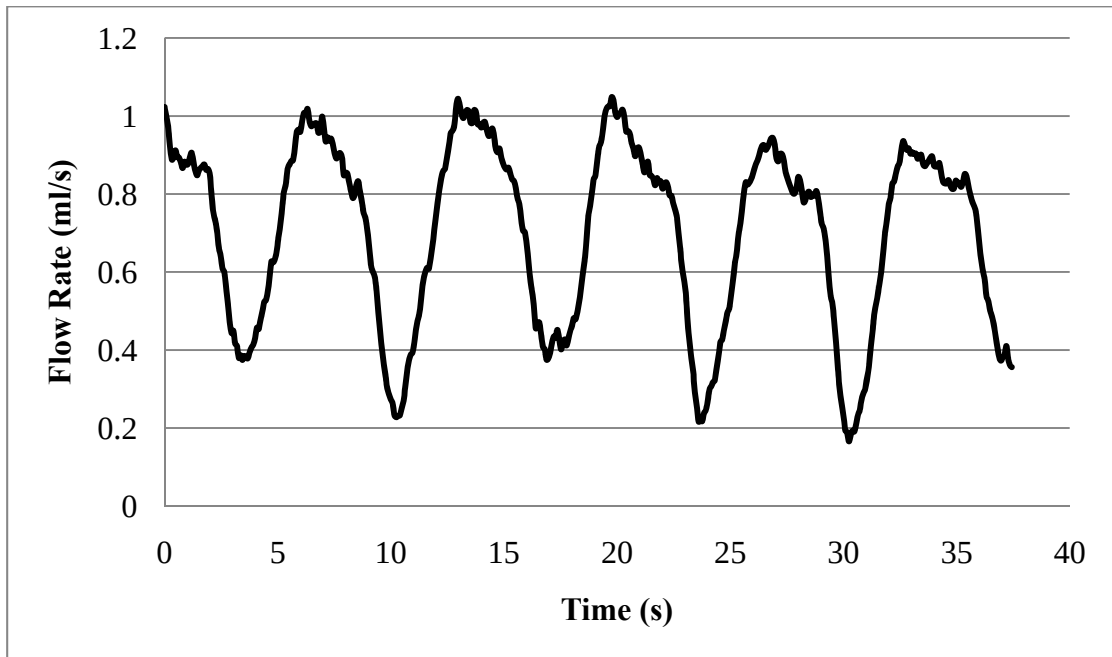
(2) subject 1 - medial peroneal vein flow with stocking



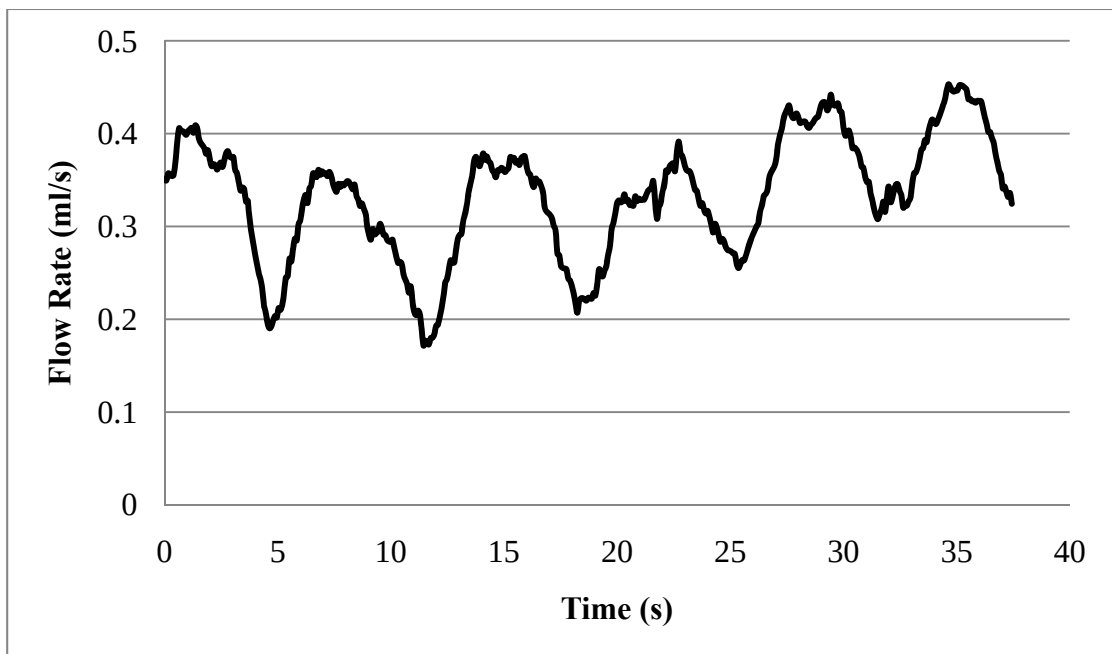
(3) subject 2 - medial peroneal vein flow without stocking



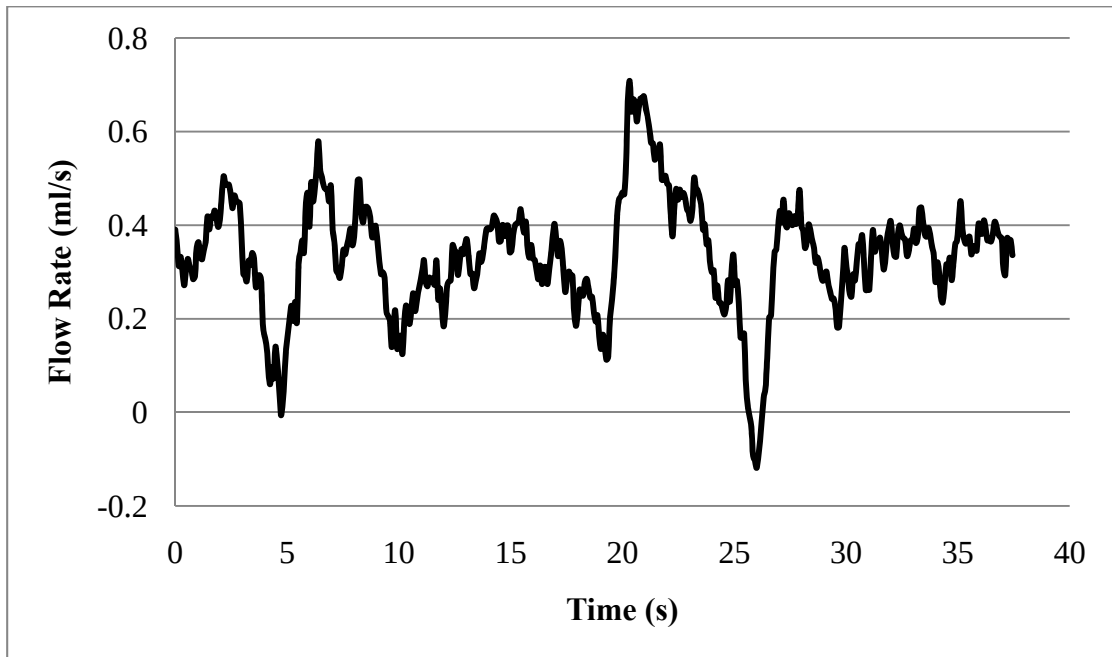
(4) subject 2 - medial peroneal vein flow with stocking



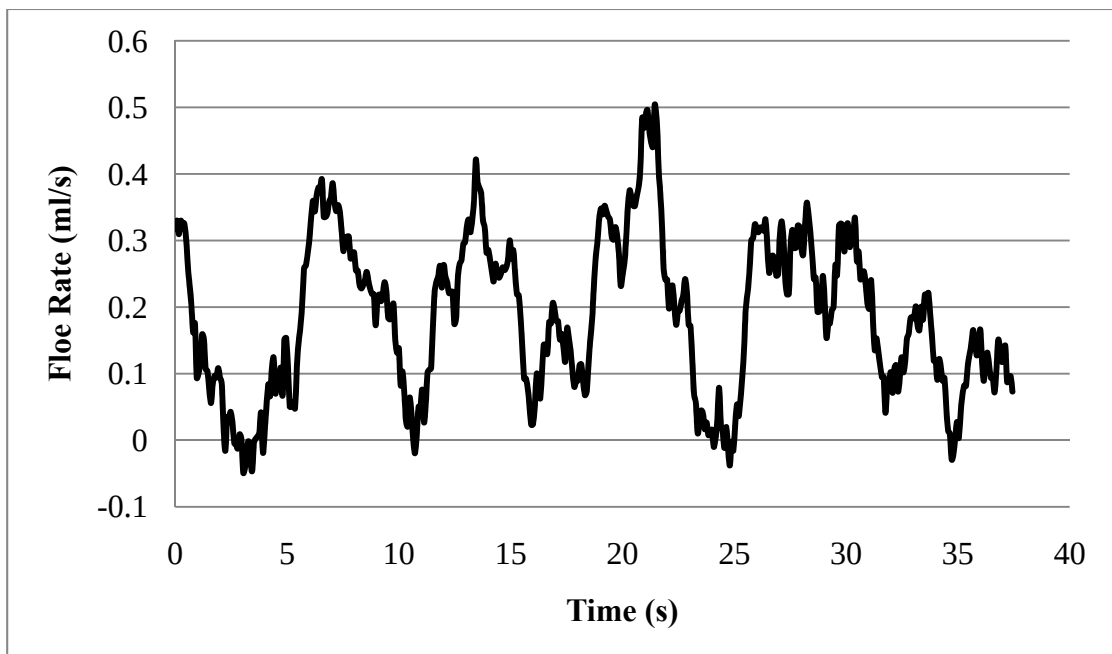
(5) subject 3 - medial peroneal vein flow without stocking



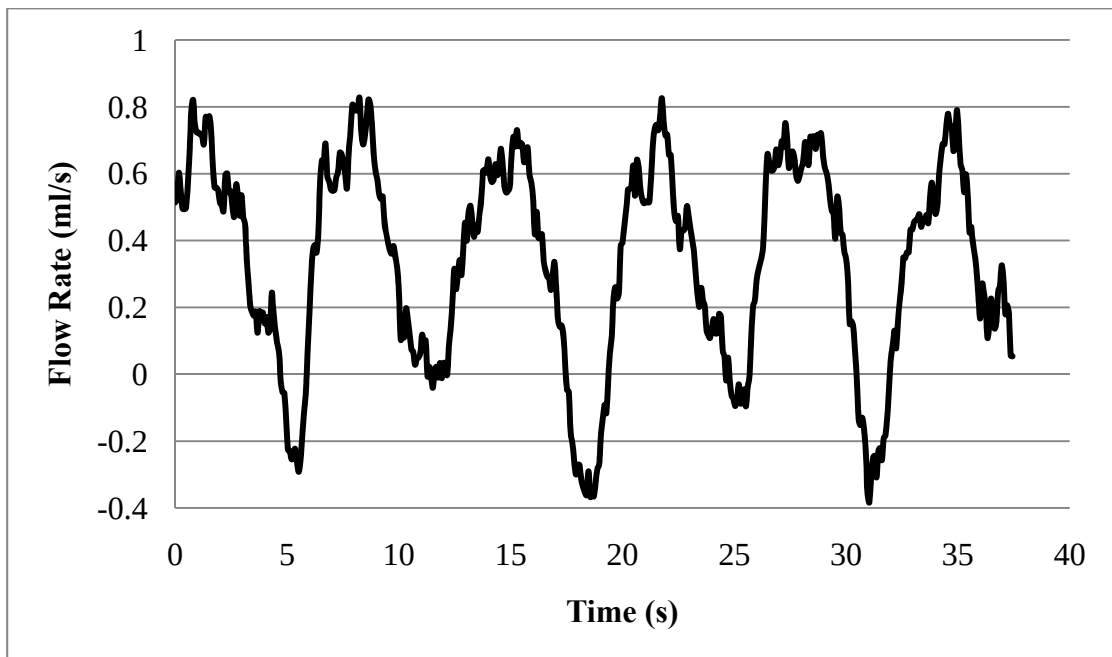
(6) subject 3 - medial peroneal vein flow with stocking



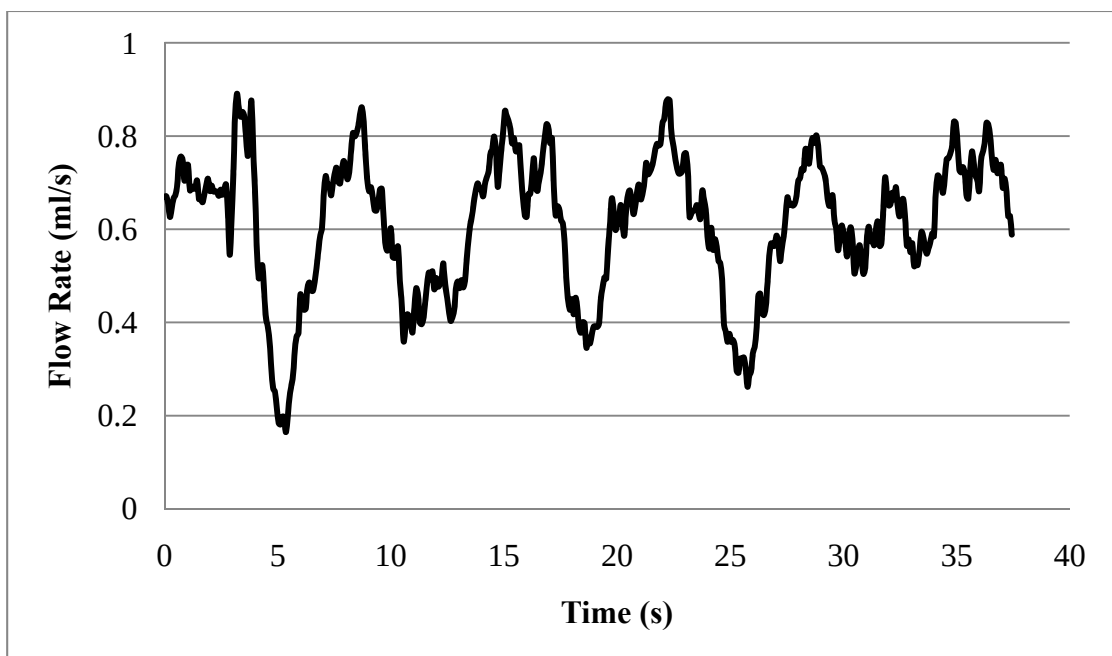
(7) subject 4 - medial peroneal vein flow without stocking



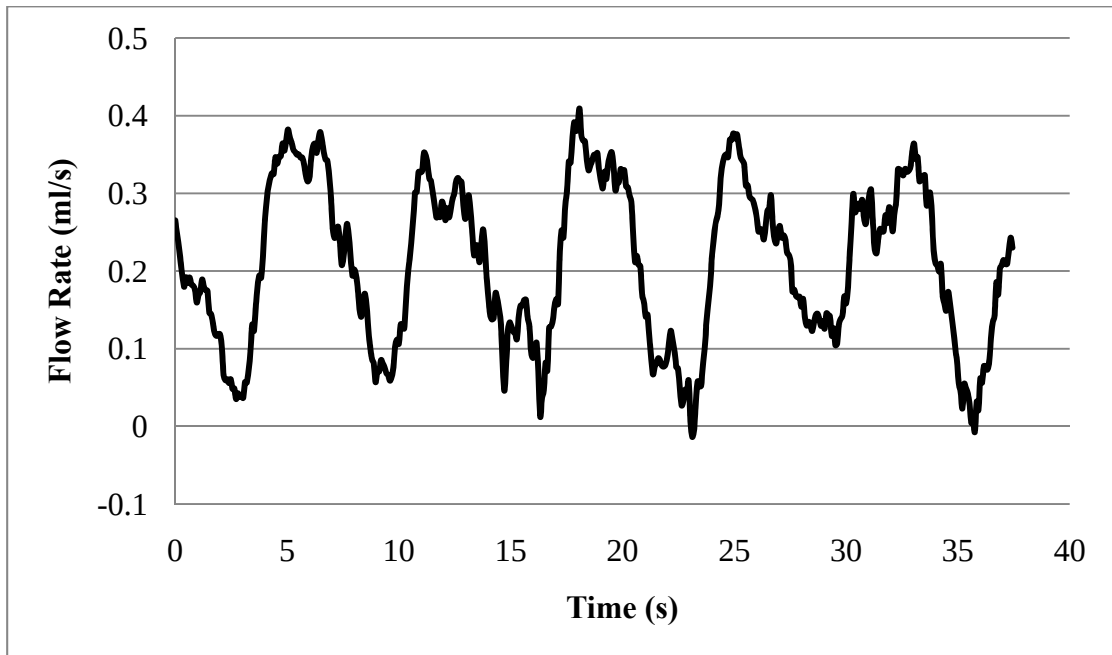
(8) subject 4 - medial peroneal vein flow with stocking



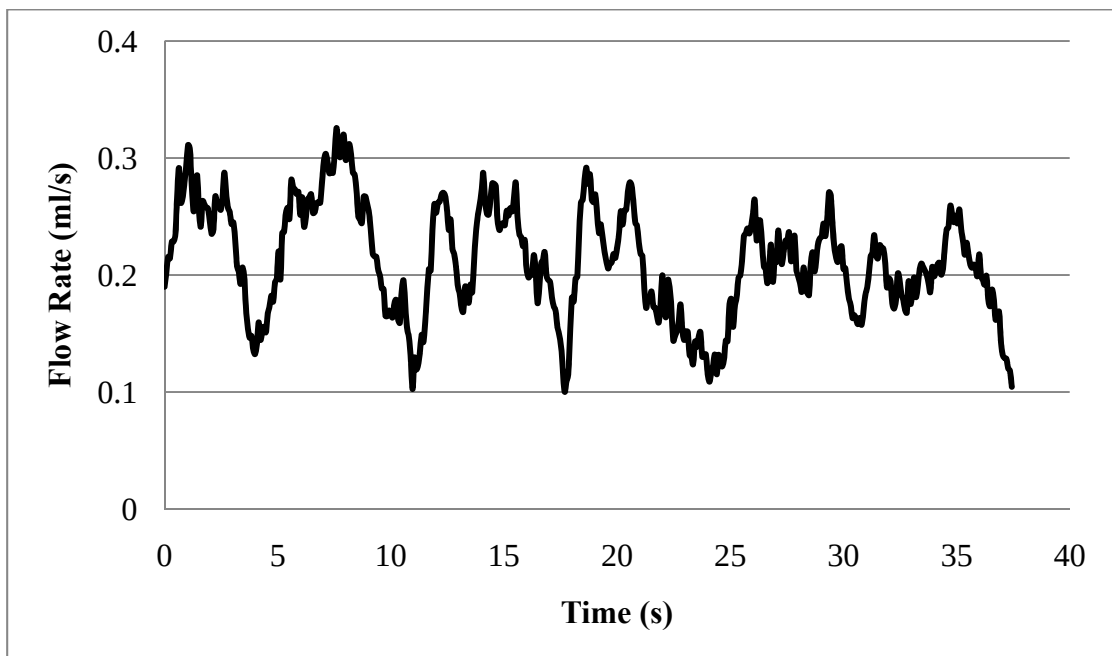
(9) subject 5 - medial peroneal vein flow without stocking



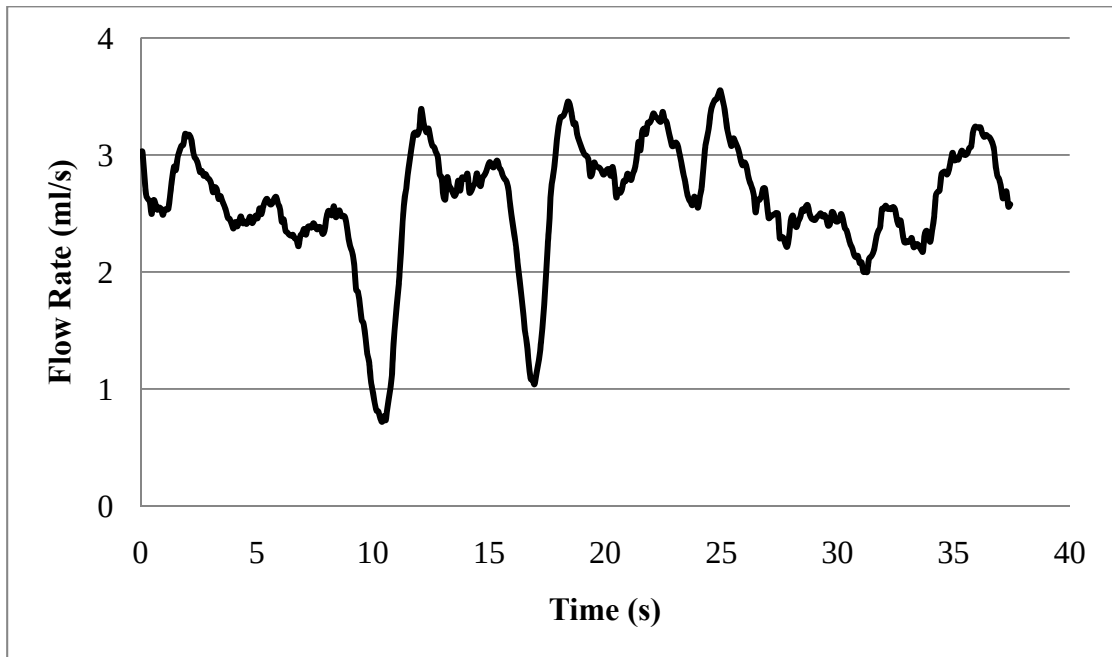
(10) subject 5 - medial peroneal vein flow with stocking



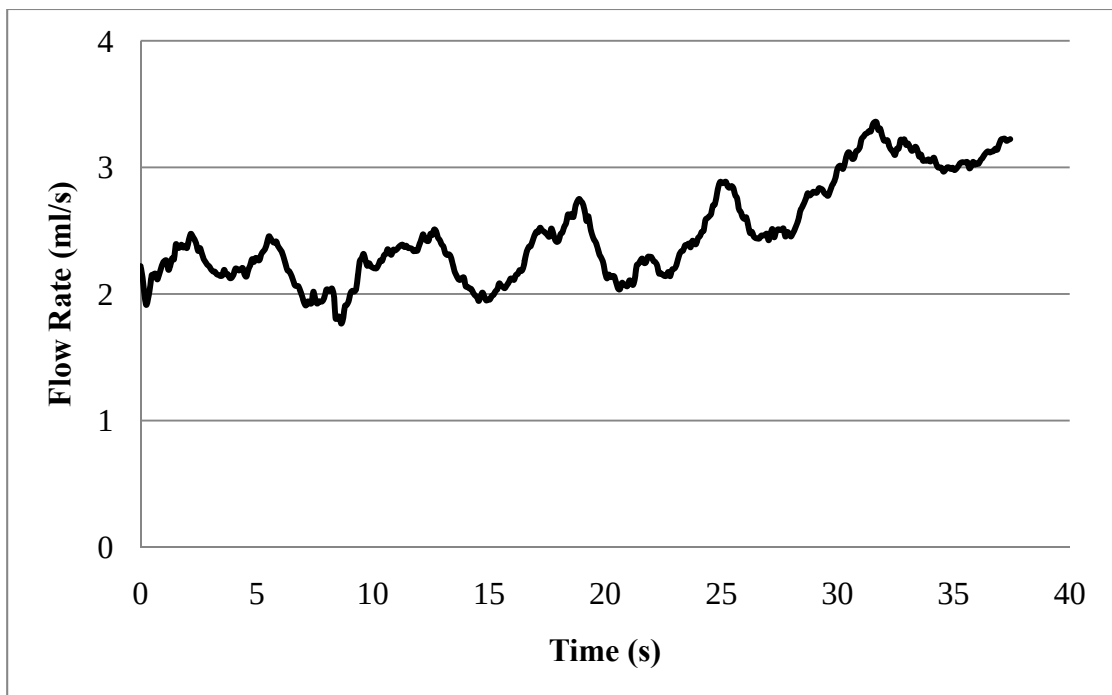
(11) subject 6 - medial peroneal vein flow without stocking



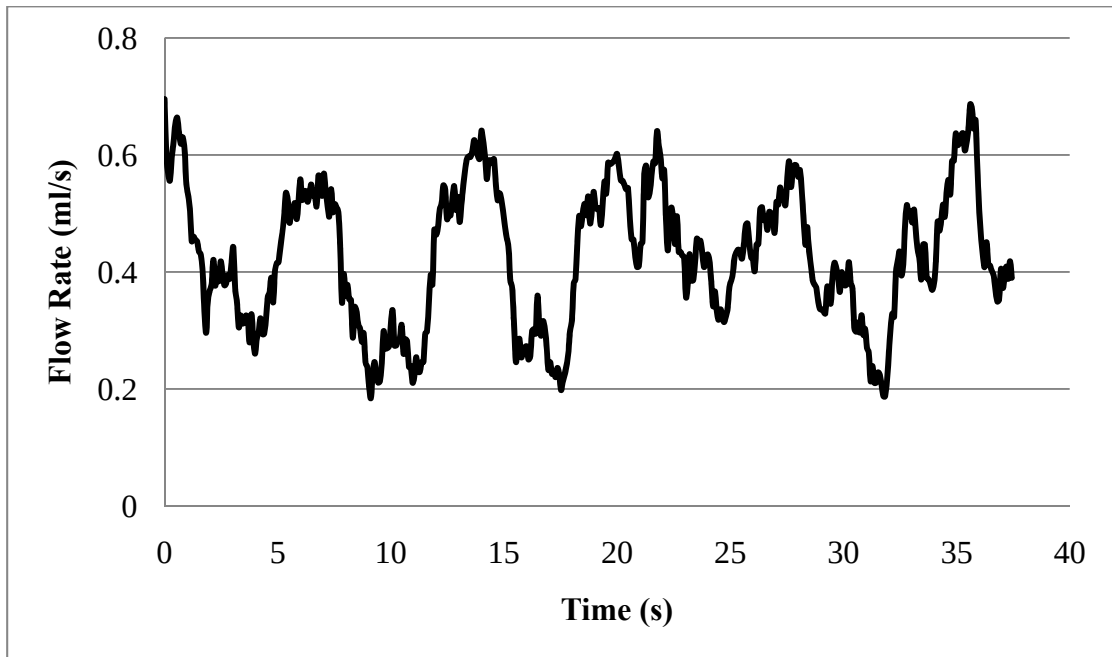
(12) subject 6 - medial peroneal vein flow with stocking



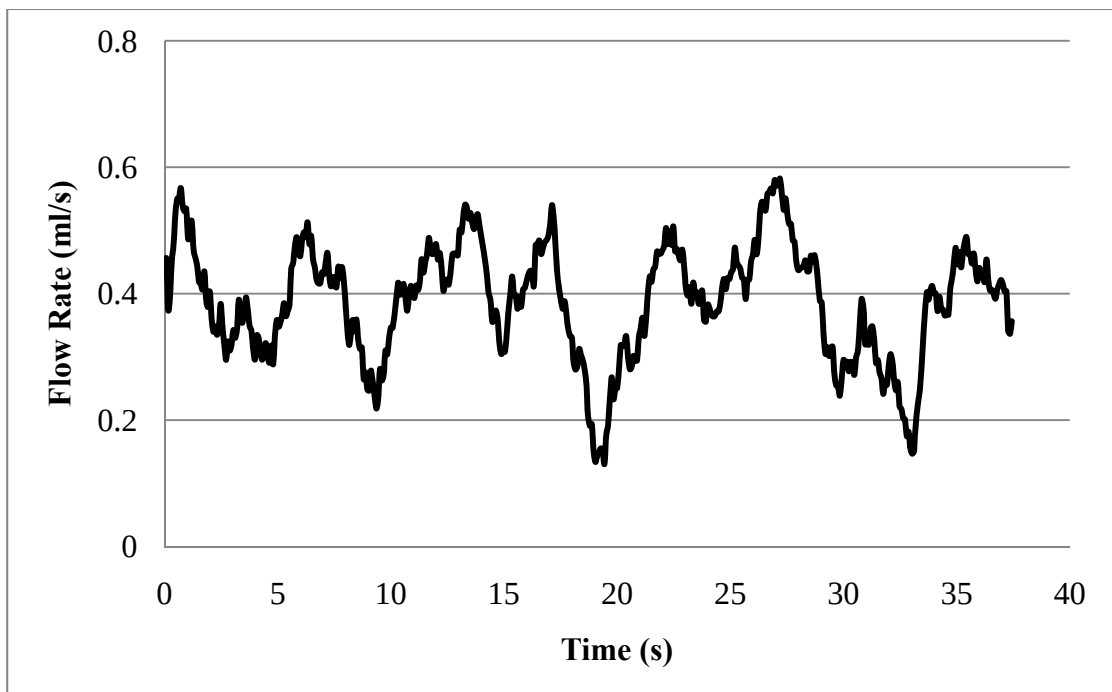
(13) subject 7 - medial peroneal vein flow without stocking



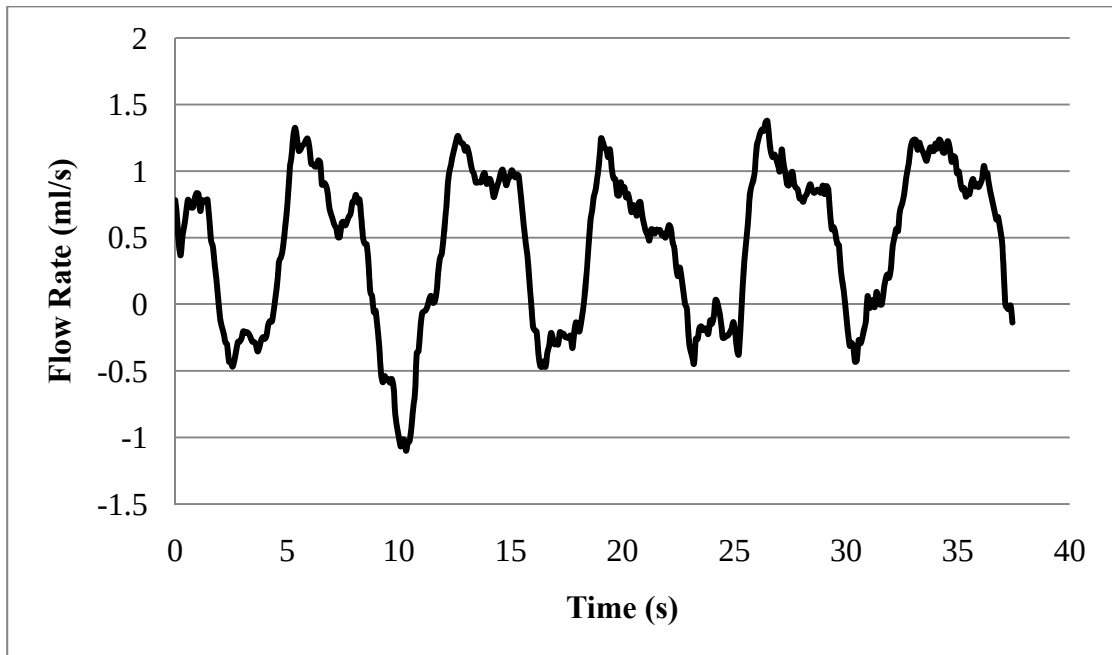
(14) subject 7 - medial peroneal vein flow with stocking



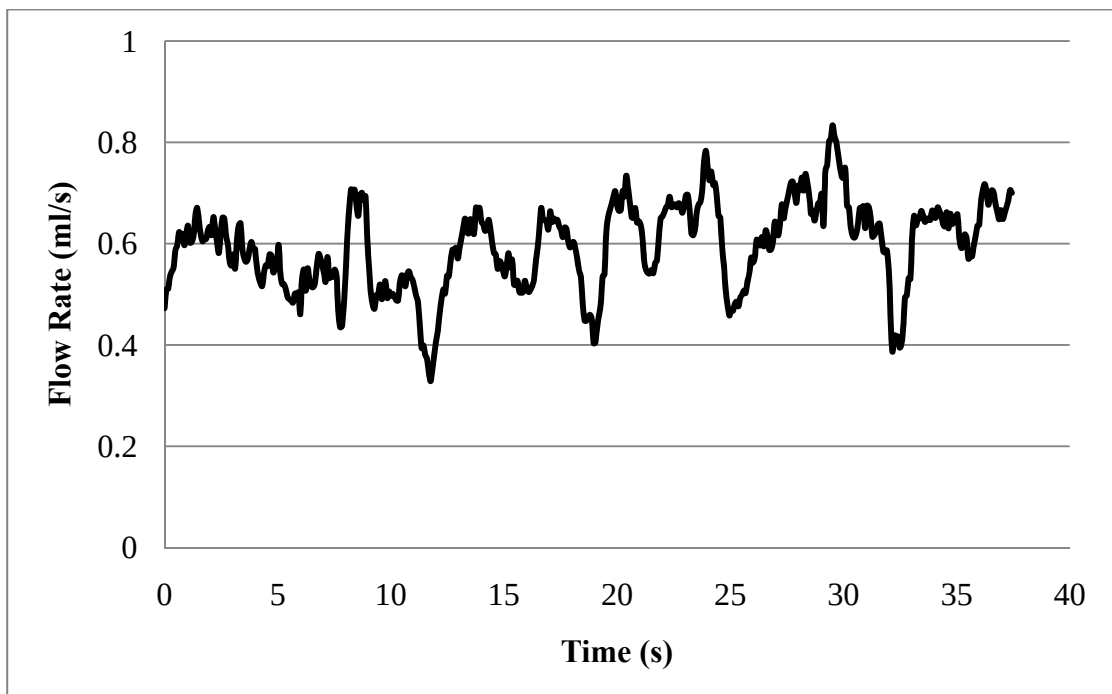
(15) subject 8 - medial peroneal vein flow without stocking



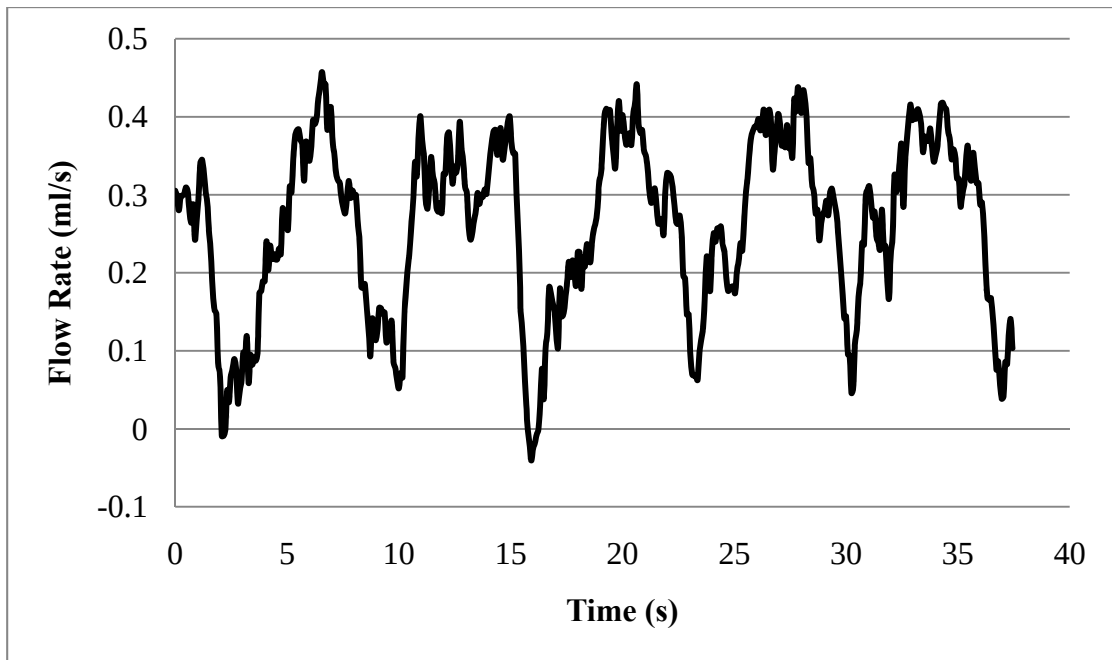
(16) subject 8 - medial peroneal vein flow with stocking



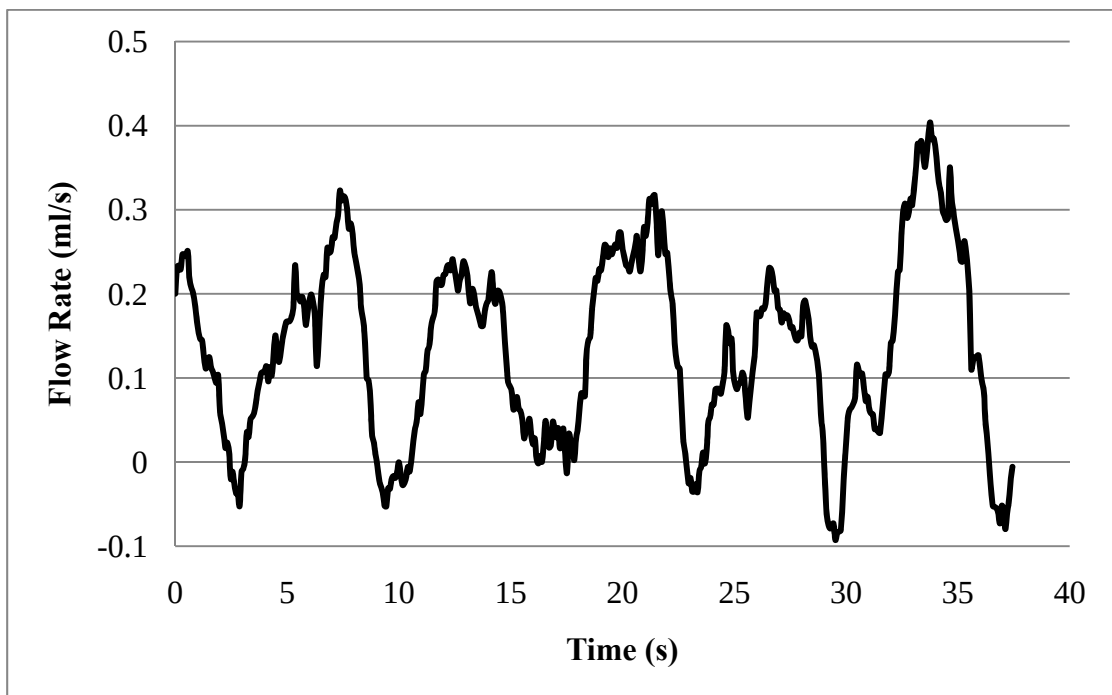
(17) subject 9 - medial peroneal vein flow without stocking



(18) subject 9 - medial peroneal vein flow with stocking



(19) subject 10 - medial peroneal vein flow without stocking



(20) subject 10 - medial peroneal vein flow with stocking

Appendix B

List of Publications

Journal Papers

Wang Y, Pierce IT, Gatehouse PD, Wood NB, Firmin DN, Xu XY. Analysis of flow and Wall Shear Stress in the peroneal veins under external compression based on real time MR images. Med Eng Phys. 2011 (accepted subject to minor revision).

Conference Papers and Presentations

Wang Y, Wood NB, Firmin DN, Xu XY. The effects of external compression on tissue deformation in the lower leg. 1st International Conference on Computational & Mathematical Biomedical Engineering. Swansea. Nithiarasu P, Löhner R, van Loon R (eds). 2009; 380-3.

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